European Scholar Journal (ESJ)
Available Online at: https://www.scholarzest.com
Vol. 3 No.3, March 2022
ISSN: 2660-5562

PSEUDOMONAS AERUGINOSA: A REVIEW ARTICLE

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Article history:

Received: 17th January 2022
Accepted: 14th February 2022
Published: 27th March 2022

Abstract:

The gram-negative bacteria *P. aeruginosa* has occurred as a severe hospital infection. These bacteria is common in hospitals and is a commensal bacterium found on the skin surface, in the nose, in the upper respiratory system, and in the intestines of up to 40% of healthy people. This percentage climbs in direct proportion to the length of a patient's stay in the hospital. In the absence of topical therapy, 70% of patients' burn sites are cultured by the third week, indicating that *P. aeruginosa* has established itself as a dominant member of the flora. Cases of nosocomial pneumonia account for 16% of all Cases of nosocomial pneumonia. 12 % *P. aeruginosa* is responsible for 12 percent of hospital-acquired urinary tract infections, 8% of surgical wound infections, and 10% of bloodstream infections. It's also to responsible for septicemia, which accounts for 30% of all deaths and has high (60%) fatality rates in burn units.

Keywords: Gram-Negative Bacteria, *P. aeruginosa*

INTRODUCTION:

Pseudomonas aeruginosa is a bacterium recognized for its potential to cause disease in vulnerable persons, as well as its environmental flexibility. as well as the ability to be able to adapt to and thrive in a variety of ecological situations The bacterium has the ability to utilise a It can thrive on a wide range of organic compounds, which gives it an edge in ecological niches where resources are scarce.. (William *et al*., 2005;Winsor *et al*., 2009; Moore, 2011) .

Pseudomonas aeruginosa can create a variety of harmful proteins that Not only do they harm tissue, but they also interfere with the immune system's protective mechanisms. Powerful poisons infiltrate and eliminate host cells in or near the colonization position, as well as degradative enzymes which irreversibly change connective tissue in many organs. (Todar, 2002; Krzeslak, 2009). it is also known for its high resistance to many. Scientists are studying this bacterium for a variety of reasons, including its capacity to cause illness and are resistant to antibiotics, as well as its metabolic capabilities and survival flexibility in different environment. (Krzeslak, 2009).

GENERAL CHARACTERISTICS

Luke, identified rod-shaped particles in certain patients' blue-green pus diseases in 1862, is thought to have been the first to report Pseudomonas aeruginosa in human infections. Sedillot had earlier seen similar colouring on dressings for surgery, which is The pigment pyocyanin produced by *P. aeruginosa* is now established to be the cause. In 1882, Gessard identified this microbe from army wound sites and named it Bacillus pyocyaneus. (Lyczak, *et al*.,2000) Pyocyanin (blue-green), pyoverdine (yellow-green and fluorescent), and pyorubin (red-brown) melanin are among the pigments secreted by P. aeruginosa (Brown) (Govan, 2007). Pyoverdin is widely synthesized in low-iron conditions, and it may play a role in bacterial iron metabolism. Pyocyanin (come from "Pyocyaneus") which is "blue pus," which is a symptom of *P. aeruginosa* supportive infections. (Todar, 2002; Brooks *et al*., 2007)

TYPICAL ORGANISM

Pseudomonas aeruginosa is a Gram-negative bacillus that does not generate spores and does not form capsules. It is motile via one or two polar flagella. It is a strictly aerobic aerobe, but if nitrate is supplied as a terminal electron acceptor, it can grow anaerobically. (Govan, 2007), It can be found as a single bacterium, in pairs, or in short chains., and measures approximately (0.6x2m). (Brooks, *et al*., 2004). They thrive on low-carbon and low-nitrogen environments, such as simple media and damp surfaces. *P.aeruginosa* is also capable of degrading polycyclic aromatic hydrocarbons and producing lectins, rhamnolipids, quinolones, hydrogen cyanide, phenazines when found in soil. (William, *et al*., 2005).

