Chapter

Pseudomonas aeruginosa: Diseases, Biofilm and Antibiotic Resistance

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Abstract

Pseudomonas aeruginosa is Gram negative bacteria that can adapt to extreme environmental conditions and withstand to different antibacterial agents. It si responsible for arrays of infections both community and hospital acquired especially ICU infections. Respiratory tract infection, blood stream infection, wound infection, burn infection, and urinary tract infections ware top five *P. aeruginosa* infections. Additionally as an opportunistic bacteria, it may be associated with healthcare infections in intensive care units (ICUs), ventilator-associated pneumonia (VAP), central line-associated blood stream infections, surgical site infections, otitis media, and keratitis. *P. aeruginosa* can form biofilms as self-produced extracellular matrix to protects the cells from antibiotics and the host immune response. Antibiotic resistance was an prominent feature of this pathogen and can donate it one of the three resistance patterns: Multidrug (MDR), extensive drug (XDR) and pan drug resistance. It exploit many resistance mechanisms ranged from overexpression of drug efflux systems protein, modifying enzyme production, reducing the permeability and using shelters like biofilms.

Keywords: *P. aeruginosa*, UTIs, RTIs, wound infections, antibiotic resistance, biofilm

1. Introduction

Pseudomonas aeruginosa (P. aeruginosa) is considered as a part related to normal intestinal flora as well as a considerable pathogen that is accountable for various ICU-acquired infections in patients who are critically ill. The nosocomial infections related to such organism involve meningitis, blood stream infections, urinary tract infections, respiratory tract infections, wound infections and otitis media [1, 2]. Study samples have been gathered from patients with the next disease: *P. aeruginosa* ear infection might be categorized into otitis media, malignant outer otitis, simple external otitis (or swimmer ear) and perichondritis. Particularly, otitis media can be defined as one of the middle ear inflammations impacting the pediatric population and might be divided as chronic and acute [3]. *P. aeruginosa* can be specified as one of the opportunistic bacteria related to health-care infections in VAP, ICU, central line related blood stream infections, surgical site infections, urinary tract infections, burnt wounds, keratitis and otitis media [4, 5]. *P. aeruginosa* might be specified as a bacterial pathogen that causes extreme chronic infections in the immuno-compromised individuals. The capability of *P. aeruginosa* for creating biofilm, that were communities regarding the cells which are encased in self

produced extracellular matrix, protecting the cells from antibiotics as well as host immune responses [6]. The biofilm have the ability of augmenting the persistent infections related to *P. aeruginosa* and high antibiotic resistance level in comparison to planktonic bacterial cells, whereas the treatment of infections resulting from such organism are difficult due to the existence of its innate resistance to various antibiotics (β-lactam and penem group of antibiotics), along with its capability for acquiring more resistance mechanism to several antibiotic types, such as fluoroquinolones, aminoglycosides and Beta-lactams [7]. *P. aeruginosa* implicated disease are indicated in the following way:

1.1 *P. aeruginosa* associated respiratory tract infection

P. aeruginosa can be defined as a significant organism resulting in chronic infections in the bronchiectasis, due to its ability for maintaining virulence in spite of antibiotic therapies via creating biofilm and developing antimicrobial resistance. In addition, bronchiectasis is one of the chronic airway diseases specified via irreversibly damaged as well as dilated bronchi resulting in recurrent bronchial sepsis episodes. This leads to poor mucus clearance, and vicious cycle related to persistent bacterial colonization, inflammation, airway obstruction along with progressive destruction of the tissues [8]. Also, *P. aeruginosa* in the cystic fibrosis (CF) bronchiectasis was related to steeper reduction in the function of lungs and elevated mortality and morbidity. Its existence in bronchiectasis is related to diseases with more severity, yet if there was direct impact on the progression of disease or if *P. aeruginosa* one of the indicators of current clinical severity still debated [9, 10]. Also, the rate of *P. aeruginosa* chronic infections in patients experiencing bronchiectasis vary from 9 and 31%, and its commonness in large, multi-centre population from many nations yet to be evaluated [11, 12]. Furthermore, CF lung was hostile, heterogeneous and stressful environments for the invading bacteria, while the populations of *P. aeruginosa* should have the ability of overcoming such issues for persisting and surviving, whereas the postulated stressors in CF lung involve osmotic stress because of mucus, oxidative and nitrosative stresses because of host responses, sub-lethal antibiotics' concentrations, along with the existence of other microorganisms [13].

