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The Importance of Pseudomonas Aeruginosa in the Course of Burn Diseases and the Urgency of Combating it

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Abstract: A Gram-negative opportunistic bacteria called Pseudomonas aeruginosa is commonly linked to delayed wound healing, especially in cases of persistent skin injuries. It poses a significant challenge to clinical wound care because to its capacity to build biofilms, release virulence factors, and compete with other species. P. aeruginosa interferes with wound healing through a variety of molecular and cellular pathways, according to recent research. Results show that it disrupts important stages of healing by altering host immunological responses, breaking down extracellular matrix elements, and preventing keratinocyte migration. Critical virulence factors like exotoxin A, elastases, pyocyanin, and rhamnolipids are regulated by its quorum-sensing mechanism Furthermore, the synthesis of polysaccharides and alginate, which are components of the biofilm matrix, offers defense against antibiotics and host defenses. The wound microbiota is altered by interactions with other bacteria, such as antagonistic effects on Staphylococcus epidermidis and synergistic partnerships with Staphylococcus aureus. Promising therapeutic substitutes have demonstrated effectiveness in breaking up biofilms and lowering pathogenicity. These findings highlight the significance of focusing on P. aeruginosa as well as its ecological interactions in order to improve wound healing results and create more potent therapies. In the context of cutaneous wound healing, this review sought to emphasize the pathogenic role of P. aeruginosa and its interactions with other microbial species.

Keywords: Pseudomonas aeruginosa, burns, epidemic, burn center, widespread drug resistance, microbiota.

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Introduction. The biological process of wound healing is intricate and dynamic, comprising a coordinated series of cellular and molecular processes that repair injured skin. Hemostasis, inflammation, proliferation, and remodeling are some of the overlapping stages of this process that depend on a strictly regulated environment and the interaction of systemic and local variables. The equilibrium of the local microbiota is upset when skin integrity is compromised, increasing the likelihood that opportunistic and pathogenic microbes may colonize the wound. *Pseudomonas aeruginosa* stands out among these bacteria due to its capacity to colonize open wounds and obstruct the course of wound healing. Its presence modifies the local microbial ecology and disrupts the healing process by affecting immune responses and postponing resolution [1,2,3]. By affecting immune responses and postponing the resolution of inflammation, its presence not only modifies the local microbial ecology but also impedes the healing process. Infection outcomes are further complicated by the microbial shift brought on by *P. aeruginosa* colonization, which frequently results in competitive relationships with other microbes such *Staphylococcus aureus*, *Klebsiella pneumoniae* and *Streptococcus pyogenes***.** Up to 75% of patient deaths following the initial resuscitation of burn patients are caused by an infectious process. The high frequency and severity of these infections, as well as their numerous potential locations, are caused by a number of factors: the destruction of the skin makes it easy for microorganisms to enter; the presence of necrotic tissue gives them an ideal growth medium; invasive monitoring creates additional entry points; and, finally, nonspecific immune function alteration permits microbial proliferation. A common gram-negative, aerobic, non-fermenting bacterium found in nature is *Pseudomonas aeruginosa*. With a preference for humid, even nutrient-deficient, conditions, soil, plants, or flowing water can serve as reservoirs [4,5,6,7]. *P. aeruginosa* is one of the most important causes of dangerous nosocomial infections, primarily affecting immunocompromised individuals, due to its ease of growth in both the natural world and hospital settings, as well as its ability to develop antibiotic resistance mechanisms. Healthcare personnel's hands are the primary source of infection among hospitalized patients, although contact with contaminated surfaces and items can also result in infection. Over the past 30 years, there have been comparatively few documented outbreaks in burn units brought on by multidrug-resistant (MDR) bacteria. Few of these are from wealthy nations, and screening and diagnostic methods have evolved recently [8,9,10]. Iron concentrations were especially high in the wound environment, which greatly increased *P. aeruginosa's* capacity for pathogenicity. The repressor proteins of Psl (Polysaccharide of the Biofilm Matrix), a molecule essential for biofilm formation and bacterial aggregation, have been demonstrated to be inhibited by high iron levels in the wound microenvironment. Furthermore, the pathogen's capacity to elude host immune responses and endure in chronic wound environments is greatly enhanced by iron availability. Because *P. aeruginosa* infections significantly affect the prognosis of burn patients and outbreaks are frequent in burn units, they remain a major concern [11,12,13]. We think that in order to combat one of the biggest challenges to contemporary medicine—microorganisms resistant to several antibiotics—research in this area should be encouraged, as should the sharing of knowledge. Developing novel therapeutic strategies requires an understanding of how *P. aeruginosa* interacts with both host tissues and co-infecting bacteria. There is presently little comprehensive information about how *P. aeruginosa* dynamically interacts with other bacteria inside the wound niche and how this influences healing outcomes, despite a large number of research on its virulence. Thus, the purpose of this study is to examine *P. aeruginosa's* pathogenic role and its interactions with other bacteria in the healing of skin wounds [14,15].