CULTURAL CHARACTERISTICS

Pseudomonas aeruginosa is an obligate aerobe that can grow on a variety of culture media and can produce a grape-like or rotten-potato odor. (Labarca *et al*., 1998). Blood is hemolyzed by some strains. *P. aeruginosa* produces spherical, smooth colonies that are bright greenish in color. It frequently creates pyocyanin, a nonfluorescent bluish

pigment that diffuses into the agar.. (Brooks, *et al.*,2007; Govan, 2007). Three colony forms are possible with P. aeruginosa isolates. When isolated from natural sources such as soil or water usually result in a small, squalid colony. In general, while clinical isolated colony are one of two smooth colony types.,One form resembles a fried egg, being huge, smooth, flat edges, and raised appearance or produce anthor form, which is commonly found in respiratory and urinary system secretions, has a mucoid look due to the development of alginate slime. Colonization and virulence are thought to be aided by the smooth and mucoid colonies. (Todar, 2008).

GROWTH CHARACTERISTICS

P. aeruginosa growth optimally in 37°C, however it has also been recorded growing at 42°C and 4°C. (Iglewski, 1991); Its ability to grow at 42°C distinguishes it from other fluorescent Pseudomonas species. (Brooks,*et al.*,2007;Todar,2008). It has oxidase activity. Although it does not ferment carbs, it does oxidize glucose in many strains. Colony morphology, oxidase positivity, the presence of distinctive colors, and growth at 42 °C are commonly used to identify it.. (Brooks,*et al.*,2007).

PATHOGENESIS OF *PSEUDOMONAS AERUGINOSA.*

Pseudomonas aeruginosa is a common pathogen organism that can easily be isolated from the natural environment and humans (Lister, *et al.*, 2009), and it is now widely recognized as an important opportunistic pathogen that causes severe infection because it is pathogenic only when introduced into an environment lacking in normal defenses. (Lee,*et al.*,2005). This could result in the compromised host's death. (Sakata *et al.*, 1996).

A. Respiratory infections: *P. aeruginosa* causes respiratory infections almost exclusively in people who have an impaired lower respiratory tract or a weakened systemic defense system. Patients which have chronic obstructive pulmonary disease and congestive failure of the heart are at risk for primary pneumonia. (Hoiby and Rosendal, 1980). Mucoid strains of *P.aeruginosa* colonize the lower respiratory tract of cystic fibrosis patients, making treatment difficult, if not impossible. (Marty *et al.*, 1998; Govan, 2007).

B. Endocarditis: *P.aeruginosa* affects intravascular drug users' heart valves as well as prosthetic heart valves. (Mandelle *et al.*, 1995). By directly invading the endocardium from the bloodstream, the organism establishes itself. (Pollack, 1998).

C. Bacteremia: *P. aeruginosa* is the most common cause of bacteremia in immunocompromised people. (Todar, 2002; Japoni *et al.*, 2009). Hematologic malignancies, immunodeficiency related to AIDS, neutropenia, diabetes mellitus, and severe burns are all predisposing factors. Pseudomonas bacteremia is most commonly contracted in hospitals and nursing homes. *Pseudomonas* causes nearly a quarter of all Gram-negative bacteremias acquired in hospitals. (Todar, 2002).

D. External otitis cases, such as "swimmer's ear," *P.aeruginosa* is the most common bacterial pathogen. The bacterium is rarely detected in a healthy ear, but it regularly colonizes the external auditory canal as a result of injury, maceration, inflammation, or simply damp and humid conditions. (Strauss, *et al.*, 1982; Mims, *et al.*, 1993).

E. *P.aeruginosa* infections in the eye: *P.aeruginosa* infections in the eye can be fatal. This infection is one of the most common causes of bacterial keratitis. (Brooks, *et al.*, 2004, Japoni *et al.*, 2009). By synthesis of many enzymes including exotoxin A, elastase, and alkaline protease, the bacterium can quickly multiply and create a devastating infection that can result in the loss of the entire eye. (Govan, 2007; Todar, 2008).

