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Analysis of Epidemiological Indicators of Pseudomonas Aeruginosa and Its Significance in Medical Practice

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Abstract: Patients with cystic fibrosis, burn injuries, immunodeficiency, cancer, chronic obstructive pulmonary disease (COPD), and serious infections needing ventilation, such COVID-19, can contract Pseudomonas aeruginosa (P. aeruginosa), a Gram-negative opportunistic bacteria. Additionally, P. aeruginosa is a model bacterium that is frequently utilized in various scientific fields. Rapid advancements have been made in the study of host-pathogen interaction, specifically host immune networks involving autophagy, inflammasome, non-coding RNAs, cGAS, etc., in addition to ongoing, intense efforts to comprehend bacterial pathogenesis of P. aeruginosa, including virulence factors (LPS, quorum sensing, two-component systems, six type secretion systems, outer membrane vesicles (OMVs), CRISPR-Cas and their regulation). Furthermore, we now have a better understanding of P. aeruginosa pathogenesis and host defense because to a number of technological advancements, including bioinformatics, metabolomics, scRNA-seq, nanoparticles, drug screening, and phage therapy. However, there is still much to learn about how P. aeruginosa and host immune responses interact, including drug resistance mechanisms caused by known or unknown bacterial virulence factors and mammalian cell signaling pathways. In order to screen and develop mechanism-tested novel drugs to treat intractable infections, particularly those caused by multi-drug resistant strains, new theoretical and practical platforms are required due to the widespread use of antibiotics and the slow development of effective antimicrobials. The analysis of this pathogen's characteristics has advanced into molecular and mechanistic details as well as dynamic and holistic perspectives thanks to advances in research instruments and technology. The current state of P. aeruginosa biophysical traits, behaviors, virulence factors, invasive regulators, and host defense patterns against its infection are all thoroughly reviewed and discussed here. These developments indicate new avenues for future research and contribute to the development of novel and/or alternative therapeutics to fight this clinically significant pathogen.

Keywords: Cystic fibrosis (CF), antibiotic resistance, virulence factors, Pseudomonas aeruginosa, infection, acute and chronic infections, and animal modeling

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Introduction. Pseudomonas aeruginosa is a multi-drug resistant (MDR) opportunistic pathogen that can cause acute or chronic infections in immunocompromised people with cancer, cystic fibrosis, chronic obstructive pulmonary disease (COPD), traumas, burns, sepsis, and ventilator-associated pneumonia (VAP), including COVID-19. In biofilm states, P. aeruginosa can endure in extremely hard conditions, such as a hypoxic atmosphere. Additionally, because P. aeruginosa mutates quickly and adapts to become resistant to antibiotics, treating an infection is very challenging. Additionally, because P. aeruginosa thrives on damp surfaces, it is one of the top-listed organisms that cause hospital-acquired infections, which are frequently found in medical devices (ventilation). Significantly, Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, *P. aeruginosa* and *Enterobacter* are all MDR ESKAPE pathogens. The WHO has designated P. aeruginosa with arbapenem resistance as a "critical" group of bacteria that require new medicines in clinics immediately.According to epidemiological research, antibiotic-resistant bacterial illnesses kill around 700,000 people annually [1-5]. The overall resistance of P. aeruginosa isolated from European populations was 12.9%.P. aeruginosa-caused hospital-acquired infections are becoming a major healthcare issue as they continue to develop resistance to traditionally effective medications. According to the 2016 EPINE survey, hospital-acquired infections in Spain are most frequently caused by Escherichia coli and P. aeruginosa, with P. aeruginosa accounting for 10.5% of clinically isolated bacterial infections. P. aeruginosa is the fourth most prevalent pathogen in European hospitals, accounting for about 9% of nosocomial infections, according to the 2011–2012 HCAIs report. Similarly, P. aeruginosa is responsible for 7.1% of HCAIs in the US. Furthermore, according to the 2016 European Center for Disease Prevention and Control (ECDC) epidemiological study, P. aeruginosa is responsible for a number of infections acquired in intensive care units (ICUs), such as bloodstream infections, urinary tract infections, and pneumonia flare-ups. Additionally, data from the China Antimicrobial Surveillance Network (CHINET) (http://www.chinets.com/) revealed 301,917 clinically isolated pathogenic strains, with P. aeruginosa accounting for 7.96% of nosocomial infections after *Escherichia coli*, *Klebsiella pneumoniae* and *Staphylococcus aureus* [6-12]. All things considered, P. aeruginosa poses a serious worldwide risk to human health.In order to enhance human health, the aforementioned statistics require the discovery of therapeutic targets as well as the creation of novel therapies and potent P. aeruginosa vaccines. However, the increasing number of MDR strain cases has made these initiatives extremely difficult. The regulatory and functional processes of virulence factors, gene expression regulators, secretion systems, quorum sensing, and antibiotic resistance, as well as host-pathogen interaction and new technological advancements, are all covered in this article. The organism's high intrinsic and acquired resistance to several modern medicines makes P. aeruginosa infections more difficult to treat. The World Health Organization (WHO) and the Centers for Disease Control (CDC) have designated P. aeruginosa as one of the priority pathogens, or ESKAPE (Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa, and Enterobacter species), for which new antimicrobial development is critically needed. The significant acute and chronic infections brought on by this pathogen are discussed in this review. We give a summary of existing antibiotic therapies and how P. aeruginosa’s development of antibiotic resistance has led to their failure. Lastly, we go over a number of animal models that were created to evaluate both acute and chronic P. aeruginosa infections, and we highlight some fascinating research on the creation of cutting-edge antibiotic-free methods to fight P. aeruginosa infections [13-19].