The main purpose of this brief review is to analyze the importance of *Pseudomonas aeruginosa* during burn diseases and the relevance of combating it based on reputable scientific research.

A Synopsis of the Typical Skin Wound Healing Process. Numerous molecular, cellular, and clinical facts are involved in the normal physiological process of wound healing, which repairs injured tissues. Hemostasis, inflammation, proliferation, and remodeling are all stages of this process. Immediately following tissue damage, hemostasis is activated, leading to the creation of a fibrin mesh—a protein-based scaffold that stops bleeding and offers a structural matrix for cell adhesion and signal integration—which initiates wound healing. Additionally, this fibrin network promotes the concentration and release

of chemical mediators called growth factors, which are signaling proteins that control important cellular processes like migration, proliferation, and differentiation [1-5]. Neutrophils and macrophages infiltrate the injured area during the inflammatory phase, which comes after the hemostasis stage. Neutrophils create an extracellular matrix to catch opportunistic pathogens like Pseudomonas aeruginosa, and these immune cells first attempt to eradicate the bacteria through phagocytosis. However, pro-inflammatory cytokines like IL-1, IL-1β, IL-6, and TNF (Tumor Necrosis Factor) are secreted by macrophages, which also attract other leukocytes to the wound site and prepare the area for tissue regeneration through the excretion of TGF (Transforming Growth Factor). In order to maintain epithelial integrity and produce extracellular matrix components necessary for tissue healing, keratinocytes, fibroblasts, and myofibroblasts move and multiply during the proliferative phase. A more structured extracellular matrix replaces the granulation tissue during the remodeling phase, which results in revascularization, a decrease in cellularity, and a partial restoration of tissue function. Depending on the type and severity of the injury, these stages may overlap in time even though they happen in a sequential order. In order to achieve functional tissue regeneration and avoid the development of chronic wounds, each phase must be properly resolved [6-11]. Because *P. aeruginosa* secretes exotoxins and forms biofilms, it can impair immune responses, prolong inflammation, and have a particularly significant pathogenic potential throughout the inflammatory and proliferative phases. Because *P. aeruginosa* secretes exotoxins and forms biofilms, it can disrupt immune responses, prolong inflammation, and impede keratinocyte migration, which ultimately delays wound closure and promotes chronic infection. This makes *P. aeruginosa's* pathogenic potential especially relevant during the inflammatory and proliferative phases [12,13].

