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THE NEGATIVE ROLE OF *PSEUDOMONAS AERUGINOSA* IN THE PRACTICE OF SURGICAL DISEASES AND THE URGENCY OF COMBATING IT

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Abstract. With a very big genome and remarkable genetic aptitude, *Pseudomonas aeruginosa* is an aerobic, rod-shaped, Gram-negative bacterium that can survive in a wide range of settings and withstand a wide range of physical circumstances. Because of its biological adaptability, *P. aeruginosa* is a major cause of infections linked to healthcare across the globe and can cause a wide variety of illnesses in people with severe underlying medical disorders. The majority of P. aeruginosa's clinical presentations are community-acquired and healthcare-associated infections. Numerous virulence factors that *P. aeruginosa* possesses work against the host's defenses. In order to combat the majority of antibiotic classes, it can cause direct harm to host tissue while leveraging high levels of acquired and inherent antimicrobial resistance mechanisms. A major treatment problem is *P. aeruginosa's* ability to co-regulate numerous resistance mechanisms by constantly shifting targets. Therefore, new methods for creating anti-Pseudomonas drugs are desperately needed. Here, we go over the main *P. aeruginosa* infections and talk about new treatment approaches that could be developed for clinical usage to address antibiotic resistance and *P. aeruginosa* infections. Vectored immunoprophylaxis (VIP), an alternative to conventional vaccinations, uses a safe and efficient adeno-associated virus (AAV) gene therapy vector to generate therapeutic monoclonal antibodies (mAbs) at sustained levels *in vivo* from a single intramuscular injection. We will highlight AAV-VIP as a promising innovative therapeutic platform, address current and emerging treatment methods for *P. aeruginosa* infections, and give an overview of *P. aeruginosa* biology and important pathogenic pathways in this review.

Keywords. Infections, Pseudomonas, Resistance, Antibiotics, New Methods, Bacteriophages, Immunotherapy, Vaccines.

Introduction. Among the ESKAPE pathogens (which also include *Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa,* and *Enterobacter species*) that demonstrate both virulence and multidrug resistance is *Pseudomonas aeruginosa* (*P. aeruginosa*), which is acknowledged as a pathogen of global significance. The World Health Organization has identified ESKAPE infections as a high priority for

which better antibiotics are desperately needed, taking into account the global burden of disease, patient morbidity, and multidrug resistance. One nosocomial bacterial infection that is very common in people with cystic fibrosis (CF) is *P. aeruginosa*. By the time they reach adulthood, over 40% of CF patients have persistent *P. aeruginosa* infections, which is linked to declining lung function and a higher risk of death [1-5]. *Pseudomonas aeruginosa* causes substantial morbidity and mortality and is still challenging to treat due of its widespread and developing antibiotic-resistance mechanisms, even after the development of multiple anti-*Pseudomonas medicines. P. aeruginosa* ranks third among urinary tract infections linked to catheter use and is the second most frequent cause of ventilator-associated pneumonia in the US. It is responsible for 75% of all deaths of patients with severe burns and is the fourth most common cause of hospital-associated infections (HAIs), accounting for 20% of all HAIs in the US and Europe. Additionally, it was discovered that among patients with lower respiratory tract infections, *P. aeruginosa* was the fourth most frequent cause of death [6-11]. When *P. aeruginosa* is initially discovered, antibiotic therapy is the primary line of defense; however, effective eradication is not always maintained. Alternative treatment approaches, such as antibody-based strategies, are required to prevent *P. aeruginosa* infection and persistence because the pathogen has developed intrinsic resistance to several classes of antibiotics and there are currently no approved vaccines for its prevention and treatment. When investigating the molecular epidemiology of *P. aeruginosa* isolates from hospital-acquired infections, CF patients, or the environment, high clonal diversity is frequently seen. A closer examination shows that this is only true for isolates that are antibiotic-sensitive; isolates that have MDR/XDR traits are excluded. Most isolates are linked to different genotypes. Indeed, for decades, there have been multiple reports of epidemic outbreaks and alarms involving MDR/XDR strains in hospital settings. The information from these research and reports has strengthened the case that MDR/XDR global clones, sometimes referred to as "high-risk" clones, are proliferating in many hospitals throughout the world [12-19]. Multidrug-resistant *P. aeruginosa* or DTR-*P. aeruginosa*, usually results from a combination of multiple complex resistance mechanisms, including decreased expression of outer membrane porins (OprD), hyperexpression of AmpC enzymes, increased efflux pump activity, and mutations in penicillin-binding protein targets. *P. aeruginosa* has been identified as a common co-infecting pathogen (23.8%) in COVID-19 patients, which has been found to increase the severity of the baseline illness. The authors also reported that *P. aeruginosa* is frequently found in the sputum of COVID-19 patients. According to a special report on antibiotic resistance in the United States, the rate of hospital-onset MDR *P. aeruginosa* cases increased by 32% in 2020 as a result of COVID-19 [1, 4, 7, 9, 10]. The pathogenesis, history,

