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Review article

Microbiology and Pathophysiology of Diabetic Foot Ulcers: Insights into Biofilm-Mediated Chronic Infection

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Abstract
Diabetic foot ulcers (DFUs) represent a major, costly complication of chronic diabetes mellitus. DFUs often precede lower-extremity amputations. The development of chronic DFUs is driven by a complex interplay of underlying pathophysiology. This is primarily represented by peripheral neuropathy and macro/micro-angiopathy. This would compromise tissue integrity and host immunity. These pathological changes create an optimal environment for persistent poly microbial infection. This is critically sustained by the formation of highly protected bacterial biofilms. This review comprehensively details the mechanisms of DFU pathogenesis, the evolving microbial etiology, and the pivotal role of the biofilm matrix in mediating enhanced antimicrobial tolerance. A clear understanding of the synergistic relationship between impaired host defenses and biofilm persistence is essential for developing holistic, targeted management strategies. This incorporates aggressive debridement and novel anti-biofilm agents.
Keywords. *Diabetic Foot Ulcers, Biofilm, Neuropathy, Angiopathy.*

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Introduction

DFUs are a devastating global health burden, affecting up to 15 % of all individuals with diabetes mellitus during their lifetime. DFU is the most common cause of non-traumatic lower extremity amputation (1). The transition from a simple lesion to a chronic infected wound stem from the systemic compromise of host defenses and tissue integrity. The pathology of the DFU is not attributable to a single factor, but it is driven by a vicious cycle involving three primary components: 1) Pathophysiological compromise (neuropathy and ischemia); 2) Microbial etiology (polymicrobial colonization); and 3) Biofilm persistence (structured infection) (2). Chronicity and resistance to therapy arise when opportunistic colonizers establish themselves as a sophisticated matrix-embedded community. The biofilm evades immune clearance and resists antimicrobial drugs (3). This comprehensive review aims to elaborate on the precise mechanisms by which these components converge. The review provides a detailed academic perspective on the pathogenesis and the specific challenges posed by biofilm-mediated infection in the diabetic foot.

Epidemiological Overview of Diabetic Foot Ulcer

Current epidemiological data indicate a rising trend in diabetic complications, with the lifetime risk of developing a foot ulcer now estimated between 19% and 34%(4). While the annual incidence remains stable in some regions, global point prevalence has reached approximately 6.3% (5). Recent studies emphasize the chronic nature of the condition, notably reporting recurrence rates as high as 60% within five years. In addition, a five-year mortality rate is 50% following the initial ulceration (6,7). Ulceration remains the critical pathway to major surgical intervention. Furthermore, the non-healing DFUs are preceding approximately 80% to 85% of non-traumatic lower extremity amputations (8). Although historical data cited a 15-fold increase in amputation risk, contemporary epidemiological assessments indicate that individuals with diabetes are 10 to 20 times more likely to undergo an amputation compared to their non-diabetic counterparts. This increases in the risk of amputations depends on geographic location and access to multidisciplinary care. Furthermore, once a major amputation occurs, the five-year survival rate drops significantly below 30% to 50%. The drastic fall in the survival rate highlights the lethal nature of these complications (9). The clinical and socioeconomic burden of these complications is substantial. Foot-related issues are the leading cause of hospital admissions among all long-term diabetic complications. These complications contribute to increased rates of systemic illness and death, with roughly 90,000 non-traumatic amputations performed annually due to diabetic foot pathology.

Elderly patients demonstrate a heightened vulnerability to ulceration and are more likely to develop secondary infections such as abscesses and osteomyelitis(9). Recent epidemiological estimates point out a substantial shift in the global diabetes landscape. Some countries are expected to see the greatest increase in Type 2 diabetes incidence over the next two decades. According to Recent studies, the number of diabetic patients is predicted to increase from 537 million in 2021 to 783 million by 2045, with more than three-

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quarters of this population living in low- and middle-income nations (10). This rapid escalation is driven by urbanization and aging populations. The major increase in the number of diabetic patients is directly related to an increased global burden of DFUs. Which currently affects roughly 18.6 million people each year. Addressing these complex complications necessitates a multidisciplinary management approach. Coordinated team-based care includes vascular surgery, podiatry, infectious disease, and endocrinology. The evidence suggests that multidisciplinary management care can reduce amputation rates by up to 85% while significantly mitigating long-term health decline (11,12).