The main purpose of this brief review is to analyze the epidemiological indicators of Pseudomonas aeruginosa and its importance in medical practice based on reputable scientific research.

By secreting a number of virulence factors that aid in effective infection and disease-causing, *P. aeruginosa* is able to adapt to the unfavorable environment in hosts. First, the endotoxicity of the lipid A in lipopolysaccharide (LPS) allows tissue injury, attachment, and identification by host receptors. LPS is a crucial surface structural element that protects the exterior leaflet and posion host cells. Biofilm development and antibiotic tolerance may be associated with LPS. Second, adhesion, antibiotic resistance, and nutrition exchange are all influenced by out membrane proteins (OMPs). Additionally, the flagellum, pili, and other adhesins are linked to drug resistance brought on by biofilm formation. Fourth, there are six different kinds of secretion systems, such as flagella (T6SS-associated), pili (T4SS), and multi-toxin components type 3 secretion system (T3SS). These systems are involved in host colonization, adhesion, swimming, and swarming in response to chemotactic signaling. Lastly, exopolysaccharides like alginate, Psl, and Pel may hinder bacterial clearance while aiding in the production of biofilms [6-11]. When it comes to toxins, T3SS is a complicated system that can seriously hinder host defense by injecting cytotoxins like ExoU, ExoT, ExoS, and ExoY. These cytotoxins have an impact on the intracellular environment, particularly by preventing phagocytosis and bacterial clearance. By blocking ADP ribosylation activity, exotoxin A (ETA) can prevent host protein synthesis. Additionally, pyocyanin is toxic to hosts, increasing the severity of illness, harming host tissue, and impairing organ function. Additionally, a broad class of lytic enzymes that influence other virulence factors includes phospholipase C, esterase A, alkaline protease (AprA), LipC lipases, and LasA and LasB elastases. Furthermore, trachea or lung epithelial cells may be directly harmed by rhamnolipids-mediated lung surfactant degradation and tight junction destruction.Additionally, as iron uptake systems, siderophores (pyoverdine and pyochelin) aid in bacterial survival in iron-deficient environments to increase virulence.In order to prevent clearance, antioxidant enzymes like superoxide dismutases, alkyl hydroperoxide reductases, and catalases (KatA, KatB, and KatE) counteract the activity of reactive oxygen species (ROS) in phagocyte settings [3-9].

Models of Systemic Infection and Blood Stream. Various methods have been employed to infect animals with P. aeruginosa in their blood and systems. For instance, systemic infection with P. aeruginosa has been technically induced by intravenous (i.v.), intraperitoneal (i.p.), or tail vein injections. Additionally, P. aeruginosa has been administered retroorbitally to induce sepsis and systemic infection. It has been demonstrated that a systemic infection with P. aeruginosa increases pro-inflammatory cytokines in the blood and tissues, resulting in additional morbidities such septic arthritis and gallbladder injury [5,6,7].

Models of Immunocompromised Infection. Immunocompromised individuals are extremely susceptible to P. aeruginosa infection, as was previously mentioned. It should come as no surprise that animal models have been created to evaluate the effects of P. aeruginosa infection in immunocompromised hosts. For instance, Takase et al. showed that P. aeruginosa infection in the calf muscle of immunocompromised mice (produced by cyclophosphamide) resulted in significant mortality in these mice, which was mediated by P. aeruginosa's production of pyoverdine and pyochelin siderophores. In a another investigation, P. aeruginosa was demonstrated to cause leukopenic immunosuppressed mice to die within 46 to 59 hours. Similarly, wounds in neutropenic immunocompromised C57BL/6 mice are susceptible to P. aeruginosa-enhanced infection, as Mahmoud et al. showed. P. aeruginosa infection was demonstrated in a different investigation [11-19].