and current treatment approaches of *P. aeruginosa* will be covered in this review. Additionally, the relationship between nosocomial infections and chronic infections in patients with cystic fibrosis (CF) will be highlighted, along with the use of antibody therapy for *P. aeruginosa* infections and the potential use of adeno-associated virus vector-mediated expression of monoclonal antibodies (mAbs) as an alternative prophylactic platform for long-term passive immunity against *P. aeruginosa* infections [11-15].

The main purpose of this analytical manuscript is to summarize the results of many years of scientific research on the negative role of *Pseudomonas aeruginosa* in the practice of surgical diseases, complications or concomitant diseases that it causes, and the relevance of combating it.

History of Hospital Acquired P. aeruginosa. Infection *P. aeruginosa* was first identified by Sédillot in 1850, but it wasn't until Freeman's 1916 article that they described the entry and dissemination pathways in hosts that resulted in either acute or chronic infection. *P. aeruginosa* is a common microbe that can survive in a variety of environments, including living plants, animals, and humans, because of its strong ability to survive with little nourishment and withstand extreme conditions. Because of its strong survivability, this virus continues to exist in both hospital and community settings. In addition to being isolated from swimming pools, hot tubs, home humidifiers, soil, and vegetation, *P. aeruginosa* has also been discovered in antiseptics, sinks, cleaning supplies, medications, hydrotherapy pools, and respiratory treatment equipment. The majority of severe *P. aeruginosa* infections are hospital-acquired, despite the fact that the bacteria is widely distributed in both nature and society. An illness that a patient contracts while undergoing medical treatment and is unrelated to their initial diagnosis is known as a hospital acquired infection (HAI). The cost burden associated with healthcare-associated infections (HAIs) has significantly increased in recent years [1-8]. The total yearly direct cost of healthcare-associated infections (HAIs) in the United States is estimated to be between $28 billion and 45 billion USD. Although bacterial infections are the most frequent cause of HAIs worldwide, viral, fungal, or parasitic diseases can also be considered the causal agents of HAIs. Nosocomial infections caused by Gram-negative bacteria, inclusive of *P. aeruginosa*, are of particular concern due to the low permeability of the bacterial cell wall, and capacity to both acquire and upregulate intrinsic resistance mechanisms against antibiotic treatment. Given its presence in hospital water, medical equipment, and the ability to persist on dry inanimate objects for six hours to six months, *P. aeruginosa* is an opportunistic pathogen that is commonly linked to persistence in healthcare settings [9-14].

***P. aeruginosa's* molecular biology and structural traits.** Gram-negative, facultative aerobic, bacillus-shaped, and non-spore-forming, *P. aeruginosa* is thought to be saprophytic. The circular genome (~5–7 Mbp, strain-dependent) of *P. aeruginosa* contains more than 5000 core genes that are shared by all isolates. Up to 90% of the bacterial genome is made up of these core genes, which are constant across all species and are mostly housekeeping genes. The relatively variable accessory genomic elements up to 200 kbp show that *P. aeruginosa* can acquire