Pathophysiological Underpinnings of DFU Development

Chronic hyperglycemia initiates a cascade of micro- and macrovascular damage that fundamentally alters the biomechanical and healing capacity of the foot (13).

Diabetic Neuropathy

Neuropathy in DM is manifested in three critical forms:

Peripheral Sensory Neuropathy

This is the most common initiating factor. Chronic hyperglycemia leads to the accumulation of sorbitol and fructose via the polyol pathway. That causes oxidative stress and damage to Schwann cells and nerve fibers. This will lead to loss of protective sensation. Means minor repetitive trauma (e.g., shoe pressure, walking on a foreign object) goes unnoticed, leading to initial skin breakdown (13).

Motor Neuropathy

Damage to efferent fibers causes denervation and atrophy of the intrinsic foot muscles. This results in biomechanical deformities such as hammer toes and the medial collapse seen in Charcot neuroarthropathy. These deformities shift plantar pressures to abnormal focal points, creating areas of high pressure and sheer force. All of these abnormalities lead to hyperkeratosis and ulceration (13). Hyperkeratosis is not only a symptom of motor neuropathy; it also serves as a crucial mechanical catalyst for tissue degradation. Raising of focal peak plantar pressures during the gait cycle in the insensate neuropathic foot is caused by hyperkeratosis. This acts as an external foreign body. This localized mechanical stress, along with the fact that hyperkeratotic skin doesn't stretch, causes moderate pressure to increase progressively. This will lead to inflammatory autolysis of the soft tissue underneath. This "autolytic" process makes subepidermal hematomas and hygromas form under the hyperkeratotic tissues. Eventually, this process will cause typical "punched-out" neuropathic ulceration when the subcutaneous tissue fails (11).

Autonomic Neuropathy

The autonomic nervous system plays a crucial role in regulating blood flow in various tissues. Loss of sympathetic vasomotor tone can lead to arteriovenous shunting. Blood will go directly from arteries to veins, bypassing capillaries. These critical changes will negatively affect the skin. Loss of sudomotor function results in anhidrosis. This causes the skin to become dry, cracked, and inelastic. Fundamentally, these major pathophysiological changes compromise the stratum corneum integrity. This important skin layer is the foot's primary physical defense against microbial invasion (13).

Diabetic Angiopathy and Ischemia

Peripheral Artery Disease (PAD) in DM is often characterized by calcification and atherosclerotic occlusion of distal vessels. These major findings distinguish DM PAD from non-diabetic PAD. Impaired Perfusion and ischemia lead to hypoxia at the tissue level. This is a major inhibitor of all phases of wound healing, particularly the proliferative and remodeling phases. Macrophages require adequate oxygen tension for phagocytosis and to generate reactive oxygen species. Ischemia critically reduces the delivery of necessary growth factors, vascular endothelial growth factor, and platelet-derived growth factor. Reduction in these factors inhibits the healing process. Furthermore, impaired perfusion limits the effective concentration of systemic antibiotics at the wound bed (13).

Impaired Immunocompetence

High glucose levels impair neutrophil and macrophage function, including chemotaxis, phagocytosis, and oxidative burst. This will contribute to a state of immunosuppression, which allows colonizing bacteria to become invasive infections (13). DFUs fundamentally disrupt the transition from the inflammatory phase to the proliferative phase. This cardinal interference with wound healing results in a state of chronic non-healing. This "pro-inflammatory stasis" is marked by an excess of pro-inflammatory cytokines, particularly

tumor necrosis factor-alpha (TNF-α) and interleukin-1 beta (IL-1 beta), which remain abnormally high. The main reason behind this high pro-inflammatory cytokine is that M1-polarized macrophages are always active. These cytokines cause the body to make too many matrix metalloproteinases, and at the same time, stop making tissue inhibitors of metalloproteinases (TIMPs). This imbalance leads to the swift breakdown of the extracellular matrix (ECM) and essential growth factors, including transforming growth factor-beta (TGF-beta) and vascular endothelial growth Factor (VEGF). Ultimately, these critical changes in the healing process cause inhibition in the development of granulation tissue and the commencement of re-epithelialization(14).

Microbial Etiology and the Role of the Skin Microbiota

The wound environment provides a unique, highly favorable growth medium for diverse organisms. This is due to chronic exudate, necrosis, and diminished host immunity (15).

