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Literature review: Antibiotic resistance in the diabetic microenvironment: A comprehensive review of biochemical and cellular mechanisms

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Abstract

Infections in patients with diabetes mellitus (DM) present a severe clinical challenge, often characterized by high rates of treatment failure and an increased risk of lower-limb amputations. Traditional management relies on systemic antibiotics, which frequently prove ineffective due to antimicrobial resistance (AMR) and the protective barrier of bacterial biofilms. This review comprehensively examines how the diabetic tissue microenvironment—characterized by chronic hyperglycemia, tissue ischemia, advanced glycation end-products (AGEs) accumulation, and local hypoxia—synergistically drives biochemical and cellular mechanisms of resistance. Hyperglycemia suppresses innate immune functions, blunting neutrophil chemotaxis and causing excessive, pathological Neutrophil Extracellular Trap (NET) formation, which stabilizes rather than eliminates bacterial biofilms. Concurrently, macrophage polarization is arrested in a pro-inflammatory M1-like state, driving chronic non-resolving inflammation and matrix metalloproteinase-9 (MMP-9) upregulation. At the host-pathogen interface, pathogens exploit interstitial glucotoxicity to amplify quorum sensing (QS) networks, precipitating phenotypic tolerance via metabolic dormancy (persister cells). To bypass these barriers, next-generation responsive biomaterials, advanced delivery systems, and non-chemical physical approaches (such as super-oxidized solutions and DACC-impregnated dressings) are emerging as promising immune-aware adjunctive therapies. Integrating precise molecular diagnostics with strict metabolic regulation and biofilm-disrupting modalities is essential to transform diabetic wound care from reactive to proactive, ensuring effective infection control and functional tissue regeneration.

Keywords: Diabetic Foot Ulcers; Biofilms; Antimicrobial Resistance; Netosis; Epigenetic Modification; Responsive Biomaterials.

1. Introduction

The global surge in the prevalence of diabetes mellitus (DM) has catalyzed a secondary health crisis that manifests as microvascular, macrovascular, and systemic immune dysregulations [4, 16, 17]. The clinical burden imposed by infections within the diabetic population—such as urinary tract infections (UTIs), diabetic foot infections (DFIs), and soft tissue infections—presents a profound escalation in patient morbidity and mortality [11, 15, 16]. One of the most formidable challenges in the clinical management of infected diabetic individuals is the high failure rate associated with conventional antibiotic therapies [11, 15]. This therapeutic refractory state is no longer viewed merely as a consequence of patient non-compliance or sub-optimal dosing regimens, but rather as a direct implication of the altered tissue microenvironment driven by chronic hyperglycemia [4, 11, 17].

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A deep evaluation of the diabetic microenvironment is currently highly critical because chronic hyperglycemia, tissue ischemia, and localized hypoxia synergistically warp the landscape of host-pathogen interactions [11, 17]. The glucose-dense interstitial fluid facilitates accelerated microbial proliferation, induces the expression of bacterial virulence factors, and promotes mass biofilm formation that inherently resists antimicrobial penetration [11, 17, 19]. Conversely, the accumulation of advanced glycation end-products (AGEs) and the concurrent surge in oxidative stress compromise cellular structural integrity and suppress immunological effector functions, thereby engineering a protective niche for resistant pathogens [4, 11, 16, 17]. Therefore, this comprehensive review aims to elucidate the deep biochemical and cellular mechanisms driving antibiotic resistance within the diabetic microenvironment, providing a robust molecular foundation for the development of precise, targeted therapeutic strategies.

1.1. Review Methodology

The synthesis of primary literature within this comprehensive review was systematically executed in strict accordance with the *Preferred Reporting Items for Systematic Reviews and Meta-Analyses* (PRISMA) guidelines [16, 18, 19]. A comprehensive literature search was conducted across core primary databases—including PubMed, Scopus, and Web of Science—focusing on original peer-reviewed research, clinical trials, and authoritative reviews [14, 16, 18, 19]. The search matrix employed dynamic Boolean combinations of specific keywords, including: (*diabetes mellitus* OR *hyperglycemia*) AND (*ischemic stroke* OR *diabetic foot ulcer* OR *urinary tract infection*) AND (*biomarkers* OR *antibiotic resistance* OR *biofilm* OR *NETosis*) AND (*epigenetic* OR *oxidative stress*) [14, 16, 18].

