Editorial Commentary

Biofilm and diabetic foot ulcer healing: all hat and no cattle

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Is there evidence that biofilm has an important role in the etiology of non-healing diabetic foot ulcers? Biofilm is touted as the new reason for wound chronicity that has until recently been an unrecognized cause of our failures in wound healing. The term biofilm is not new. Historically it has been associated with recalcitrant infections in patients with orthopaedic implants. Recently, the wound healing literature has proposed that biofilm essentially acts as a protector of bacteria resulting in colonization, infection and impaired healing. Many pharmaceutical companies tout new anti-biofilm products. There is a new focus on animal studies with biofilm infections, and clinical studies with antibiofilm products. However, there is very little real clinical evidence that biofilm impedes diabetic wound healing.

The same type of phenomena occurred when the term "bioburden" was identified as the cause of wound chronicity twenty years ago. Bioburden was used to describe a critical, quantitative level of bacterial colonization that contributed to wound failure prior to being observed by clinicians as being actively infected. Antimicrobial dressings such honey, silver, and iodine were introduced by industry to combat the bioburden. Most of the evidence was based on bench top research that demonstrated a specific wound product would reduce bacteria in vitro. Unfortunately, bench top research of these products often does not translate into clinical success.

We could not identify any studies of topical dressings with silver, honey or antibiotics that measured "bioburden" before, during, or after therapy in patients with diabetic foot ulcers. To the best of our knowledge, there are no studies that show these products prevent clinical infection. Gardner and colleagues evaluated quantitative bacterial cultures using quantitative polymerase chain reaction (qPCR) in patients with diabetic foot ulcers without clinical signs of infection. She found no association between quantitative cultures and poor wound healing (1). The clinical evidence for silver, honey and iodine paste products suggests no benefit in most randomized controlled trials (RCTs) to treat diabetic foot ulcers or diabetic foot infections (2-4).

The same is true of biofilm. The *in vitro* and *in vivo* animal work suggests there could be a plausible mechanism of action and an opportunity for novel interventions. However, the clinical evidence is much weaker than some experts would lead you to believe. Small studies, ranging from 15 to 165 subjects, report the prevalence of biofilm to be 23%, 39%, 46%, 60%, and 100% (5-9). Consequently, biofilm is not present in all chronic wounds, and in many cases, it is not present in most wounds. To the best of our knowledge, no studies report on the prevalence of biofilm in diabetic foot infections. Similarly, there is no evidence to show that the prevalence of biofilm is different in diabetic foot ulcers that healed and diabetic foot ulcers that did not heal.

Given the above observations, the clinical data about biofilm and wound healing are potentially misleading. In fact, several studies claim that "anti-biofilm" treatment has been successful against biofilm when biofilm was not measured at any time during the study. Despite the lack of measurement of biofilms, these studies concluded that anti-biofilm treatments resulted in better clinical outcomes (8) because biofilm was eradicated. Several RCTs have demonstrated an improvement when the topical therapy described as "anti-biofilm" was used. We are not

questioning the clinical results of the study, but rather the conclusions reached. The data and results cannot support a claim that the "anti-biofilm treatment" affected biofilm when there were no accepted measures of biofilm at any time during the study.

We identified one small cohort study of 17 patients with diabetic foot ulcers (DFUs) with biofilm that were treated with an iodine paste product every other day for seven days (10). Malone and colleagues measured quantitative cultures with DNA sequencing and real-time qPCR and measured biofilm with scanning electron microscopy and/or fluorescence *in situ* hybridization to confirm the presence or absence of biofilm. Eleven patients had ≥1 log reduction of bacteria, and six patients had no effect or an increase in the microbial load. However, biofilm was not eliminated from any of the subjects. Interestingly, wound debridement was withheld because of the concern it would reduce biofilm, and other standard treatments such as off-loading were not mentioned in the study (10).

The rationale and outcomes of biofilm studies that report clinical efficacy are not valid at face value. If biofilm could be expected to be present in only half of the cases, it would seem prudent to make sure the presence of biofilm was part of the inclusion criteria in an "anti-biofilm" intervention study. Why would an anti-biofilm treatment make a difference in wound healing if only half of chronic wounds have biofilm? It is like evaluating gastric bypass surgery in people with a normal body mass index. In addition, there are a number of studies and therapies that have no effect on biofilm, and yet randomized clinical studies report very high rates of DFU healing. If biofilm was a pivotal part of wound chronicity, why would these treatments work. For instance, RCTs of total contact casts report 90% of patients heal. Clearly, immobilization in a transitional cell cancer (TCC) does impact biofilm.

As healthcare reimbursement transitions from volume based to value based, better evidence about the role of biofilm in diabetic foot ulcer healing and in chronic wounds is needed. Future studies which are designed to study the impact therapies on biofilm must include well accepted measures of biofilm throughout the study. Poorly designed studies will waste resources and time, which is not acceptable in the era of value-based care. Based on the published literature, it is premature to conclude that the prevalence of biofilm burden in a wound is directly related to wound chronicity. Well-designed prospective randomized studies are needed to further understand the role of biofilm in wound chronicity. Only then can rationale treatment options be based on evidence-based medicine

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Footnote

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