genetic elements through horizontal gene transfer (either transformation, conjugation, or transduction) [1-7]. For instance, P. aeruginosa pathogenicity island 1 (PAPI-1) and PAPI-2 are two genomic islands that contain pathogenic processes unique to P. aeruginosa. Both islands encode a large number of virulence genes and are well-characterized in the clinical strain PA14, which is extremely virulent. Additionally, Pseudomonas's capacity to endure in a variety of conditions—particularly in clinical settings that are subjected to constant sanitation—is greatly influenced by accessory genomic components. While acquired antibiotic resistance is obtained through supplementary genomic elements, intrinsic antibiotic resistance mechanisms are encoded within the core DNA. Multi-strain outbreaks in healthcare settings are a result of the transmission of acquired antibiotic resistance between strains [12-19]. A key virulence factor in the pathophysiology of *P. aeruginosa*, lipopolysaccharide (LPS) is a structural element of the cell membrane present in Gram-negative bacteria. A lipid A domain, a core oligosaccharide, and an O-antigen make up LPS, and each of these components is essential to bacterial physiology and defense against the host defense system. In addition to being essential for colonization and pathogenicity, the primary task of LPS is to give the outer membrane (OM) structural integrity. Similar to other Gram-negative bacteria, *P. aeruginosa* has a cell wall made up of an outer membrane, peptidoglycan layer, and inner membrane [7-11].

Pathogenesis mechanisms. *P. aeruginosa* can infect plants, insects, and mammals, among other animals, due to its opportunistic nature. Because of its ability to colonize and stay on artificial surfaces, *P. aeruginosa* is especially dangerous for elderly and immunocompromised patients in hospital settings. Through contact with fomites, ingestion of contaminated food, water, or aerosols, or entry through wound infections, this opportunistic pathogen can be easily isolated from the skin, throat, and stool of healthy people. Once P. aeruginosa enters the host, it deploys a diverse arsenal of mechanisms that can be exploited for successful infection and evasion of the host immune system. Many gene activities have been demonstrated to contribute to P. aeruginosa pathogenicity, including those involved in biofilm development, quorum sensing, protein secretion, LPS, outer membrane vesicle (OMV) production, and bacterial motility [1, 8, 11, 12].

Current Approaches to P. aeruginosa Treatment. Strategies for Treating Antibiotics Now Available. So far, antibiotic therapy is the only approved treatment for *P. aeruginosa* infections. Both known risk factors and the infection's progression are important considerations for creating a treatment strategy, and each should be assessed individually. Because of the rise in antimicrobial resistance, empirical antibiotic treatment is usually initiated if the infection is severe. This treatment should include two different classes of antibiotics to increase the likelihood of effective treatment. Treatment usually depends on in vitro susceptibility testing, and whenever feasible, it should be customized accordingly**.** In addition to the variety of antibiotics used to treat *P. aeruginosa* infections, the combination of B-lactam antibiotics like penicillin and ß-lactamase inhibitor has been shown to have synergistic effects, increasing the effectiveness of ß-lactam antibiotics. The first line of treatment for *P. aeruginosa* infections is aminoglycoside and beta-lactam

penicillin, though many broad spectrum antibiotics have also been shown to be effective against *P. aeruginosa* infections [10-15].

Pseudomonas biofilms are protected from harsh environments by a complex matrix of extracellular polymeric substances that includes glycopeptides, lipids, and lipopolysaccharides. The number of infections caused by antibiotic-resistant *P. aeruginosa* is steadily rising globally. Because of *P. aeruginosa's* high intrinsic resistance and capacity to develop resistance to all classes of antibiotics, antibiotic resistance will remain a challenge. The scientific community is making progress in the areas of bioinformatics, microbial genomics, target identification and screening techniques to find new potential therapeutic targets, and molecular mechanisms for persistence and antibiotic resistance in *P. aeruginosa*, but the number of new antibiotics being developed has drastically decreased [7-12]. Since bacteria in biofilms are 1,000 times less susceptible to antimicrobial therapy than those that are not, new management strategies are required for *P. aeruginosa* infections that result in the formation of biofilms. The exopolysaccharides, Psl, Pel, and alginate are important components of *P. aeruginosa* biofilms and are important for adhesion, biofilm architecture, antibiotic resistance, and host defense mechanisms. In the early stages of biofilm formation, polysaccharide PSL facilitates bacterial adhesion to a new surface, cell movement, and communication with other biofilm cells. During infection, the polysaccharide PSL shields cells from oxidative damage and phagocytosis. Alginate prevents biofilm bacteria against opsonophagocytosis, free radicles generated by immune cells and antibiotics and highlights emerging techniques to suppress *P. aeruginosa* biofilm [13-18].