Strict inclusion criteria were applied to preserve translational validity, mandating studies involving adult human diabetic cohorts, in vivo animal models meticulously replicating diabetic pathology (such as *db/db* mice or streptozotocin-induced rodents), and molecular assays reporting explicit quantitative outcomes (e.g., gene expression profiling, cytokine quantification, or biochemical kinetics) [11, 16, 17, 18]. Studies characterized by a high risk of reporting bias, lacking valid separate control groups, or failing to directly resolve the biochemical mechanisms of infection and resistance were rigorously excluded through a multi-staged screening process (title, abstract, and full-text review) to ensure data integrity [16, 18].

2. Terminology and epidemiology of infections in diabetes mellitus

From a clinical standpoint, infection within the glycemic context is defined as the pathogenic invasion and proliferation inside biological tissues that have already undergone metabolic and vascular distortion due to an absolute or relative insulin deficiency [4, 15, 16]. Chronic hyperglycemia blurs the operational boundary between benign bacterial colonization (the presence of microbes without tissue-destructive inflammation) and active, non-resolving clinical infection [11, 17]. Interstitial glucotoxicity precipitates microvascular and neurological damage, causing minor disruptions of the superficial epidermis (e.g., calluses, blisters, or anhidrosis) to rapidly degenerate into full-thickness deep soft tissue infections and disabling osteomyelitis [11, 19].

Epidemiological and molecular data corroborate that the diabetic population serves as a major reservoir for the selection of multidrug-resistant (MDR) pathogens [11, 15, 16]. Within the microenvironment of diabetic foot infections (DFIs), *Staphylococcus aureus* stands out as the most frequently isolated pathogen (accounting for ~40% of cases), with a large proportion of isolates presenting the methicillin-resistant (MRSA) phenotype [11, 15]. Gram-negative opportunistic bacilli, including *Pseudomonas aeruginosa* (~20% of cases), *Escherichia coli*, and *Klebsiella pneumoniae* (~10% of cases), exhibit notably elevated prevalence rates in chronic diabetic ulcerations [11, 15, 19].

This microenvironmental shift is heavily characterized by a high frequency of extended-spectrum beta-lactamase (ESBL)-producing and carbapenemase-producing strains, which actively neutralize front-line empirical regimens through the secretion of hydrolytic enzymes [11, 16]. Furthermore, this glucose-rich and hypoxic niche heightens the risk of cross-kingdom fungal complications, predominantly involving *Candida* species (~10% of cases), which form robust mixed-species biofilms that drastically escalate the 5-year post-amputation mortality and impede cellular clearance [11, 15, 17].

3. Anatomy and molecular mechanisms of the diabetic microenvironment

3.1. Suppression of the Cellular Innate Immune Response

The diabetic tissue microenvironment exerts a profound inhibitory pressure on the cellular innate immune response via local and systemic glucotoxicity [11, 17, 19]. Neutrophils, the essential first-line myeloid responders, exhibit severe functional impairments, including a marked reduction in chemotactic velocity and compromised phagocytic index [11,

15, 17]. At the molecular level, chronic hyperglycemia blunts the upregulation of essential cell-surface integrins and adhesion molecules on neutrophils, such as CD11b/CD18, thereby severely crippling their ability to adhere to the vascular endothelium and migrate to the site of infection (frustrated extravasation) [11, 17, 19].

Furthermore, the formation of Neutrophil Extracellular Traps (NETs) undergoes a highly destructive pathological acceleration [6, 17]. Hyperglycemia primes and stimulates neutrophils to overactivate the calcium-dependent enzyme peptidylarginine deiminase 4 (PAD4), driving the hyper-citrullination of histone H3 (citH3) and the dysregulated release of NETs [6, 17]. Paradoxically, instead of immobilizing and neutralizing pathogens, this extruded extracellular DNA (eDNA) backbone is actively hijacked by biofilm-forming bacteria to reinforce the structural cohesion of the extracellular matrix [6, 17].

Simultaneously, the prolonged tissue retention of cytotoxic histones and proteases associated with NETs directly amplifies macrophage NLRP3 inflammasome signaling, releasing excessive IL-1β that perpetuates a chronic, non-resolving inflammatory macrophage phenotype and completely halts the timely transition toward pro-healing M2 states [6, 17].