Despite significant advancements in basic pathogenesis and host defense research as well as preventative and therapeutic development with P. aeruginosa over the past few decades, our understanding of this bacterium remains limited, which hinders the search for novel effective therapeutics in clinical settings. Many of the questions need to be clarified. (1) In the setting of antibiotic misuse or normal evolution, how do drug-resistant invasive bacteria arise? (2) How many additional virulence factors, particularly those with exceptional virulence, are important for bacterial pathogenesis and evolution but have not yet been identified and described? How do the components of the bacteria cause and avoid the human immune system's activation, phagocytosis, and clearance? (4) What novel mechanisms underlie the rise in

antimicrobial treatment resistance? (5) How can novel host factors be more effectively identified to enhance protection against this bacterium? (6) Is it possible for the scientific community to create a comprehensive, methodical set of guidelines that will help uncover new antimicrobials, immune modulators, and other therapies that alter disease? [5-11].

Discussion. *Pseudomonas aeruginosa* is a significant Gram-negative opportunistic bacteria that can cause up to 40% of severe acute and chronic infections with high morbidity and mortality rates. *P. aeruginosa's* high intrinsic and acquired resistance to several of the current antibiotics makes it a very difficult infection. The significant acute and chronic infections brought on by this pathogen are discussed in this review. We then go over the several animal models that have been created to analyze P. aeruginosa pathophysiology and evaluate treatments for this disease. We then go over existing therapies (vaccines and antibiotics) and give a summary of their benefits and drawbacks. Lastly, we discuss fascinating research on cutting-edge antibiotic-free methods for managing P. aeruginosa infections. Their work is a great resource for scientists, doctors, and students who want to learn more about *P. aeruginosa* because it is a rare thorough analysis that goes deeply into both human defense and bacterial pathogenesis. This comprehensive and perceptive summary of current studies ought to enhance our comprehension of the balance between *P. aeruginosa* invasion and host responses [2,4,5,7]. There are still a lot of unsolved concerns regarding *P. aeruginosa*, from basic to clinical and practical aspects, despite the tremendous progress made over the years. To better understand *P. aeruginosa* and improve our design to combat the illness caused by newly emerging drug-resistant strains, more research is still needed. In order to thrive in the harsh external and internal environment, *P. aeruginosa*, an opportunistic infection that causes major morbidity, devastating illnesses, shortened life spans, and high mortality in humans, has an intricate regulatory system that is interconnected and mutually controlled. In this comprehensive review and other papers, researchers have investigated the virulence factors of P. aeruginosa, including as LPS, adhesion factors, elastase, secretion systems, and OMVs. The most recent advancements in gene editing, nucleic acid-based antibiotics, phage therapy approaches, immunization techniques, nanoparticle production, and novel antibiotic formulations and compounds were also covered by the authors. We have also discussed a variety of host immune responses, including cell types, innate and adaptive immunity, and recent advancements in immunological research [8-14].

Conclusions. As an opportunistic infection that causes significant morbidity, crippling illnesses, shortened life spans, and high mortality in humans, *P. aeruginosa* has a sophisticated regulatory system that is interconnected and mutually controlled to survive with the harsh external and internal environment. Scientists have examined the virulence factors of *P. aeruginosa*, including LPS, adhesion factors, elastase, secretion systems, and OMVs, in this thorough review and other publications. Authors also discussed the latest developments in gene editing, nucleic acid-based antibiotics, phage therapy strategies, vaccination methods, nanoparticle manufacturing, and new antibiotic formulations and compounds. Additionally, we have covered a wide range of host immune responses, such as cell types, innate and adaptive immunity, and new developments in immunological research.

Their study is a rare comprehensive review that delves deeply into both host defense and bacterial pathogenesis, making it an invaluable resource for scientists, physicians, and students who wish to learn more about *P. aeruginosa*. This thorough and insightful overview of recent research should improve our understanding of the equilibrium between *P. aeruginosa* invasion and host reactions. Even with the enormous advancements over the years, there are still many unanswered questions about *P. aeruginosa*, ranging from basic to clinical and applied aspects. More research is still required to better understand *P. aeruginosa*, which will enhance our design to more successfully fight the infection caused by emerging drug-resistant strains.

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