1.2 *P. aeruginosa* associated wound and burn infection

P. aeruginosa is specified as a major pathogen isolated from the burn patients worldwide [14], also it is opportunistic bacterium related to VAP, ICU, burns and surgical site infections [15] and it is a significant pathogens included in burn infections [16] and one of the main nosocomial pathogens in the burn patients, and quickly acquiring antibiotic resistance; therefore, develop efficient therapeutic method was one of the main strategies to combat the infections [17]. Particularly in burn centers, the progressive increase and high occurrence of MDR *P. aeruginosa* threating patients with extreme burn injuries [18, 19], while burn wound infections were major complications happening following the burn injuries and might be related to dangerous clinical complications and elevated mortality and morbidity [20]. In addition, burn injuries includes the primary host's barrier, the skin, that is directly placing hosts at risks of infections [21], whereas the burn wounds were main public-health problems worldwide. Infections are difficult problems in burn patients, since the skin, one of the barriers against microbes, was destroyed and immunity agents have no ability for reaching the infection sites. There were correlations between the infection severity and the burn's extent [22]. *P. aeruginosa* is a typical bacterium in the nosocomial infections, particularly in burn units.

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Furthermore, burn patients, due to the loss of skin barrier, showed high vulnerability to infections [23]. Novel therapeutic agents against the *P. aeruginosa*, improve the effectiveness of present antimicrobial agents and degrade biofilm in burn wounds, were needed [24], such bacterium is causing 75% of deaths in the burned patients, as it might be developing persistent biofilm related to infections, expressing many virulence factors, as well as mechanisms of antibiotic resistance. A few of such virulence factors have been proteases like elastase and alkaline protease, or toxic metabolites including pyocyanin and microorganisms with the ability of producing cyanide, that is inhibiting the cytochrome oxidase regarding host cells [25]. Furthermore, multiple antibiotic resistant *P. aeruginosa* was a considerable cause of burn wound infections and, soft tissue and skin infections. Due to its resistance to majorly utilized antiseptics and antibiotics, there was lack of therapeutic options for efficient treatments [26]. Usually, *P. aeruginosa* attacking patients with wound and burn infections, in which more complications of primary condition, might happen and often causing bacteremia [27].

1.3 *P. aeruginosa* associated urogenital infection

UTC is one of the major microbial diseases with considerable economic impacts on society [28]. Even though that almost all UTIs were resulting from *E. coli*, a lot of epidemiological reports showed an increase in the infection's rates resulting via a few of opportunistic organisms involving *P. aeruginosa*. Also, the pathogenesis mechanisms and antimicrobial susceptibility regarding *P. aeruginosa* were badly understood [29]. UTC is a major microbial infection in humans and representing considerable burden on health-care systems. UTI might be simple, in terms of affecting healthy people, or complicated, in terms of impacting people with compromised host defenses and/or urodynamics, like the ones with urinary catheter, while there were some differences between un-complicated UTI as well as catheter associated UTIs (CAUTIs) in the clinical manifestations, pathophysiology and causative organisms. Thus, uncomplicated CAUTI and UTI might not be similarly approached, or the risks of complications and treatment failure might be increased [30]. Also, complicated UTI (cUTI), occurs in immuno-compromised patients or in the patients with functional or structural abnormalities of the urinary tract (UT), were related to high treatment failure rates and dangerous complications, particularly relapse as well as the development related to antibiotic resistance [31]. cUTIs is from the major healthcare-related infections.

In patients experiencing cUTI, *P. aeruginosa* is deserving distinctive attention, due to the fact that it might be affecting patients experiencing considerable underlying conditions [32]. Also, *P. aeruginosa* is a main nosocomial uropathogen. In addition, *P. aeruginosa* is considered as the 3rd major pathogen resulting in hospital-acquired CAUTI [33]. It might be tolerating a lot of physical conditions and a lot of antibiotics via various mechanisms of resistance [34]. The continuous increase in antibiotic resistance all over the world is disturbing [28]. Increasing the multi-drug resistance in the bacterial uropathogens is emerging and considerable public-health problems [35]. Catheter-associated UTC (CAUTI) is responsible for 40% of the nosocomial infections in hospitalized patients [33]. *P. aeruginosa* a multifaceted pathogens resulting in many biofilm mediated infections, involving CAUTIs. The majority of catheter-associated infections were caused by the own perineal flora of patient, yet the existence of catheter is increasing the chances of being colonized through cross transmission regarding nosocomial bacteria too.