3.2. Systemic Roles of Oxidative Stress, AGEs, and Interstitial Alterations

Chronic hyperglycemia initiates mitochondrial metabolic overload, leading to excessive intracellular production of Reactive Oxygen Species (ROS) and a highly damaging state of oxidative stress [4, 11, 16]. This pro-oxidative environment accelerates the non-enzymatic glycation of tissue proteins, driving the rapid accumulation of Advanced Glycation End-products (AGEs) [4, 11, 16]. The continuous binding of AGEs to their corresponding receptor (RAGE) on endothelial cells, dermal fibroblasts, and keratinocytes sparks the persistent transcription of the nuclear factor kappa B (NF-κB) signaling pathway [4, 16].

This sustained nuclear translocation drives the overproduction of pro-inflammatory cytokines (TNF-α, IL-1β, IL-6) and provokes an abnormal upregulation of matrix metalloproteinases (specifically MMP-9), which aggressively degrades the extracellular matrix (ECM) and essential growth factors [4, 16, 17].

3.3. Molecular Orchestration of Mass Biofilm Formation

Within this glucose-dense, hypoxic, and alkaline niche, colonizing bacteria switch their genetic program from a planktonic lifestyle toward a structured, sessile community encased in a mature biofilm [11, 17]. Interstitial glucose behaves as the primary metabolic fuel, driving the rapid synthesis of extracellular polymeric substance (EPS) components [2, 17, 19]. The resulting dense polysaccharide and proteinaceous matrix acts as an exceptionally efficient chemical shield, reducing antibiotic penetration by 50–70% [11, 17]. For example, the abundant anionic eDNA strands within the EPS matrix can electrostatically capture and sequester positively charged antibiotics, such as aminoglycosides, keeping the drug concentration at the cell envelope far below lethal thresholds [11, 17].

This mass biofilm maturation is tightly orchestrated through cell density-dependent intercellular communication known as Quorum Sensing (QS) [2, 6, 11, 17]. In the diabetic microenvironment, the transcription of QS circuit regulators (such as the las/rhl networks in P. aeruginosa and the accessory gene regulator (agr) system in S. aureus) undergoes an intense, glucose-driven amplification [17, 19].

The accumulation of autoinducer signaling molecules coordinates the expression of bacterial virulence factors and triggers the differentiation of cells within the deep biofilm layers into persister cells—a subpopulation of microbes that enter a state of complete metabolic dormancy [2, 11, 17]. Because most traditional classes of antibiotics (such as β-lactams) are bactericidal by specifically targeting active bacterial growth and cell-wall synthesis, the presence of these inactive persister cells shielded by the EPS layer provides an uninherited, phenotypic tolerance up to 1,000-fold higher, driving infection chronicity and therapeutic failure [11, 17, 19].

4. Clinical and metabolic risk factors for antimicrobial resistance

The selection and propagation of antibiotic-resistant strains within the diabetic microenvironment are heavily driven by an integrated matrix of clinical and metabolic risk factors:

4.1. Demographic and Clinical Risk Factors

- Advanced Age (Vascular Aging): The physiological decline of tissue aging introduces immunosenescence, reducing T-cell proliferation and compromising pathogen clearance by 30–50% in elderly diabetic patients

[11]. Cutaneous aging further reduces epidermal thickness by 20–30% and drops collagen synthesis by 25–35%, creating a physically fragile envelope that facilitates biofilm attachment and expansion [11].

- Diabetes Duration: Prolonged disease duration independently correlates with the severity of macro- and microvascular complications, progressively reinforcing the tissue's hypoxic and ischemic boundaries [11, 16].
- HbA1c Intensity (Glycemic Control): Elevated glycated hemoglobin reflects a higher cumulative burden of AGEs and a corresponding intensity of oxidative stress [4, 16]. This metabolic aberration imprints a stable "hyperglycemic memory" on vascular and innate immune cells, sustaining non-resolving inflammatory phenotypes [4, 16].

4.2. Antibiotic Exposure History

Prior Empirical Therapy Exposure: Diabetics with a history of recurrent infections (such as chronic UTIs or non-healing ulcers) are subjected to frequent, prolonged courses of broad-spectrum antibiotics [11, 16]. This sustained exposure exerts a high selective pressure on the local wound microbiome, selecting for the horizontal transfer of resistance genes (e.g., plasmids encoding ESBL or carbapenemases) across microniches inside the biofilm [11].