F. Infections of wounds and burns: Almost any opportunistic pathogen are able to infect burns and wounds, but the gram-negative rod *P. aeruginosa*, which actually can color burns with its blue-green fluorescent pigments or damaged tissue and may lead to septicemia later, is one of the most common and difficult to treat. (Nester *et al.*, 1982; Alinaqvi *et al.*, 2011).

G. Infection of the urinary tract: The bacteria enters the urinary tract by catheters and instruments, as well as irrigation solutions. (Martinez *et al.*, 1999). Because antibiotics increase its selection in hospital patients, *P. aeruginosa* is more frequently identified in hospital-acquired urinary tract infection. (Glauser, 1986).

H. Bones and joints Infections. Usually these infection caused by Direct inoculation of the bacteria or by the hematogenous dissemination of the germs from the main infection sites. In IV (Intra-venus) drug users, blood-borne infections are most commonly encountered in association with urinary tract or pelvic infections. *P.aeruginosa* is particularly fond of the axial skeleton's fibrocartilagenous joints. (Todar, 2002)

I. Infections of the gastrointestinal tract. In maternity facilities and paediatric wards, gastrointestinal illness epidemics can arise in newborns and early children as a result of contaminated milk feeds. (Govan, 2007).

VIRULENCE FACTORS

1. Pathogenic *P. aeruginosa* Cell SurfaceVirulence Factors

a. Biofilm Formation

Biofilms mean complex microorganisms colonies that are attached surface- aggregates encased in a slime, a self-secreted extracellular polysaccharide matrix. (Sutherland, 2001; Stoodley *et al.*, 2002). They can be found in a variety of natural and manmade habitats, and they provide a variety of protected dynamic microenvironments for their constituent microbial cells. Biofilms mature into effective barriers to antimicrobial agents and the human immune system, resulting in long-term colonization and/or infection at the biofilm formation site. (Olson *et al.*, 2002).

b. Flagella

Flagella are complex proteic structures seen on the surface of *P. aeruginosa* that form a filamentous polar appendage. Flagella are gram-negative bacteria's principal motile appendages, and they allow *P. aeruginosa* to swim in a screw-like motion. Flagella are important in pathogenesis because they adhere to epithelial cells by attaching to a shared membrane component. (Feldman *et al.*, 1998). Flagella, on the other hand, are highly immunogenic, making their presence for *P. aeruginosa* a liability for following infection. Because of that, in persistent infections, *P. aeruginosa* can adapt by selecting a flagellar mutants to elude the host's response. (Mahenthiralingam *et al.*, 1994).

c. Pili

Pili or fimbriae are *P. aeruginosa*'s tiny surface appendages filaments. The pili of these bacteria are among few prokaryotic pili that play a role in bacterial movement. The retractile features of *P. aeruginosa* pili cause this motility, which permits Rather than swimming, *P. aeruginosa* spreads via moist surfaces. (Mattick, 2002). Pilli aids colonization because, like flagella, pili are essential for colonization adhesion by attaching to the epithelial cell membrane. (Hahn, 1997).

d. Lipopolysaccharide (LPS)

Lipopolysaccharide is one of the virulence factors produced by *Pseudomonas aeruginosa* (Cryz *et al.*, 1984; Tang *et al.*, 1996). Lipopolysaccharide is the term that refers to a type is made up of three components:1- lipidA, that attaches the membrane; 2-core oligosaccharide (core), which is short sugars chain built onto lipid A; 3- O-antigen, the polymer that consist of repeated oligosaccharide units attached to the lipidA and core. Antigenic identification of *P. aeruginosa* serotypes is based on varied O-specific polysaccharide chains. Furthermore, LPS contributes to *P.aeruginosa*'s has outer-membrane permeability that is low, that functions synergistically together with multidrug efflux pumps which is recently identified , raising severe clinical issues because it failed the antimicrobial medicines from reaching the bacteria. (Hancock, 1998).