The majority of episodes related to short term catheter associated bacteriuria were asymptomatic and resulting from single organisms, whereas long term catheterization is promoting colonization and multi-bacterial infections. The prolonged

duration related to catheterization bacteriuria was specified universal due to the biofilm' formation on the surface of catheter [36]. In addition, the high occurrence of CAUTI in the hospitals, their clinical manifestations, like cystitis, urethritis, meningitis, pyelonephritis, death and urosepsis, also the related economic challenges underscoring the requirement for the infections' management, while *P. aeruginosa* might be resulting in complicated UTIs, especially in individuals with catheters, that might result in pyelonephritis, whereas a few sub-groups appearing with more susceptibility to infections, like women and elderly, the contributions of other host factors in addition to the bacterial virulence factors for successful infections still fairly understudied. Furthermore, *P. aeruginosa* UTIs were extremely antibiotic resistant and requiring intensive and costly treatment [37].

1.4 *P. aeruginosa* associated otitis media

Otitis media (OM) can be considered as a major cause of fever as presentation in pediatric population. Chronic suppurative otitis media (CSOM) (also termed as chronic otitis media) is one of the ear diseases stages where there are ongoing chronic infections related to middle ear with no intact tympanic membrane, such disease is one of the inflammations of middle ear as well as mastoid cavity, while the characteristic presentation was persistent or chronic otorrhoea throughout (2–6) weeks via perforated tympanic membrane [38]. In addition, OM considered as group of the complex inflammatory disorders impacting the middle ear that might be chronic or acute [39]. CSOM (also referred to as chronic otomastoiditis, chronic active mucosal otitis media and chronic tympanomastoiditis), is one of the inflammations of middle ear as well as mastoid cavity, present with recurrent ear discharge or otorrhea via perforated tympanic membrane [40]. Chronic (OM) is a perforation related to tympanic membrane with infection. Mostly, it occurs in underdeveloped nations.

Culture and sensitivity reports are showing the main pathogens accountable for chronic OM were *P. aeruginosa* and *S. aureus* [41]. Bacteria's dispersal from biofilm in the middle ear, serve as bacterial reservoir, might be explaining the recurrent as well as chronic nature related to CSOM [42]. *P. aeruginosa* is one of the significant CSOM pathogens showing multiple resistances to the antibiotics with increase in frequency and make the treatment of patients extra difficult [43]. *P. aeruginosa* is a major organism result in CSOM, is one of the notorious pathogens with MDR attribute [44]. Also, *P. aeruginosa* is invading the human middle ear epithelial cells (HMEECs) as well as inducing cytoskeletal rearrangements [39], while the antibiotics resistance that is considered as worldwide health challenge is not a future threat anymore, yet current problem to all clinical setting's facets. Therefore, treating OM effusion is a main concern [45].

1.5 *P. aeruginosa* associated meningitis

Community acquired meningitis resulting from *P. aeruginosa* has extremely increased mortality rates and uncommon [46]. It is related to prior neurosurgical procedure and hospital-related onset. Generally, bacterial meningitis is developing many cerebrovascular complications, from which the intracerebral hemorrhage is rare [47]. In addition, Multidrug Resistant (MDR) strains were identified in patients with neurosurgical interventions and patient with nosocomial exposure. This study is providing one of the fatal cases regarding community-acquired MDR pseudomonal meningitis [48]. One of the uncommon causes of ventriculitis and meningitis is *P. aeruginosa*, yet is commonly related to considerable mortality and morbidity [49]. Majorly, there is history of neurosurgical procedure in patients who