Initial Colonization and Polymicrobial Nature

DFU infections are almost universally polymicrobial. which reflects the synergistic nature of the pathogens and their ability to thrive in varied oxygen environments. Early superficial infections are the first infections appears on diabetic patients' feet. These are dominated by skin commensals that become opportunistic pathogens, chiefly Gram-positive aerobes like *Staphylococcus aureus* (often including *methicillin-resistant S. aureus* (MRSA)) and *Streptococcus species*. These infections are often localized and mild (13).

Chronic/Deep Infections

The presence of tissue necrosis, ischemia, and deep tracts creates anaerobic niches. These infections involve a broader spectrum of gram-negative and gram-positive organisms (e.g., *Pseudomonas aeruginosa*, *Proteus spp*, strict anaerobes *Bacteroides spp*, and *Peptostreptococcus*). This bacterial mix is highly correlated with the development of deep-space abscesses and osteomyelitis. Which demands prolonged intravenous antimicrobial therapy (13).

Dysbiosis of the Skin Microbiota

Dysbiosis is an imbalance in the microbial community structure, which is a key factor in DFU formation. Diabetic patients often exhibit a shift in the skin microbiota towards less diverse and often more pathogenic communities. This shift happens even on intact skin. This predisposes the host to rapid and successful colonization by virulent bacteria once a wound occurs. The change in skin pH and the high glucose concentration in the interstitial fluid of the wound act as selective pressures favoring the growth of specific opportunistic pathogens (15).

The Critical Significance of Biofilms in DFUs

The transition from transient colonization to a chronic non-healing state is often the direct result of biofilm formation (2). Biofilms are sophisticated communities of microorganisms irreversibly attached to the wound surface, and encapsulated in a self-produced Extracellular Polymeric Substances (EPS) matrix (1). The following will emphasize the importance of biofilms in DFUs**.**

Enhanced Virulence and Immune Evasion

The EPS matrix, a hydrated mesh of polysaccharides, proteins, lipids, and extracellular DNA, confers exceptional protection to the colonized bacteria.

Physical Protection

The matrix prevents the physical access of neutrophils and macrophages. Which are the primary immune cells responsible for the clearance of infection (1).

Chemical/Immune Subversion

Biofilm bacteria continuously release virulence factors like hydrogen cyanide, exoenzyme S, exotoxin A, and pyocyanin for *P. aeruginosa*, and Panton-Valentine leukocidin and α hemolysin for *S. aureus*. These factors cause low-grade persistent chronic inflammation. This chronic stimulation leads to a cycle of tissue damage driven by the excessive release of host enzymes and matrix metalloproteinases, which degrade the extracellular matrix proteins necessary for the formation of granulation tissue and healing. This state of chronic inflammation is termed "frustrated healing"(2). The structural integrity and pathogenicity of biofilms in DFUs are determined by quorum sensing (QS). This is a sophisticated cell-to-cell communication mechanism controlled by small signaling molecules known as autoinducers. As bacterial density grows in

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the wound bed, the concentration of these autoinducers reaches a critical point. This level of autoinducers causes a coordinated shift in gene expression throughout the microbial community. This collective coordination is critical for the formation of the EPS because QS governs the secretion of polysaccharides, proteins, and extracellular DNA (eDNA). This mix of extracellular substances protects the colony from host immune cells and systemic antibiotics. By enabling this multicellular behavior, QS allows the biofilm to maintain metabolic homeostasis and coordinate the release of virulence factors. Eventually, this effect of QS makes the infection more resistant to standard therapy than its planktonic counterparts (1).

Clinical Relevance and Treatment Challenges

The clinical detection of biofilms is challenging because they may not cause the classic acute signs of infection. The presence of biofilm is suspected in any DFU that is non-healing despite adequate offloading and standard care (16).

Antimicrobial Resistance

Resistance to antibiotics is the primary clinical problem. Biofilm organisms are often phenotypically tolerant. Meaning that they are not genetically resistant, but their physical structure and physiological state make them tolerant to antibiotics at standard doses (16). The EPS matrix must be physically removed through sharp or surgical debridement. This process not only reduces bacterial load but also disrupts the protective niche. These changes allow the host immunity and antibiotics to act on the remaining planktonic cells (2).

Mechanisms of Biofilm-Mediated Antimicrobial Resistance

Resistance is a multi-faceted process combining physical, physiological, and genetic mechanisms.