e. Quorum Sensing (QS)

P. aeruginosa appears to use mechanism that contol bacterial cell mass and permits cell-to-cell communication to regulate the synthesis of many of the extracellular virulence factors. Bacteria can perceive their surroundings, analyze data, and counter correctly; nevertheless, It was only recently discovered that they can sense their own cell density, interact with one another, and function as a population rather than individual cells. (Fuqua *et al.*, 1994; Gray, 1997).
Many Gram-negative bacteria exhibit a phenomena known as quorum sensing (QS). (Kipnis et al., 2006) Small chemicals called acyl homoserine lactones, also called autoinducers, allow bacteria to communicate with each other across the cell membranes. After a specific bacterial mass is reached, these particles approach a concentration threshold that allows coordinated gene expression in an entire bacterial population as cofactors of transcriptional regulators. (Kipnis et al., 2006) Quorum sensing (QS) can occur inside a single bacterial species or between multiple species, and it has the ability to control a variety of processes. *P. aeruginosa* is one of the most researched quorum sensing bacteria. In the las system, lasI directs the synthesis of 3-oxo-C12HSL, which interacts with LasR and activates target promoters; in the rhl system, lasI directs the synthesis of 3-oxo-C12HSL, which interacts with LasR and activates target promoters. (Pearson, 1994). The rhlI gene creation causes C4HSL to be produced, which interacts with the RhlR transcriptional regulator and activates target gene promoters in the rhl system. (Winson and colleagues, 1995). LasR/3-oxo-C12HSL activates the expression of rhlR and rhlI, forming a regulatory cascade between these two systems.. (Latifi *et al.*, 1996).

2. SECRETED VIRULENCE FACTORS

1. Pigments:

a. Pyocyanin

Pyocyanin (from "pyocyaneus") denotes "blue pus," a sign of *P. aeruginosa* supportive infections (Todar, 2002; Brooks, *et al.*, 2004). Pyocyanin is a blue-green pigment metabolite of *P. aeruginosa* that has been linked to a number of pathogenic consequences, including enhancing the IL-depressing host response (Leidal *et al.*, 2001; Allen *et al.*, 2005) and inducing neutrophil death (Allen *et al.*, 2005).

b. Pyoverdin

Pyoverdin is widely synthesized in low-iron conditions, and it may play a role in bacterial iron metabolism. Because iron deprivation of an infecting pathogen is a critical aspect of the human innate defense mechanism, *P. aeruginosa* is starved for iron when infecting its host. *P. aeruginosa* produces two siderophores to deal with this problem: pyochelin and pyoverdin. These sideophores are then secreted to the cell's outside, where they attach securely to iron and take it back inside the cell. (1993, Cox) Pyoverdine has also linked to virulence (Meyer, *et.al.*, 1996). When it was discovered that pyoverdin modulates the production of exotoxin A and an endoprotease in *P. aeruginosa*, as well as their secretion.(Lamont, *et al.*, 2002).

2. Enzymes

a. Protease IV

Protease IV can cleave fibrinogen, which is a component of the blood clotting mechanism (Elliott and Cohen1986) (Walsh and Ahmed 2002). After vascular injury, fibrinogen is given to a fibrin cloth. Hemorrhage is a symptom of *P. aeruginosa* infection and is caused by fibrinogen dysfunction (Elliott and Cohen, 1986). Furthermore, protease IV may destroy a variety of biologically important host proteins, including plasminogen and immunoglobulin G (IgG), as well as complement components 3 and C1q, Plasminogen (Plg) plays a vital part in the delicate balance of blood clotting,

and *P. aeruginosa* can bind it to his extracellular surface. Other proteases can activate plasminogen by converting it to active plasmin which is a protease that can breaks down fibrin. Plasminogen hypothesized to have additional physiological activities that pathogenic microorganisms could exploit. Plg is a protein that binds to several human cells and aids and guides relocation all over the body. (Da Silva *et al.*,2004).

b. Elastase

Elastase, also known as lasB, is a proteinase released into the extracellular space by *P. aeruginosa* using a type II secretion system. Proteins have been demonstrated to be degraded by it. Elastase B has also been found to stop fibroblasts from growing. All of these traits are common in *P. aeruginosa*-caused chronic ulcer infections (Schmidtchen *et al.*, 2003). It has been found to have a role in *P. aeruginosa* pathogenesis by degrading elastin, collagen, and noncollagen host proteins, as well as affecting the host basement membrane's integrity. (Bejarano, 1989).