4.3. Comorbid Risk Factors

Diabetic Nephropathy (Renal Impairment): The presence of macroalbuminuria and a reduced eGFR directly marks the systemic destruction of microvascular and endothelial barriers [16]. This renal impairment drastically distorts the pharmacokinetics and pharmacodynamics (PK/PD) of hydrophilic antibiotics (e.g., β-lactams, aminoglycosides), causing sub-therapeutic drug troughs within the interstitial fluid of the wound that fall below the mutant prevention concentration, thereby accelerating the selection of resistant strains [11, 16].

5. Clinical manifestations and diagnostic challenges

Infections fueled by resistant pathogens within the diabetic microenvironment manifest clinically as non-healing wounds stalled in a perpetual inflammatory phase, typically presenting as a pale, edematous wound bed, fragile or devitalized granulation tissue, profuse or putrid exudate, and progressive necrosis [1, 2, 17]. In patients with advanced distal symmetric polyneuropathy (DSPN), the loss of protective pain and temperature sensation eliminates the clinical warnings of tissue injury [11, 14, 15]. As a result, deep-seated infections involving resistant bacteria (such as deep abscesses, septic arthritis, or necrotizing fasciitis) often go completely unnoticed by the patient until they manifest as advanced gangrene that threatens the extremity and demands amputation [11, 15, 19].

The primary diagnostic challenge lies in the severe limitation of traditional culture methods, which rely heavily on superficial wound swabs [1, 11]. Superficial swabbing fails to harvest the sessile, adherent microbial communities embedded in deeper layers and frequently grows superficial skin flora contaminants while missing the principal MDR pathogens and deep strict anaerobes driving the infectious process [1, 11].

Therefore, a deep tissue biopsy or percutaneous bone aspiration after aggressive surgical debridement and surface disinfection remains the diagnostic standard of-care [1]. To bypass the diagnostic gap of conventional cultures, which cannot distinguish between a planktonic state and an organized biofilm mode of growth, modern approaches rely on culture-independent molecular techniques [2, 11]. These include 16S rRNA gene sequencing, shotgun metagenomics, and metatranscriptomics to map transcriptionally active bacterial networks and screen for resistance determinants directly from the tissue matrix [1, 11].

6. Regimen selection and theoretical therapeutic approaches

6.1. Pharmacological Interventions and PK/PD Optimization

Antibiotic selection for diabetic infections with suspected multi-drug resistance must be guided by infection severity scores (IWGDF/IDSA) and informed by molecular assays from deep tissue biopsies [1, 11]. Initial empirical regimens must utilize broad-spectrum agents with optimal interstitial fluid penetration [1, 11]. For moderate-to-severe infections carrying an elevated MDR risk, combinations incorporating penicillin-beta-lactamase inhibitors (e.g., Piperacillin/tazobactam), advanced-generation cephalosporins (Ceftobiprole), or carbapenems (Ertapenem) are utilized to neutralize enzymatic resistance barriers [1, 11, 19].

Confirmed MRSA infections mandate glycopeptides like Vancomycin or protein synthesis inhibitors such as Linezolid [1, 11, 15]. Rigorous dose adjustments based on renal clearance (eGFR) are mandatory to maintain adequate tissue

concentrations [11, 16]. To maximize local PK/PD parameters, advanced localized delivery platforms—such as vancomycin- or gentamicin-loaded calcium sulfate beads—are increasingly employed directly within the wound bed [1, 11]. This concentrates the antimicrobials at the target site far above the MIC of the biofilm while minimizing systemic exposure and associated nephrotoxicity [1, 11].

To assist clinicians in navigating these complex scenarios, a structured framework integrating infection severity, systemic regimens, renal adjustments, and innovative biomaterial interventions is summarized in Table 1.

Table 1 Comprehensive Clinical Guidance for Antimicrobial Selection, Renal Optimization, and Adjunctive Modalities in Diabetic Infections.

