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Review Article

Infections with *Pseudomonas aeruginosa* in Burn Patients: The Host Immune Response

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Abstract: *Pseudomonas aeruginosa* is an opportunistic pathogen, gram-negative bacteria, able to colonize such injuries, *gammaproteobacterium*, found in different environmental such as soil and water. The sepsis of burn wounds causing a morbidity and mortality are complex microenvironments where infections by bacterial pathogens such as *P. aeruginosa*. The *P. aeruginosa* pathogenicity is intercede by its capacity to produce a big range of virulence factors which include biofilm formation and it is have resistance to antibiotics, environmental stresses and disinfectants, and heavy metals. The losses of the skin barrier and tissue destruction are part of the most devastating form of trauma and require medical care to maintain homeostasis.

Keywords: *Pseudomonas aeruginosa*, burn, infection, immune, response.

INTRODUCTION

A Gram-negative rod classified to the *Pseudomonadaceae* family by the name of Pseudomonas, it is moving by polar flagella. **(**Garrity *et al.*, 2005). *Pseudomonas aeruginosa* became a significant cause in wound and burn infections as well as severe mortality in burn patients**.** These bacteria's virulence traits include their ability to form biofilms, their potential to harbor genes for antibiotic resistance, and their quick motility both in vivo and in vitro. (Al-Zubaidi *et al*., 2015) from most habitats, such as soil, plants, and mammal tissue, *pseudomonas aeruginosa* can be isolated from it (Stover *et al*., 2000). This bacterium utilizes its potent binding components, such as flagella, pili, and biofilms, to thrive in water, on various surfaces, and on medical equipment (Remold *et al*., 2011). Biofilms facilitate a diversity of cell-cell interactions by bringing microbes into close proximity and they allow bacteria to resist predation by protozoa, infection by bacteriophages, and a variety of physical and chemical stresses, including nutrient limitation, desiccation, and shear forces (Davey and O'toole, 2000) Microbes living in tightly clustered, slowly growing microcolonies and encased in a matrix made of a protective biopolymer make up biofilms. The pattern life of microorganisms develop the levels are higher of immune system and antibiotic resistance (Ciofu and Tolker-Nielsen T) (2019) In both clinical settings and experimental models, the effects of *P. aeruginosa* infection on wound chronicity have been thoroughly characterized (Høgsberg *et al.*, 2011). In spite of antibiotic therapy and persistent stimulation of the host response, biofilm is now frequently acknowledged as The essential source of chronic infections (Høiby *et al*., 2011).

Pathogenicity of *Pseudomonas aeruginosa*

One of the most prevalent and dangerous diseases brought on by pathogens is burn infections, primarily gram-positive and gram-negative bacteria, (Ahmed and Israa, 2018). The complication of bacterial infection within the burn wound, which may result in more serious disease states, including sepsis, is one of the biggest issues facing the burn clinic (Brandenburg *et al.*, 2019). One of the main pathogens causing localized and systemic infections in various patient populations is an opportunistic Gram-negative bacterium named (Greenhalgh, 2017). Localized infections at various body regions, such as pneumonia caused by a ventilator and urinary tract infection, or wound infections, can spread

systemically by *P. aeruginosa* (Bassetti *et al*., 2018). At this time, injury burn septic is the major factor in illness rate and Death rate following injury burn. *Pseudomonas aeruginosa, Staphylococcus aureus,* and *Acinetobacter baumannii* infections are well-known bacteria that prevent patient recovery and can even be fatal (Gonzalez *et al.,* 2016). When the target is the extracellular matrix, a number of virulences may produce pathogenicity that promotes adhesion and/or interferes with host cell signaling pathways, *P. aeruginosa* has the ability to infect an organism and its immune system with a number of diseases, making infections nearly tough to enucleate (Skariyachan *et al*., 2018). Exotoxin A, Alginate, Type III Secretion System, Lipopolysaccharide, Flagellum, Type IV Pili, Proteases, and Quorum Sensing, and others are among the virulence factors that contribute to pathogenicity. Secretion Systems Type VI, Biofilm Formation, and in the Air Oxidant Generation. These are significant virulence agents that affect the immune system in a variety of ways. Burn sick quickly pick up a variety of pathogens from their skin and surroundings, and if they are hospitalized for treatment, they are very likely to pick up MDROs and HAIs from hospital surfaces, patients, personnel, and equipment. Infections caused by biofilm are prevalent in burn sick, Stewart and Parker (2019).