Physical Diffusion Barrier

The efficacy of antibiotics against biofilm-forming cells is severely compromised by the extracellular matrix (ECM). This prevents the rapid flow of the antimicrobial agents. A key mechanism is the sequestration of antibiotics by specific ECM components. For instance, the polyanionic exopolysaccharide, alginate, and negatively charged eDNA are produced by *P. aeruginosa*. The biofilm binds and neutralizes positively charged antibiotics like aminoglycosides (e.g., tobramycin). Furthermore, glycopeptides in the case of S. *epidermidis* biofilm bind to vancomycin, preventing it from reaching its cellular target. Finally, the ECM acts as a repository for antibiotic-modifying enzymes. For example, *Moraxella catarrhalis* secretes beta-lactamases that protect neighboring susceptible species like *S. pneumoniae* from ampicillin and amoxicillin in mixed biofilms (17).

Altered Bacterial Physiology

The dense biofilm core develops steep concentration gradients for nutrients and oxygen, resulting in a metabolically inactive or slow-growing state. In this state, bacteria become tolerant to agents that require active metabolism, such as beta-lactams, which target cell wall synthesis. Persister cells are a small subpopulation of non-dividing, metabolically dormant bacterial cells. They are highly tolerant to multiple antibiotics. These cells survive therapy and are the source of recurrent infection after antibiotic withdrawal. Unlike antibiotic resistance, which is inherited, persister cells are genetically similar to the colony's susceptible members but have a different metabolic profile. These cells undergo a condition of dormancy known as “metabolic quiescence”. In this dormancy, persister cells inhibit the pathways that most antibiotics target. Examples of these critical pathways are cell wall formation and protein translation. As a result, while routine antibiotic treatments can effectively eliminate metabolically active planktonic and surface biofilm cells, latent persister cells remain unaffected. Once the antimicrobial pressure is removed, these cells "re-awaken," returning to an active state and repopulating the wound. This process is the primary cause of the chronic recurrence and recalcitrance seen in diabetic wound infections (17).

Horizontal Gene Transfer

The high cell density facilitates conjugation and transduction, rapidly disseminating true genetic resistance genes. Examples of those genes are those encoding for beta-lactamases, or efflux pumps, among the polymicrobial community (17).

Phenotypic Tolerance vs. Genetic Resistance in Biofilms

Understanding the distinction between phenotypic tolerance and genetic resistance is critical for effective treatment (Table 1).

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Genetic Resistance (True Resistance)

Genetic resistance refers to the stable, heritable change in a microorganism's DNA that makes it less susceptible to an antibiotic. True resistance is a permanent change passed down to all daughter cells.

Phenotypic Tolerance (Biofilm-Mediated)

Phenotypic tolerance is a temporary, non-heritable state of reduced susceptibility induced by the physical EPS and physiological dormancy conditions within the biofilm. Biofilm-mediated tolerance is reversible upon biofilm disruption (17).

Table 1. Comparison between Phenotypic Tolerance and Genetic Resistance

Feature	Phenotypic Tolerance	Genetic Resistance
Nature	Temporary, non-heritable state	Permanent, heritable change in DNA
Cause	Biofilm structure, EPS, and low metabolism	DNA mutation or gene acquisition
Susceptibility	High minimal inhibitory concentration (MIC) only while in biofilm	High MIC always (in biofilm or planktonic)
Reversibility	Reverts to a susceptible planktonic state when biofilm is disrupted	Remains resistant regardless of the environment
Example	Slow-growing cells surviving beta-lactam treatment	*MRSA* producing penicillin-binding protein 2a (PBP2a)

Current Diagnostic Techniques for DFU Biofilms

Accurate diagnosis is crucial but challenging due to the inadequacy of superficial swabs. Quantitative tissue biopsy is the preferred method. which is a deep tissue specimen after aggressive debridement and cleansing. The established threshold is a bacterial load of > 10^5 colony forming unit CFU/g of tissue for diagnosing infection(13). Traditionally, the clinical diagnosis of infection in DFUs was based on the "gold standard" quantitative threshold of >10^5 CFU/g of tissue. However, accumulating research suggests that this numerical metric may not be adequate. To determine the true pathogenic potential of chronic biofilms, modern microbiological evaluations emphasize a "quality over quantity" approach. Pointing out that microbial diversity and the presence of particularly aggressive pathogens, such as *Pseudomonas aeruginosa*, can induce chronicity even at lower absolute levels. In the DFU's complex ecosystem, synergistic interactions between commensal and pathogenic species can increase the biofilm's overall virulence. These interactions would make the compositional profile and expression of specific virulence factors more reliable predictors of clinical outcomes than bacterial density (1). Confocal scanning laser microscopy allows 3D visualization of the intact biofilm architecture in situ.