Discussion. Ten to fifteen percent of nosocomial infections globally are caused by the bacterial pathogen *Pseudomonas aeruginosa*. This opportunistic bacterial pathogen is the primary cause of morbidity and mortality in patients with cystic fibrosis and is known to produce major difficulties in immunocompromised patients. Antibiotic therapy is now the only defense against *P. aeruginosa* infections. Multidrug-resistant *P. aeruginosa* strains are more common now, which is a serious issue in healthcare settings because of the pathogen's acquired and adaptive resistance mechanisms. Since there are currently no licensed vaccines that are approved to prevent *P. aeruginosa* infections, other treatment alternatives are desperately needed [1-4]. History of Hospital Acquired *P. aeruginosa*. Infection *P. aeruginosa* was first identified by Sédillot in 1850, but it wasn't until Freeman's 1916 article that the paths of entry and spread in hosts that resulted in either acute or chronic infection by *P. aeruginosa* were described. *P. aeruginosa* is a common microbe that can survive in a variety of environments, including living plants, animals, and humans, because of its strong capacity to forgo minimal nutrients and withstand harsh conditions. This pathogen continues to exist in both community and hospital settings as a result of its strong survivability. In communities, *P. aeruginosa* has been isolated from soil, plants, swimming pools, hot tubs, home humidifiers, and antiseptics. It has also been discovered in sinks, cleaning supplies, medication,

respiratory therapy equipment, and hydrotherapy pools. Despite *P. aeruginosa's* widespread distribution in both nature and society, the majority of severe infections are acquired in hospitals. When a patient contracts an infection while undergoing medical treatment that is unrelated to their initial diagnosis, it is referred to as a hospital acquired infection (HAI). The cost of HAIs in healthcare environments has significantly increased in recent years [5-11]. A safe and efficient adeno-associated virus (AAV) gene therapy vector is used in vectored immunoprophylaxis (VIP), an alternative to conventional vaccines, to generate therapeutic monoclonal antibodies (mAbs) at sustained levels in vivo from a single intramuscular injection. The biology and major pathophysiological mechanisms of *P. aeruginosa* will be briefly reviewed, along with new and existing approaches to treating *P. aeruginosa* infections and the potential of AAV-VIP as a novel therapeutic platform [7-10]. Here, we explore the use of AAV VIP for prevention and treatment of P. aeruginosa, but this platform could be applied to other bacterial infections where effective treatments remain elusive. With the recent FDA approvals of Luxturna and Zolgensma, AAV gene therapies are rapidly becoming tools for mainstream medicine, which holds great promise for the field of VIP. Previously, we showed that AAV-mediated expression of C. difficile toxin-specific antibodies protects mice from toxin challenge, demonstrating the potential of AAV VIP as an alternative or adjunctive treatment for recurring bacterial infections [14-20].

Conclusions. In addition to increasing antimicrobial resistance, *P. aeruginosa's* stealth virulence factors have made it a pathogen of public health concern for which there is no effective vaccine. *P. aeruginosa* is a clinically relevant bacterial pathogen linked to nosocomial infections, high infection rates in immunocompromised individuals, and chronic infections in CF patients.

Here, we explore the use of AAV VIP for prevention and treatment of P. aeruginosa, but this platform could be applied to other bacterial infections where effective treatments remain elusive. With the recent FDA approvals of Luxturna and Zolgensma, AAV gene therapies are rapidly becoming tools for mainstream medicine, which holds great promise for the field of VIP. Previous research showed that AAV-mediated expression of C. difficile toxin-specific antibodies protects mice from toxin challenge, demonstrating the potential of AAV VIP as an alternative or adjunctive treatment for recurring bacterial infections.

Novel anti-Pseudomonas therapies are desperately needed to stop the spread of antibiotic resistance. Numerous novel therapeutic agents are currently being developed, and they are primarily focused on a narrow spectrum, pathogen-specific, anti-virulence, and patient-specific approach. In vitro, animal models, and human studies, novel alternative therapies such as immunotherapy, bacteriophage therapy, and iron-chelating agents have shown promising results, but there are still many obstacles to overcome before they can be used in the clinic; controlled clinical trials are required to ensure their safety and efficacy before they are used for routine care.

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