The Role of Pseudomonas aeruginosa in Skin Wound Healing ***Pseudomonas aeruginosa*** is a Gram-negative opportunistic pathogen that can adapt to a variety of environmental and host-associated niches. It has a wide range of virulence mechanisms that allow colonization, immune evasion, and tissue destruction. One of the main adaptive traits of *P. aeruginosa* is its ability to interact with host defense systems, especially by binding to vitronectin glycoprotein, which is normally found on the extracellular matrix (ECM) and controls the recruitment of defense cells. *P. aeruginosa* grows in both acute and chronic wounds by creating a complex biofilm structure made of polysaccharides such alginate, Pel, and Psl. Extracellular DNA, structural proteins, fimbriae, and type IV pili protein further solidify these biofilms, allowing the pathogen to cling to the surface and create microcolonies. In addition to increasing antibiotic resistance, the biofilm physically protects bacteria from immune cells like neutrophils and macrophages. Lastly, it disrupts the complement system, which exacerbates chronic inflammation [1-7]. In order to increase its pathogenicity, *P. aeruginosa* also secretes a variety of extracellular proteins and toxins. These include pyocyanin, elastase, and alkaline protease, which all play a role in tissue deterioration, oxidative stress, and host immune signaling modulation. The Type III Secretion System (T3SS), a needle-like device that injects effector proteins straight into host cells, is a key factor in pathogenicity. Certain exotoxins, such as ExoS, ExoT, ExoU, and ExoY, are delivered by the T3SS system and interfere with several cellular functions, including apoptosis, intracellular signaling, and cytoskeletal integrity [8-13]. By expressing these virulence factors, *P. aeruginosa* is able to control the wound microenvironment in addition to resisting phagocytic clearance and immune antimicrobial action. This involves immunological signaling disruption, extracellular matrix component breakdown, and host cell migration and proliferation regulation. Therefore, comprehending these interconnected regulatory networks offers a starting point for developing targeted treatments meant to interfere with quorum sensing, prevent the production of biofilms, or restore immunological balance in infected wounds [18-21].

Current and Upcoming Treatments for Pseudomonas aeruginosa Skin Wound Infection Eliminating the bacterial cells is the best way to prevent *P. aeruginosa* harm in epithelial lesions. Antibiotics such levofloxacin, ciprofloxacin, gentamicin, amikacin, or tobramycin are therefore sometimes used as the first line of treatment. It is challenging to completely eliminate *P. aeruginosa* from infected tissue due to its high levels of resistance to most regularly used antibiotics, such as aminoglycosides, quinolones, and

β-lactams, as well as to conventional disinfectants. Moreover, antibiotics have limited penetration of the biofilm matrix and can only target vegetative cells. Azithromycin and aminoglycoside antibiotics are currently commonly used to treat *P. aeruginosa* infections. Nevertheless, the right dosage is necessary to eradicate every bacterial cell and prevent adverse consequences. Because it necessitates a lower dosage of each antibiotic, antibiotic synergy has been seen as a good substitute. For instance, *P. aeruginosa* has been effectively eradicated by mixing azithromycin and gentamicin with ceftolozane and tazobactam [1,4,5,6]. *Pseudomonas aeruginosa* is becoming more and more resistant to drugs, which emphasizes the need for adjuvant or alternative treatments that don't just use traditional antibiotics. A number of antimicrobial peptides, cold atmospheric plasma, photodynamic treatment, mesenchymal stromal cells (MSCs) and their extracellular vesicles (EVs), and mitochondrial transplantation have shown promise as methods to break up biofilms. A key component of managing chronic wounds is debridement, which prepares the wound bed in addition to pharmaceutical methods. By physically removing necrotic tissue, bacterial biofilms, and cellular debris, debridement lowers the bioburden and makes it easier for topical or systemic antimicrobial medicines to penetrate. It has been demonstrated that a number of techniques, including surgical, enzymatic, autolytic, and mechanical debridement, improve the production of granulation tissue and establish a favorable microenvironment for later stages of healing. Promoting epithelial healing, which entails encouraging keratinocyte migration and proliferation to rebuild the epidermal barrier, is equally crucial. Applying bioactive dressings enhanced with growth factors, extracellular matrix elements, or antimicrobial peptides is one strategy that both prevents *P. aeruginosa* colonization and speeds up re-epithelialization [11-14]. Wound healing results can be improved by combining these regenerative therapies with infect. Revisions have been made to other strategies, such as the restoration of microbial balance. Probiotics, bacteriophage treatment, and topical antimicrobials with selective activity that alter the microbiome without totally eliminating beneficial organisms are among strategies. Furthermore, biofilm-disrupting substances and quorum-sensing inhibitors can lessen *P. aeruginosa* dominance, enabling commensal species to reappear and aid in wound healing. By changing the microbial community to a non-pathogenic condition, these strategies hope to improve granulation tissue production, decrease inflammation, and hasten the healing of chronic wounds [17,18,19].