develop *P. aeruginosa* meningitis [50]. Also, *P. aeruginosa* neurosurgical meningitis is one of the uncommon entities typically associated to elevated rates or mortality and with intraventricular catheters [51]. Adult bacterial meningitis (ABM) resulted from *P. aeruginosa* was typically because of nosocomial infections and typically identified in patients experiencing post neurosurgical state [49]. Each year, approximately 16,000 are dying due to ABM [52]. Meningitis resulting from extensively drug resistant (XDR) or multidrug-resistant (MDR). Gram negative bacillary meningitis (GNBM) resulting in considerable limitations in present options of treatment [53]. One of the main challenges in antibiotic selection is the increase in meningitis resulting from extreme drug resistant bacillary [52], while antibiotic resistance in multiple *P. aeruginosa* strains is quickly-developing clinical problem [54]. The options of treatment were further limited with the involvement of central nervous system (CNS), since the colistin based regimens were disadvantaged via poor blood brain barrier penetration, frequently related to inadequate microbiological and clinical success. There was a recent increase in using intrathecal colistin and it is one of the alternatives to manage infections related to central nervous system resulting from MDR bacteria [46]. whereas *P. aeruginosa* ventriculitis and meningitis were mainly nosocomial and associated to prior neurosurgery. There is high difficulty in diagnosing as Cerebrospinal fluid Gram film as well as meningism were insensitive markers [49].

2. Biofilm formation and antibiotic resistance

Extracellular matrix is vital feature related to biofilm communities, it is surrounding the resident bacteria and it includes matrix proteins, lipid vesicles, exopolysaccharides and extracellular DNA (eDNA), whereas the 3 exopolysaccharides regarding *P. aeruginosa* biofilm matrix (alginate, Pel and Psl) [55]. Mainly, the biofilm includes bacterial derived exopolysaccharides which is protecting encapsulated bacteria from host immune cells as well as antibiotics [56]. In addition, biofilm are considered to be widespread in their nature and constituting a significant strategy carried out via microorganisms for surviving in often harsh conditions of environment. They might be effectives or leaving bad effect especially when created on medical devices or in industrial settings. Thus, studying the elimination and formation of biofilm is significant for a lot of discipline [57]. The ability of *P. aeruginosa* for creating biofilm, that were cells' communities which are encased in self produced extracellular matrix, protecting the cells from antibiotics as well as host immune [58]. Also, *P. aeruginosa* is considered opportunistic, nosocomial bacterial pathogen forming persistent infections because of creating protective communities, referred to as biofilm. Furthermore, biofilm is a significant virulence factor in *P. aeruginosa* and has considerable roles in antibiotic resistance as well as chronic burn wound infections [24], while the biofilm of *P. aeruginosa* are contributing to its survival on the abiotic and biotic surfaces and representing main clinical threat because of their increased tolerance to the antibiotics [59]. As soon as forming the biofilm, the bacteria embedded in it were recalcitrant to the anti-microbial treatment along with host immune defenses [60].

Biofilm have been specified as complex microbial communities which contain micro-colonies and surrounded by self-created extracellular polysaccharide matrix, while the biofilm matrix in *P. aeruginosa* includes 3 different exopolysaccharides: Pel, Psl and alginate. Also, the alginate can be defined as one of the polymers which contain α-L-guluronic acid and β-D-mannuronic acid with considerable roles in the structural stability as well as biofilm protection, while Psl has been specified as a polysaccharide includes repeating pentasaccharide, containing L-rhamnose,

D-glucose and D-mannose. Psl was significant in the start of the formation of the biofilm and biofilm structure protection. Pel is specified as the 3rd polysaccharide that exists in *P. aeruginosa* biofilm and was glucose rich [61]. Furthermore, the biofilm cells showing increased resistance to the environmental pressures like anti-microbial agents compared to their planktonic form [62]. Also, its populations undergoing characteristic evolutionary adaptation throughout chronic infection related to CF lung, involving decreased virulence factors' production, transition to biofilm related lifestyles, and the evolution regarding high level antibiotics resistance, whereas the populations of *P. aeruginosa* in the chronic CF lung infections generally showing increased phenotypic diversity, involving clinically significant characteristics like antibiotics resistance and toxin production, and such diversity was dynamic throughout the time, which will make precise treatment and diagnosis challenging [63].