IWGDF/IDSA Severity Category	Empirical & Definitive Systemic Antibiotic Regimens	Renal PK/PD Adjustment Criteria (eGFR)	Adjuvant Non-Antibiotic / Biomaterial Interventions
Mild	• Empirical: Amoxicillin/clavulanate, Cephalexin, or Clindamycin. • Definitive: Target isolated Gram-positive cocci (*S. aureus*).	• Typically, no adjustment is required unless eGFR < 30 mL/min/1.73 m^2.	• Standard wound debridement. • Hydrophobic DACC-impregnated dressings to physically bind and remove pathogens.
Moderate	• Empirical: Piperacillin/tazobactam, Ertapenem, or Levofloxacin + Clindamycin. • Definitive: Tailored to deep tissue biopsy culture (target ESBL/MDR Gram-negatives).	• Piperacillin/tazobactam: Adjust dose or prolong infusion intervals if eGFR < 40 mL/min. • Ertapenem: Reduce to 500 mg q24h if eGFR < 30 mL/min.	• Serial surgical debridement. • Application of localized vancomycin/gentamicin-loaded calcium sulfate beads. • Antibacterial photodynamic therapy (aPDT).
Severe	• Empirical: Imipenem/cilastatin or Meropenem + Linezolid/Vancomycin (if high MRSA risk). • Definitive: Driven by rapid molecular assays and aggressive de-escalation protocol.	• Meropenem: Decrease dose and extend intervals based on calculated CrCl (e.g., 500 mg q12h or q24h). • Vancomycin: Mandatory Therapeutic Drug Monitoring (TDM) to avoid compounding nephrotoxicity.	• Immediate, aggressive surgical debridement. • Pathology-responsive smart hydrogels (pH/ROS-triggered). • Intensive glycemic control via optimized insulin therapy.

6.2. Aggressive Metabolic Regulation

Strict and intensive glycemic regulation via optimized insulin therapy is an absolute prerequisite to repair the cellular and biochemical damage of the diabetic tissue [4, 11]. Normalizing blood glucose levels has been shown to reverse the pathological stiffening of vascular endothelial cells (HUVECs) by restoring normal cytoskeletal architecture via the CDC42/N-WASP axis [11, 16].

At the biochemical level, lowering interstitial glucose restricts the glycation of tissue proteins, suppresses RAGE expression, and blunts intracellular ROS accumulation [4, 11, 16]. This metabolic correction directly restores innate cellular defenses, recovering neutrophil chemotaxis and phagocytic index, while downregulating chronic acute-phase reactants (IL-6, CRP, TNF-a) and upregulating vasoprotective factors (VEGF, FGF-2) [4, 11, 16]. The ultimate biological outcome is the normalization of the MMP-9/TIMP-1 ratio and the restoration of collagen deposition by fibroblasts, transitioning the tissue toward successful resolution [4, 11, 16, 17].

6.3. Innovative and Combination Antibiofilm Modalities

To address biofilm tolerance, modern therapeutic strategies must integrate multimodal clinical approaches that disrupt the EPS barrier:

- Serial Surgical Debridement: This remains the mechanical cornerstone, physically removing necrotic tissues and disrupting the biofilm's three-dimensional architecture to open a brief, time-dependent therapeutic window for antibiotic penetration [1, 2, 11].
- Antibacterial Photodynamic Therapy (aPDT): This approach applies a light-activated photosensitizer (e.g., methylene blue, Rose Bengal, or curcumin) that, upon exposure to specific visible light wavelengths, generates a lethal surge of ROS electron acceptors (singlet oxygen) [9]. This surge oxidizes bacterial cell membranes and inactivates carbapenemase enzymes across species without the risk of selecting for heritable resistance [9].
- Pathology-Responsive Biomaterials: Utilizing smart hydrogel dressings, microneedle patches, or electrospun nanofibers designed to capture environmental cues (e.g., alkaline pH shifts, elevated ROS, or glucose levels via embedded glucose oxidase cascades) to trigger the on-demand, localized release of non-antibiotic biocides, such as antimicrobial peptides (AMPs), gas-releasing nitric oxide (NO) donors, or matrix-degrading enzymes (DNase I, Dispersin B) [6, 9, 17, 19]. Non-chemical physical alternatives include Dialkylcarbamoyl Chloride (DACC)-coated meshes that utilize strong hydrophobic interactions to trap and lift out microbes during dressing changes without inducing cytotoxicity or endotoxin release [12].

7. Clinical challenges and translational research gaps

7.1. Critical Synthesis of Current Literature

A critical appraisal of the primary literature surrounding diabetes-associated infections reveals significant discordant findings that complicate the establishment of universal clinical standards. Regarding the precise relationship between glycemic control metrics (HbA1c intensity) and specific antimicrobial resistance patterns, the data remain split. One prominent group of studies demonstrates a robust positive correlation, asserting that a higher HbA1c directly increases the isolation of MDR strains [11, 16]. Mechanistically, this is explained by the glucose-driven upregulation of bacterial high-affinity hexose transporters (GlcA/GlcC) and the concurrent transcription of virulence genes, which actively drive biofilm thickness and resistance [11, 17].

