Biofilm-hijacked Inflammation: The Missing Link to Hard-to-heal Wounds

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Diabetic foot ulcers (DFUs), venous leg ulcers (VLUs), and pressure ulcers (PUs) represent the most common hard-to-heal wounds. According to Armstrong,[1] "Every 1.2 seconds, someone develops a diabetic ulcer; every 20 seconds, someone is amputated." In the United States, $1 million is spent every 30 seconds on diabetic foot complications.[2,3] The news is similar for PUs; over a 10-year period, the number of PU treatments has increased 63%, costing $11 billion a year, data not indicative of improvement.[4,5] Although 70% of small (<12.4 cm^2) VLUs heal in 24 weeks, 30% do not.[6] According to the literature, chronic, hard-to-heal wounds cost the US $50 billion per year, 10 times more than the annual budget of the World Health Organization.[7,8] Fife and Carter[8] call hard-to-heal wounds a silent epidemic that affects more than 6.5 million people in the US. The question is, *Why do wounds fail to heal*?

Nonhealing wounds have constellations of common factors such as enzyme imbalances, alkaline pH levels, negative bacterial DNA mutations, host cellular senescence, and increasing bacterial loads. Each of these biological influences is detrimental to a healing wound. These patterns of low-grade negative effects have something common in origin: biofilm-controlled inflammation.

Biofilm and its subclinical activities are becoming a major source of debate and alarm. Studies consistently support bacterial virulence once the colony reaches 10^5 colony forming units; however, long before approaching this recognizable indication of infection, biofilm is attached and actively manipulating the inflammatory processes. In the past 20 years, researchers have only scratched the surface in addressing the numerous weak links in the wound healing process and the inflammatory cascade connected with biofilm.[9]

Normal wounds heal in a predictable albeit complex sequence; inflammation is a part of the normal healing progression. However, an influx of bacteria growing into a biofilm can change the healing cascade and subvert the entire process. Protected by the extracellular polymeric substance (EPS), its outer structure, and fed by the inflammatory process, biofilm becomes persistent, stalling wound healing processes and rendering traditional treatments ineffective (see Table).[10,11] Clinicians describe stalled wounds as "being stuck" in the inflammatory phase. As biofilm disregulates innate biological immune responses, the wound healing continuum from host stem cell activity

TABLE. NORMAL VERSUS BIOFILM-REGULATED INFLAMMATION

NORMAL WOUND INFLAMMATION	BIOFILM-REGULATED INFLAMMATION
• Growth factors released from platelets during hemostasis attract neutrophils, which then release proinflammatory cytokines	• Dysregulates endothelial sprouts that control growth factors, ultimately wound closure and graft attachment
• Neutrophils recruited; bacteria killed and natural debridement begins	• Induces cellular senescence, avoids antibiotic recognition
• Neutrophils recede, macrophage/fibroblast influx	• Damages and transforms bacterial DNA
• Macrophages release further growth factors that attract other cells and lead to proliferative phase	• Recruits heavy metals (calcium, iron) in the wound to perpetuate biofilm growth and strengthens the EPS substance
• Increased exudate incorporates into the extracellular polymeric (EPS) for self-feeding and ongoing nutrition of the biofilm	• Alkalizes the wound pH to slow healing and support biofilm growth
	• Compromises the immune system to make the host more susceptible to progressive and spreading biofilm-based infection
	• Neutrophil influx and secretion of proinflammatory cytokines stimulated
	• Prolonged release of metalloproteinases leading to degradation of growth factors, receptors, extracellular matrix, and impairment of cell proliferation and migration
	• Releases small molecules that triggers more inflammation

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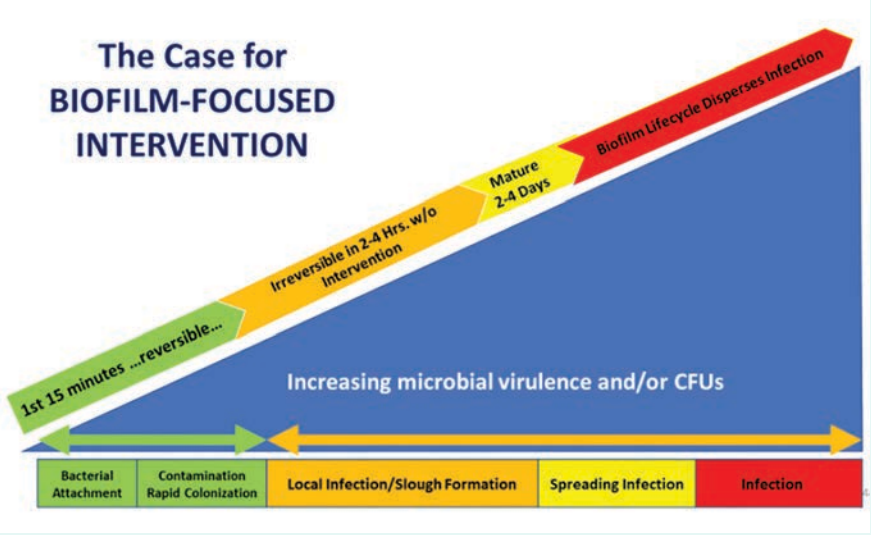

FIGURE. Unimpeded: biofilm to infection trajectory.

to normal cellular homeostatic mechanisms stalls.[9,12-14] Once diverted into the biofilm life-cycle, inflammation incubates and supports a widening circle of accelerated tissue destruction and becomes a conduit for biofilm-based infection (see Figure). Induced proinflammatory influences are not efficiently addressed by current biofilm treatment strategies through focused therapies, in light of new evidence.[10,11,13,14]

Instead of focusing on a single biofilm-centric inflammatory action in isolation, such as matrix metalloproteinases, pH, and DNA changes, recent research, using the mechanical science perspective, has confronted the heart of biofilm resilience: its protective structure, the EPS.[12-15] Within this protective architecture, biofilm can withstand onslaughts from debridement, dressings, and topical products that address the issues of planktonic and newly dispersed bacteria but fail to effectively dissolve the EPS structure, exposing hidden bacteria. Often, even stringent cleaning and disinfecting methods, such as steam sterilization, leave the EPS intact, allowing bacterial repopulation at the next bacterial exposure.[16,17]

Biofilm research is providing a microscopic view of the lurking invisible ecosystem in most hard-to-heal wounds and a growing number of acute wounds. What has been missing is the understanding that biofilm is a 3-dimensional problem that withstands segmented or siloed care focusing on biofilm activity instead of removing the biofilm foundation. Biofilm-emphasized care is a part of multimodal therapy and should focus on therapeutic goals that begin with dissolution of the protective biofilm EPS structure, destroy bacteria, and prevent biofilm reformation. To be clinically and economically effective, biofilm treatments should be evaluated according to each dimension of biofilm. ■

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