3. Antibiotic resistance

P. aeruginosa has been considered as a major cause related to nosocomial infections, also it is accountable for about 10% of all the hospital acquired infections in the world. It is still considered as one of the therapeutic challenges due to the high rates of mortality and morbidity related to it and the potential to develop drug resistance throughout the therapy. Also, standard antibiotic regimes against the *P. aeruginosa* were more and more unsuccessful due to the increase in drug resistance [64]. In addition, antibiotics resistance in the multiple strains related to *P. aeruginosa* was a clinical issue that is developing rapidly, while the definitions regarding multidrug resistance *P. aeruginosa* (MDRPA) was isolates resistant to minimum of 3 drugs from various antimicrobial categories, involving cephalosporinsand quinolones, aminoglycosides, carbapenems and anti pseudomonal penicillin were categorized as multidrug resistant. The development of antibiotic resistant bacteria in health-care is dangerous. With regard to health-care premises exactly ICUs were main microbial diversity sources. Recently, a few studies indicated that not just microbial diversity, yet also the drug resistant microbes majorly habitat in the ICUs.

Infections resulting from such organism were complicated to treat due to the existence of its innate resistance to various antibiotic types (Beta-lactam and penem group of antibiotics) as well as its capability for acquiring more resistance mechanism for a number of antibiotics classes, involving aminoglycosides, β-lactams and fluoroquinolones. With regard to molecular evolution microbes adopting many mechanisms for maintaining genomic plasticity [2], MDR isolates have been majorly specified via slow growth, cytotoxic type-III secretion system genotype, excellent biofilm forming capability, and the existence of more aminoglycoside modifying enzyme (AME) genes, non MDR isolates are re-sensitized following the inhibition regarding active efflux or improvement of membrane permeability, such target gene alteration along with the enzymatic drug modification that has been specified as the main quinolone mechanisms and aminoglycoside resistance in *P. aeruginosa* keratitis isolates [65]. Extensively drug-resistant *P. aeruginosa* (XDR-PA) that has been characterized as the strains remaining susceptible to only 1 or 2 anti-pseudomonal agent classes, became a serious issue because of a lack of effective anti-microbial treatment [66].

P. aeruginosa became resistant to a number of the antibiotics classes, which include the carbapenems, which have been viewed as reliable antibiotics for treating the multi-drug-resistant *P. aeruginosa* serious infections and have been viewed as a last-resort antibiotic therapy of the infections that have been caused by the carbapenem-resistant *Pseudomonas aeruginosa* has become more problematic, particularly

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with increasing the carbapenem resistance. Carbapenem was commonly utilized for the directed or empirical treatments when a PA infection has been suspected as a result of its natural resistance towards numerous antibiotic types [67]. None-theless, the recent data from National Antimicrobial Resistance Surveillance, Thailand (NARST), has shown an increasing CRPA trend, from about 15% of infections in the period 2000–2005 to 30% in the period 2009–2013. The rate of the CRPA which is related healthcare-associated infection (HAI) increased in past year all over the world [68].

Pseudomonas aeruginosa isolates have intrinsic resistance to the majority of the antimicrobials through the chromosomal AmpC cephalosporinases as well as low permeability to the antimicrobials, and can be accumulating extra resistance determinants through acquiring elements of the mobile genetics. *Pseudomonas aeruginosa* is of a large genome (i.e. higher than 6 MB), a high proportion of the regulatory genes and a set of the virulence determinants. The capability of using several mechanisms, which includes a decrease in the external membrane permeability, produces antibiotic degradative enzymes, efflux pump expression, production of the alginate and resistance gene transfer, the bacteria enabled showing a high resistance level to most of the utilized antibiotics [69]. Several recent researches have reported alternative and complementary options of the treatment to the infections of the combat *Pseudomonas aeruginosa*. Quorum sensing inhibitors, probiotics, phages, vaccine antigens, antimicrobial peptides, and anti-microbial nano-particles have the possibility of acting against the drug resistant strains [64].

4. Conclusion

The current review conclude the implication of *P. aeruginosa* in arrays of diseases especially RTIs, UTIs and wound infections. The widespread of it may be due to their adaptation to different environmental conditions along with virulence traits especially biofilm formation and intrinsic and acquired antibiotic resistance strategies.

Conflict of interest

There is no 'conflict of interest' for this work.

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