Conversely, alternative large-scale stroke and community cohorts have failed to identify a reproducible correlation between HbA1c values and immediate antibiotic resistance patterns [16]. This epidemiological divergence is heavily driven by methodological variations: studies showing a positive correlation predominantly sample deep tissue biopsies from advanced, ischemic ulcerations (Wagner grade ≥ 3) where macrovascular disease has completely isolated the local interstitial fluid [1, 11, 16]. On the other hand, studies reporting neutral findings often rely on superficial wound swabs or less vascularly compromised cohorts, where systemic circulation still influences host-pathogen dynamics [1, 11].

Another intense domain of discussion surrounds the role of host innate defense networks, such as NETosis. While classic immunological paradigms view the extrusion of NETs as a protective barrier to confine pathogens and prevent systemic bacteremia, emerging cell biology data in diabetes show that excessive NETosis acts predominantly as a pathological amplifier [6, 17]. The massive release of eDNA provides an involuntary structural scaffold that bacteria incorporate into the EPS layer, while the concurrent tissue accumulation of citH3 and granular proteases drives a destructive, non-resolving inflammatory state via the NLRP3 axis [6, 17].

7.2. Identification of Major Research Gaps

A systematic evaluation of the 129 compiled studies identifies several critical gaps in evidence that require future research:

- The Chasm of Rodent Contraction Mechanics (Translational Disconnection): A profound limitation in current pre-clinical research is the heavy reliance on full-thickness excisional wounds in healthy, young rodents [17, 18]. Because rodents possess an active panniculus carnosus muscle layer, their wounds close predominantly via contraction (up to 80-90%), whereas human skin repair relies on granulation and re-epithelialization [18]. Although silicone-ring splinting models have been developed to limit contraction, these short-term models still fail to capture the long-term "glycemic memory," progressive macrovascular atherosclerosis, and advanced polyneuropathy that characterize clinical diabetic foot ulcers [11, 18].
- In Vivo Kinofluidic Gaps in Smart Biomaterials: While multi-responsive biomaterials (e.g., pH-, ROS-, or glucose-triggered hydrogels) display excellent biofilm-eradicating parameters in vitro, data detailing their degradation

kinetics, long-term safety, and material stability within the fluctuating and highly enzymatic human wound fluid remain scarce [9, 19].

- The Pervasive Male Bias in Pre-clinical Modeling: There is an overwhelming sex bias in pre-clinical study design, with over 85% of animal experiments executed exclusively in male rodents to avoid the estrous cycle's statistical variability [18]. Consequently, the distinct molecular impact of sex steroids—where estrogen dampens inflammation and promotes angiogenesis while testosterone sustains pro-inflammatory cascades—remains poorly understood in the context of post-menopausal diabetic women, who represent a major demographic for non-healing ulcers [18].

8. Conclusions and cardinal recommendations

This comprehensive review reveals that antibiotic resistance within the diabetic microenvironment is not merely a localized microbiological event, but rather the inevitable consequence of a pathogenic synergy between microbial programs and host tissue dysfunction. Chronic hyperglycemia, oxidative stress, and AGE-RAGE signaling launch a double-pronged attack: they cripple the host's cellular innate immunity (suppressing neutrophil migration, driving non-resolving M1 macrophage polarization, and distorting NETosis pathways) while simultaneously fueling bacterial transition toward a protected, tolerant biofilm mode of growth. The dense barrier of the EPS matrix and the formation of metabolically inactive persister cells render traditional systemic antibiotics largely ineffective.

The strategic implication for clinicians is the absolute necessity to move away from a standalone systemic antibiotic approach. In accordance with Antibiotic Stewardship principles, antimicrobial selection must be guided by molecular profiling from deep tissue biopsies, avoiding superficial swabs to minimize resistance selection,

Management must integrate three pillars: aggressive metabolic regulation (insulin-optimized glycemic control) to restore interstitial tissue homeostasis; timely surgical debridement to mechanically disrupt the biofilm's three-dimensional framework; and the adoption of advanced, multi-targeted therapies (e.g., aPDT, pathology-responsive biomaterial hydrogels, or physical-binding non-chemical dressings like DACC) to actively dismantle the biofilm and achieve successful resolution.