Epidemiology of *Pseudomonas aeruginosa*

The nosocomial infections are causing by *P. Aeruginosa* which estimation for 11.8% to 13.8% of it (Kim *et al.*, 2000). Accountable for an high proportion of nosocomial infections are *P. aeruginosa* in critical care units (ICUs), with range of 13.2-22.6% observed (Lizioli, *et al.*, 2003) *P. aeruginosa* has been found to be a significant pathogen in burn victims in numerous investigations. According to microbiological monitoring, the first week of hospitalization is when *P. aeruginosa* colonization of burn wounds occurs most frequently (Erol, *et al*., 2004) *P. aeruginosa* is frequently specified as a common isolate infectious in burn units, and it calculation for a significant portion of the recorded infections wound, bacteremia, and VAP in these units, but patterns differ between centers (Yildirim, *et al*., 2005). Exposure to *P. aeruginosa* is virtually impossible to avoid it because it can be found wherever. An inanimate can be present on items like hospital wards, sinks, toilets, bath room, and patient care apparatus, particularly respiratory ventilators, because it is nonfastidious and has minimal nutritional requirements. Even the surfaces of fresh produce could be host to *P. aeruginosa*. The microbes have a special fondness for water, and then could be had isolated from hot tubs, cosmetics, contact lens solutions, soaps and disinfectants. Although a minor component of the typical flora of humans, it is often frequently seen at trace quantity in the gastrointestinal tract. It perhaps temporarily colony diversity of surfaces skin moist, such as aperineum, area under an arm. It has been demonstrated that *P. aeruginosa* may also invade the throat and nose (Kiskaand Gilligan, 2003).

Biofilm production of *Pseudomonas aeruginosa*

The extracellular matrix components produced by biofilms, which are concentrated collections of cells, keep the colonies jointly. The pattern of biofilm is growth enables remain cells for close to nourishment, encourages genetic material interchange, and shields cells from various chemical and environmental challenges, such as phagocyte engulfment (Davey *et al*., 2000). A biofilm is made up of itself-excrete core of protein and three exopolysaccharied that serve as its main structural constituents. They perform a variety of biological tasks, notably when it comes to the human immune system and protecting the bacterial cell from drugs (Al-Wrafy *et al.,* 2017) Sedimentary communities of microorganisms called biofilms are contained by a slimy extracellular polysaccharide matrix that the bacteria themselves create. Effective defenses against antimicrobial agents are provided by biofilms (Davey *et al*., 2000) *Pseudomonas aeruginosa* biofilm is a significant virulence factor that contributes to drug resistance and chronic burn wound infections. Existing antimicrobial drugs must be made more effective while also destroying biofilms in burn wounds and combating *P. aeruginosa* (Banar*et al*., 2016) cultivate-linked infections andnumerous of tissue are caused by biofilms. Dental caries, periodontitis, otitis media, chronic sinusitis, chronic wound alterations, musculoskeletal infections (osteomyelitis), biliary tract infections, bacterial prostitutes, native valve endocarditic, and infections brought on by medical devices are among the infections linked to biofilms (Tuon *et al*., 2022). Exopolysaccharied (EPS) serves as a matrix around bacteria in a biofilm to ensure that they are protected from the microbial truculence of the environment external or internal. Biofilms are societies of microorganisms adhering to a living or non-living surface. For result, when *P. aeruginosa* is exposed to situation of stress, the development of biofilms is frequently linked to stronger antimicrobial resistance than the planktonic form and helps evade the host immune response (Skariyachan *et al*., 2018). Additionally, biofilm bacteria display altered growth and gene transcription phenotypes (Pedrosa *et al*., 2018). The ability of *P. aeruginosa* to build biofilms on abiotic and biotic surfaces is a significant factor increasing the pathogenicity of the organism and its ability to cause deadly infections (Karatuna and Yagci, 2010). Compared to their plank tonic counterparts, bacteria groups in biofilms are typically too resistant to antibacterial drugs and techniques of host-intermediate is clearance, leading to frequent infections that are highly challenging to treat (Mah *et al.,* 2003). Extracellular polymeric matrices are made by bacterial cells that develop in biofilms and hold the biofilm community's cells together. Polysaccharides play a crucial role in the biofilm matrix's general structure and the resistance of the bacteria that have developed there to some antibacterial agents (Wozniak *et al.,* 2003). The purpose of this research is to determine which *P. aeruginosa* isolates can form biofilms and produce pyocyanin. Five developmental steps make up the intricate process of *P. aeruginosa* biofilm formation, which normally takes place in favorable environmental factors and involves several genes and regulatory processes (Harshey 2003) as in figure 1.