Discussion. An Overview of the Typical Healing Process for Skin Wounds. In order to mend damaged tissues, wound healing is a natural physiological process that involves a number of molecular, cellular, and clinical factors. Hemostasis, inflammation, proliferation, and remodeling are all steps of this process. Immediately following tissue damage, hemostasis is activated, leading to the creation of a fibrin mesh—a protein-based scaffold that stops bleeding and serves as a structural matrix for cell adhesion and signal integration—which initiates wound healing. Additionally, the release and concentration of chemical mediators known as growth factors—signaling proteins that control important cellular processes including proliferation, migration, and differentiation—are made easier by this fibrin netw. Eliminating the bacterial cells is the best way to prevent *P. aeruginosa* harm in epithelial lesions. Antibiotics such levofloxacin, ciprofloxacin, gentamicin, amikacin, or tobramycin are therefore sometimes used as the first line of treatment [3-12]. The Role of Pseudomonas aeruginosa in Skin Wound Healing *Pseudomonas aeruginosa* is a Gram-negative opportunistic pathogen that can adapt to a variety of environmental and host-associated niches. It has a wide range of virulence mechanisms that enable colonization, immune evasion, and tissue destruction. One of the main adaptive traits of *P. aeruginosa* is its ability to interact with host defense systems, especially by binding to vitronectin glycoprotein, which is normally found on the extracellular matrix (ECM) and controls the recruitment of defense cells. It is challenging to completely eliminate *P. aeruginosa* from infected tissue due to its high levels of resistance to most regularly used antibiotics, such as aminoglycosides, quinolones, and β-lactams, as well as to conventional disinfectants. Moreover, antibiotics have limited penetration of the biofilm matrix and can only target vegetative cells. Azithromycin and aminoglycoside antibiotics are currently commonly used to treat *P. aeruginosa* infections. Nevertheless, the right dosage is necessary to eradicate every bacterial cell and prevent adverse consequences. Additional strategies, such as the restoration of microbial equilibrium, have been updated. Probiotics, bacteriophage treatment, and topical antimicrobials with selective action

that alter the microbiome without totally eliminating beneficial organisms are some strategies. Furthermore, *P. aeruginosa* dominance can be diminished by quorum-sensing inhibitors and biofilm-disrupting medicines, enabling commensal species to reappear and aid in wound healing. By changing the microbial community to a non-pathogenic condition, these methods hope to improve granulation tissue production, decrease inflammation, and hasten the healing of chronic wounds [13-18].

Conclusions. By interfering with several stages of the healing process, particularly inflammation and proliferation, *Pseudomonas aeruginosa* plays a crucial pathogenic role in the healing of skin wounds. The pathogen delays wound closure and encourages persistent infection by secreting exotoxins and forming architecturally complex biofilms made of alginate, Pel, Psl, and extracellular DNA. Quorum-sensing systems (las and rhl) and intracellular signaling molecules like cyclic di-GMP control *P. aeruginosa's* virulence by coordinating the development of important components like pyocyanin, exotoxin A, elastases, and rhamnolipids. These substances deteriorate extracellular matrix components, interfere with host immunological responses, and obstruct efficient epithelium regeneration.

By interacting with host proteins like vitronectin, suppressing complement activation, and altering macrophage phenotypes, the pathogen strengthens its ability to elude immune defenses by extending the pro-inflammatory M1 phase and postponing the anti-inflammatory M2 transition necessary for tissue regeneration. By releasing AHL signals, quinolones, and other antimicrobial chemicals that prevent other pathogens like Staphylococcus epidermidis and *Streptococcus pyogenes* from adhering and forming biofilms, *P. aeruginosa* retains a competitive edge in polymicrobial environments. But other streptococcal species, such *Streptococcus parasanguinis,* can break up *P. aeruginosa* biofilms and lessen the pathogen's pathogenicity. The pathogenic potential of *P. aeruginosa* in the wound healing environment is controlled by treatments including antibiotics, peptides, and other cutting-edge substitutes like mitochondrial application.

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