Elastase B is able to interact and degrade proteins in the immune system; it has been established that elastase B can destroy immunoglobulin A (Heck, *et al.*, 1990). immunoglobulin A is the most common immunoglobulin in serum and the most common antibody type in excretions (Jenny and Michael, 2006). Elastase B can also break down immunoglobulin G (IgG), which is the most common and significant antibody (Bainbridge and Fick, 1989). Elastase also suppresses monocyte chemotaxis (Kharazmi and Nielsen, 1991), which may impair early phagocytosis clearance of *P. aeruginosa* from wound sites and following performance of microbial antigens to the host immune system. (Rumbaugh *et al.*, 1999).

c. Phospholipase C

Phospholipase C secreted into the extracellular space by *P. aeruginosa* via a type II secretion system. Hemolytic phospholipase C is found play a part in the *P. aeruginosa* pathogenesis in inflammation (Konig et al., 1996; Konig et al., 1997; Kipnis et al., 2006), and portion of the pathogenic action of hemolytic phospholipase C could exist due to surfactant inactivation (Holm et al., 1991). Moreover, hemolytic phospholipase can reduce the oxidative eruption reaction of neutrophils in the host. (Terada *et al.*, 1999).

3. Toxins:

a. Exoenzyme S (ExoS)

Bacteria growing in burned tissue create exoenzyme S, which can be identified in the bloodstream before the bacteria are present. It's been suggested that exoenzyme S inhibits the role of phagocytic cells in the internal organs and bloodstream is a defense against *P. aeruginosa* invasion. (Balachandran and Engel, 2009) ExoS is a cytotoxin which is bi - functional with two dynamic domains: an ADP-ribosyltransferase domain on the C-terminus and a GTPase-activating protein (GAP) domain on the N-terminus. ExoS' pathogenic involvement is mostly due to its activity as an ADP-ribosyltransferase, which causes cytoskeletal disruption. (Shaver and Hauser, 2004; Maresso et al., 2004). ExoS can impact the host's immunological and inflammatory responses because the C-terminal domain binds to TLR2 (Tall receptors2) and the N-terminal region binds to TLR4 (Tall receptors4). (Epelman et al., 2004).

b. Exotoxin A (ETA)

P. aeruginosa, the most common cause of burn wound infections among gram-negative bacteria (Heggers et al.,1992), can create a variety harmful proteins that can cause significant tissue damage and interfere with the defense systems of the immune system those proteins are able to penetrate host cells and destroy them in the colonization position, or harm cell membranes and connective tissues in numerous organs permanently. (krzeslak, 2009).

One of the most important virulence factors produced by this bacteria is ETA. Liu et al. were the first to identify and purify ETA (1961). Since then, ETA has been shown to be hazardous in vitro to a wide range of mammalian cells (Pollack and Anderson, 1978). It appears to play a role in both local and systemic *P. aeruginosa* disease processes. Exotoxin A possesses necrotizing activity thus thought to aid in the colonization of the bacteria. (Pittet, et al., 1998). Toxinogenic strains are more virulent than ones that are not toxinogenic. The greater survival chance in patients septicemia caused by *P. aeruginosa* is connected with the serum titer of anti-exotoxin A antibodies in the serum provides indirect evidence of the role of ETA in illness (Todar, 2008). In other instances, ETA mutants also have a lower pathogenicity. (Pittet, et al., 1998).

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