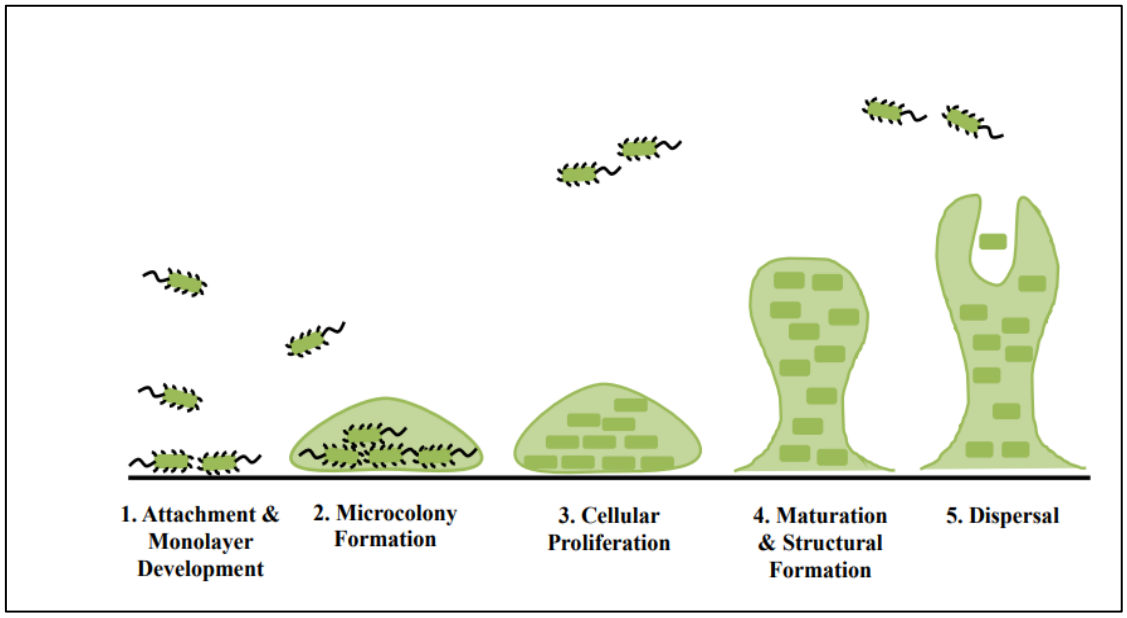

Figure 1: Life cycle of biofilm.

***Pseudomonas aeruginosa* virulence factors:**

Pseudomonas aeruginosa is a common bacterium that can be found in soil, water, and other environmental niches. It so become serious infections of plants, mammals, and other animals since it is an opportunistic pathogen (Silby *et al*., 2011). The ability of *P. aeruginosa* to create a wide variety of virulence factors and its inherent resilience to stressors environments and factors of xenobiotic including antibiotics, antiseptic, and heavy metals both contribute to the pathogenicity of the organism (Perron *et al*., 2004). The blue pigment pyocyanin, one of the main virulence agents generated, causes proinflammatory activity (Moura *et al*., 2014) and Pyoverdine, a siderophore include iron chelation and conquest, is a QS-independent controlled pigment (Schalk *et al*., 2008). Additionally, the protease and elastase, which is produced, primarily aids in the breakdown of the host tissues' elastin (Yang *et al*., 2015). Phenazines are the most significant of the extra-cellular pigments that the Genus Pseudomonas generates. The formation bydyes of soluble pyocyanin, phenazine molecule is a water-soluble blue-green, *Pseudomonas aeruginosa's* most distinctive property. Pyocyanin had used as a reversible pigment with a redox potential akin to menaquinone since the beginning (Ohfuji *et al*., 2004), The Type III Secretion System's agents of virulence offer a diversity of secretion systems, at least four of them are probably involved in virulence (Type I, II, III, and IV). One of the most intriguing virulence factors, the T3SS involves a flagellum-basal body-related mechanism for delivering proteins directly from *P. aeruginosa's* cytoplasm into the cytosol of host cells. This mechanism causes damage to the host tissues, which encourages immune avoidance and bacterial dissemination (Frank, 1997). The causes of virulence Proteins including lipase, phospholipase, alkaline phosphatase, and protease are secreted into the extracellular environment using Type II secretion mechanisms, which use a pilus-like apparatus.virulence component of "cell-to-cell" Bacterial its connectionby diffusible chemical molecules which known as quorum sensing. To cause expression of a big regulon, the Quorum must produce an adequate quantity of a secreted signal molecule known as an autoinducer **(**Pearson*et al*., 2001). acyl-homoserine lactones (AHL) and bacteria Gram-negative use the most prevalent type of autoinducers. The mechanism can easily pass through bacterial membranes. Oxohexanoyl-homoserine lactone and butanoyl-homoserine lactone are AHL pointproduct by *P. aeruginosa* (Hirakawa *et al*., 2013). *P. aeruginosa* produces pyocyanin (1-hydroxy-5-methyl-phenazine), a distinctive blue redox-effective secondary metabolite that is chloroform-soluble and a part of the tricyclic complex "phenazine" (Ran *et al*., 2003). The creation of blue pus is one of the most crucial signs of serious infections brought on by these bacteria.produced of Pyocyanin was determineto all the sixty-three isolates on King's B medium (King *et al*., 1954) and Mueller-Hinton agar media by streaking the overnight culture then incubation at 30°C for twenty-four hours.