When combined with fluorescence in situ hybridization, specific bacterial species can be identified within the structure, providing critical spatial information (2). Traditional culture-based approaches usually fail to capture the real microbial complexity of DFUs, because they are naturally biased towards fast-growing aerobic species and frequently overlook the fastidious anaerobes that dominate mature biofilms. To address these limitations, polymerase chain reaction (PCR) and quantitative PCR (qPCR) are increasingly being used to detect bacterial DNA. These accurate techniques provide critical data on virulence factor genes, e.g., *icaA, icaD*, and antibiotic resistance genes, e.g., *mecA*, without the need for viable cultures. Furthermore, next-generation sequencing and metagenomic approaches provide the most complete profile of the wound's microbiome, identifying non-culturable organisms. These molecular tools represent a paradigm shift in DFU management. These advanced diagnostic tools would shift the focus from individual isolates to the collective genetic potential of the polymicrobial community (18).

Treatment

Recent systematic reviews and meta-analyses indicate that biofilm presence is a primary determinant of treatment failure in 60 – 90 % of chronic DFUs (19). The current standard of care has shifted toward "Biofilm-Aware Wound Hygiene". This updated intervention is a rigorous four-step clinical protocol (20). The cornerstone of treatment used to be physically disrupting the EPS once in a while. However, since biofilm begins to reform within 6–12 hours and matures by 48–96 hours. For this reason, debridement must be repeated at least weekly. Following debridement, the "window of opportunity" is utilized by applying surfactants, hypochlorous acid, or acetic acid, which penetrate the weakened matrix more effectively than systemic agents. Evidence supports dressings incorporating cadexomer iodine or silver-impregnated polyabsorbent fibers, which have demonstrated the ability to reduce biofilm populations by up to 4-log units in clinical settings. Guidelines now advocate for fluorescence imaging or molecular assays (qPCR) over

traditional swab cultures, as the latter often fail to identify the slow-growing anaerobes and fungi protected within the biofilm. Using these techniques allows for an accurate follow-up.
The primary impediment to DFU recovery is the biofilm EPS matrix, which acts as a physical and chemical shield against conventional antibiotics. To circumvent this, the authors advocate for the use of multifunctional nano-delivery systems such as liposomes, polymers, and metal-organic frameworks. That can be engineered to penetrate these biological barriers (21). These nanomaterials provide a superior therapeutic outcome. These delivery systems can directly degrade the matrix using encapsulated enzymes like DNases to cleave eDNA. Moreover, these nanomaterials utilize "smart" pH-responsive mechanisms to release antimicrobial agents specifically within the acidic microenvironment of the biofilm(22). Furthermore, the integration of QR inhibitors via nanoparticles disrupts the inter-bacterial communication required for matrix maintenance, effectively shifting the treatment strategy from passive antibiotic diffusion to an active, targeted disassembly of the biofilm architecture (23). This precision-targeted approach not only enhances the local concentration of therapeutic agents but also reduces the risk of systemic toxicity and the development of further antibiotic resistance in chronic wound management.

Conclusion

The chronic nature of DFUs is driven by a complex synergy between systemic host deficiencies and the resilient architecture of bacterial biofilms. Pathophysiological factors, specifically peripheral neuropathy, impaired vascular perfusion, and a state of pro-inflammatory stasis, create an environment where the body's natural healing mechanisms are severely compromised. Within this niche, opportunistic pathogens make the transition from simple colonization to highly structured biofilm communities. These biofilms are encapsulated in an EPS matrix that acts as a physical and chemical shield. This barrier effectively neutralizes host immune cells and conventional antimicrobial therapies. The persistence of these infections is further mediated by QS and the presence of metabolically dormant persister cells, which allow the microbial community to survive treatment and repopulate the wound. This will lead to high rates of recurrence and amputation. Consequently, effective management requires a paradigm shift toward "biofilm-aware wound hygiene". This new protocol prioritizes frequent, aggressive debridement to physically disrupt the EPS matrix. Emerging strategies, such as the use of multifunctional nano-delivery systems and quorum-sensing inhibitors, offer promising avenues for penetrating these biological barriers. Shifting the therapeutic focus from passive antibiotic use to the active disassembly of biofilm structures. However, further exploration and rigorous laboratory investigation of these novel therapeutic strategies are imperative to validate their clinical efficacy and ultimately mitigate the profound risk of lower-extremity amputation.

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