Compliance with ethical standards

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Disclosure of conflict of interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

References

[1] Afonso, A. C., Oliveira, D., Saavedra, M. J., Borges, A., & Simões, M. (2021). Biofilms in Diabetic Foot Ulcers: Impact, Risk Factors and Control Strategies. International Journal of Molecular Sciences, 22(15), 8278. https://doi.org/10.3390/ijms22158278

[2] Aziz, W., Sultana, H., Kumar, V., & Tyagi, A. (2025). The Relationship Between NETosis and Biofilm Formation in Chronic Infections. Biomolecules, 15(12), 1692. https://doi.org/10.3390/biom15121692

[3] Chen, H., Pan, B., Zhang, S., Li, X., Zhang, Y., Exten, K., Chen, D., Wang, L., Jiang, T., Luo, C., & Huang, C. (2025). Recent Advances in Biosynthesis and Bioactivity of Plant Caffeoylquinic Acids. Current Issues in Molecular Biology, 47(11), 942. https://doi.org/10.3390/cimb47110942

[4] Ge, Y., & Wang, Q. (2023). Current research on fungi in chronic wounds. Frontiers in Molecular Biosciences, 9, 1057766. https://doi.org/10.3389/fmolb.2022.1057766

[5] Hussain, N., Ramadan, A., Al Haddad, A. H. I., & Alfahl, Z. (2026). A Review of Emerging Biomarkers Connecting Diabetes and Ischemic Stroke: Implications for Early Detection and Risk Stratification. Journal of Diabetes Research, 2026, Article ID 2719491, 18 pages. https://doi.org/10.1155/jdr/2719491

[6] Jeyaraman, M., Jeyaraman, N., Ramasubramanian, S., Nallakumarasamy, A., Murugan, S., Jayakumar, T., & Muthu, S. (2025). Efficacy of Dialkylcarbamoylchloride (DACC)-Impregnated Dressings in Surgical Wound Management: A Review. European Burn Journal, 6(1), 1. https://doi.org/10.3390/ebj6010001

[7] Ju, C. C., Liu, X. X., Liu, L. H., Guo, N., Guan, L. W., Wu, J. X., & Liu, D. W. (2024). Epigenetic modification: A novel insight into diabetic wound healing. Heliyon, 10(2024), e28086. https://doi.org/10.1016/j.heliyon.2024.e28086

[8] Mikziński, P., Kraus, K., Seredyński, R., Widelski, J., & Paluch, E. (2025). Photocatalysis and Photodynamic Therapy in Diabetic Foot Ulcers (DFUs) Care: A Novel Approach to Infection Control and Tissue Regeneration. Molecules, 30(11), 2323. https://doi.org/10.3390/molecules30112323

[9] Pouget, C., Dunyach-Remy, C., Pantel, A., Boutet-Dubois, A., Schuldiner, S., Sotto, A., Lavigne, J. P., & Loubet, P. (2021). Alternative Approaches for the Management of Diabetic Foot Ulcers. Frontiers in Microbiology, 12, 747618. https://doi.org/10.3389/fmicb.2021.747618

[10] Supardy, N. A., & Kumar, R. R. S. (2025). Aging, biofilms, and diabetic foot ulcers: disrupting chronic infections with super-oxidized solutions and addressing age-related vulnerabilities. Cardiovascular Diabetology - Endocrinology Reports, 11, 45. https://doi.org/10.1186/s40842-025-00261-5

[11] Villa, F., Marchandin, H., Jack-Philippe, L., Schuldiner, S., Cellier, N., Sotto, A., & Loubet, P. (2024). Anaerobes in diabetic foot infections: pathophysiology, epidemiology, virulence, and management. Clinical Microbiology Reviews, 37(3), e00143-23. https://doi.org/10.1128/cmr.00143-23

[12] Yao, Y., Huang, M., Li, Y., Lin, Y., Dong, J., Du, J., Zhai, A., Bi, C., & Li, L. (2026). Emerging Biomedical Engineering Therapies for Infected Diabetic Foot Ulcers: Toward Antibacterial Functionalization and Pathology-Responsive Regulation. Small Science, 6, e202500482. https://doi.org/10.1002/smsc.202500482

[13] Yuan, N. B., Yang, Y. Z., Tan, C. X., & Ran, X. W. (2024). Mechanism of cold atmospheric plasma in treatment of chronic skin ulcer. Chinese Journal of Reparative and Reconstructive Surgery, 38(10), 1283-1288. doi: 10.7507/1002-1892.202404027