***Pseudomonas aeruginosa* that effect on immune system**

Microbes living in tightly clustered, slowly expanding microcolonies and encased in a matrix made of a protective biopolymer make up biofilms. The microorganisms in this life mode develop the highest levels of resistance against the immune system and our current selection of medications (Hall *et al*., 2017 & Ciofu *et al*., 2019). Due to the prolonged nature of biofilm-associated infections, the inflammatory state brought on by biofilm uncommonly entails activation of both the innate and adaptative immune response. *P. aeruginosa* causes a number of persistent biofilm infections, including pneumonia connected to ventilators with tracheal tubes, chronic wound infections, urinary tract infections with or without catheters, and cystic fibrosis (CF) lung infections (Hoiby *et al*., 2015). Neutrophils,

macrophages, dendritic cells, natural killer (NK) cells, and the complement system make up the majority of the innate immune response that is activated in response to *P. aeruginosa* biofilm (Jensen *et al*., 2007). The LPS is the main element of *P. aeruginosa's* outer membrane. Bacterial LPS normally consists of a non-repeating core oligosaccharide, a distal polysaccharide or O-antigen), and a hydrophobic domain known as lipid A (or endotoxin) (PierGB; Ramphal R. 2005). Acquired (or adaptive) immune systems and the host's innate (TLR4, NLRP1, NLRP2, and NLRP3) are both significantly activated by LPS. This leads to dysregulated inflammatory responses that eventually increase morbidity and mortality (Mandell *et al*., 2009). *P. aeruginosa* is a Gram-negative bacterium that can cause a number of opportunistic illnesses, especially in immunocompromised patients. These illnesses include dermatitis, urinary infections, and a wide range of systemic infections, particularly in hospitals (Haüsslerand Becker, 2008). Due to its high level of genetic flexibility and ability to modify its phenotype, *P. auruginosa* is pathogenic. This bacterium produces more virulence factors and becomes more pathogenic. When *P. aeruginosa* is exposed to stressful situations, alterations is occurs in its growth mode result, which produces biofilms. Thus, by encouraging the communities of bacterial growth as a whole, biofilms give the technique of adaptive species, the ability to adapt and build resistance to pharmaceutical industry-developed antibiotics, as well as the creation of genes involved in antimicrobial defense and signaling molecules that regulate biofilm activity (Davies J; Davies D. 2010). Physical barriers against invasive pathogens are provided by skin and mucosa, which they a component of the non-specific innate immune system. Burns or wounds damage the barrier and impair the immune system, allowing opportunistic bacteria to infect the body (Kindt *et al*., 2007). Host immune responses during infection must be launched by Pattern Recognition Receptors upon recognition of Pathogen Associated Molecular Patterns (PAMPs). Flagellin and LPS are the two main PAMPS that are identified by Toll-Like Receptor (TLR) 5 and TLR4, respectively, in *P. aeruginosa* infections (Lavoie *et al*., 2011).

Antibiotic resistant of *Pseudomonas aeruginosa*

One common bacteria that causes nosocomial infections, especially in burn patients, is *pseudomonasaeruginosa* (Church *et al*., 2006). *P. aeruginosa* infections are notoriously difficult to treat due to the organism's inherent resistance to a wide range of medication classes and its ability to develop resistance to all available medicines (Pirnay *et al*., 2003). Multidrug-resistant *Pseudomonas aeruginosa* (MDRPA) isolates have been reported in numerous studies; these isolates are typically resistant to aminoglycosides, carbapenems, antipseudomonal penicillins, quinolones, and cephalosporins (Falagas *et al*., 2006). The therapy standard for bacterial infections that the immune system is cannot to contain and eliminate is antibiotics. Each family of antibiotics has a unique bactericidal mode of action (MoA), such as! Cephalosporins (Cefalexin or Cefradine) and beta-lactams (Penicillin and Amoxicillin) prevent the formation of bacterial cell walls.Gentamicin and tobramycin are aminoglycoside antibiotics that target bacterial ribosomes to decrease protein synthesis, whereas ciprofloxacin is a fluoroquinolone antibiotic that blocks DNA replication and repair (Rang, *et al*., 2000). Aminoglycosides, beta-lactams (imipenam but not penicillins), third and fourth generation cephalosporin, and fluoroquinolones are among the anti-pseudomonal medications. In addition, MDR P. aeruginosa strains are being treated with the poorly tolerated medication colistin. Prudent prescription practices and prompt but robust antibiotic administration have improved the course of treatment for some illnesses, including (Döring, 2010). Aminoglycosides, beta-lactams, quinolones, and macrolides are the four general categories into which antibiotics can be placed (Keyser *et al*., 2008). Understanding these categories of antibiotics and how contemporary medicine employs them in the treatment of disease is crucial. Antibiotics either kill germs or limit their growth, depending on how they are used. Stopping harmful microorganisms that are infecting a patient can depend on both of these processes. Antibiotics are essential for treating infections in individuals, but they are also applied to animals reared for human consumption. Antibiotics are given to cattle to promote growth and prevent sickness (McEachran *et al*., 2015). The number of production ofanimal that are accessible to purchase by consumers rises as a result of the usage of antibiotics. There is extensive use of antibiotics on a daily basis. These medications must be used in both clinical settings and in agricultural settings. Antibiotics are either produced using versions of live things or are created from them. Most early antibiotics were generated in this way; Natural produced by fungi or bacteria whose environment has been change in an industrial setting. Using of Those chemicals that in ways this are helpful to healthy human. The modification of other antibiotics yields biosynthetic antibiotics. To create newer medications, existing drugs (such as first-generation antibiotics) can be used as a model. It is crucial to develop novel chemicals that target particular bacteria while being safe for humans. These were various methods for antibiotics to target, incapacitate a pathogenicity of bacterial, but the precise processes by which they work against bacteria were not known when they were initially found to be effective against them. Targeting particular bacterial activities and structures is crucial for examples include ribosomes, prokaryotic cell walls, and DNA replication since they are less likely to have negative impacts on people (Walsh, 2003). Antibiotics can inhibit the synthesis of cell walls in several ways. The beta-lactams are the first group and they consist of vancomycin, carbapenems, penicillin, and cephalosporin. Penicillin can be categorized into one of five categories. These include: (Keyser *et al*., 2008) penicillins narrow-spectrum sensitive to an penicillinase act as enzymeproduct by some organisms whichsplitting penicillin (McEachran *et al*., 2015) restricted-spectrum, penicillinase-resistant penicillins (Walsh, 2003) broad spectrum aminopenicillins (Brudzynski and Sjaarda 2014) anti-pseudomonal broad-spectrum penicillins (Dunkle *et al*., 2014) andpenicillins with a wider spectrum. cephalosporins divided into first- generation, second, third, or fourth are another class of drugs included in the beta-lactam family. The mechanism of action of penicillin, cephalosporins, and

carbapenems is to prevent transpeptidases from generating the layers of peptidoglycan (Walsh, 2003). The derivatives of Vancomycin are operate which binding to transglycosylases, Achains that generating by transglycosylases enzyme, this chains joined together to form peptidoglycans (Walsh, 2003). When a bacterial cell wall is the target of an antibiotic, the antibiotic causing the rupture of cell then finally results in lysis of the cell. The creation of the normal cell wall can be stopped, which is a good strategy to stop the growth of bacteria (Brudzynski and Sjaarda 2014).

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