A comprehensive biofilm-based management approach

Improving standard care for all wound types

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Preface

*In 2016, I participated in a working group on wound biofilm with colleagues from academic settings, teaching hospitals, and wound care clinics. Together we published Expert Recommendations for Optimizing Outcomes in the Management of Biofilm to Promote Healing of Chronic Wounds (*Wounds*. 2016;28[suppl 6]:S1-S20). Rising to the forefront of our discussion was the need for increased awareness of biofilm biology, prevalence, clinical significance and the need for educational resources on the optimal approach to managing wound biofilm. This perspective paper is based on the previously published recommendations and provides a concise overview of BBWM™.*

It has been proposed that biofilm in wounds impairs healing and can lead to more severe infections.[1,2] There have been significant advances in understanding wound biofilm: the high prevalence, challenge of detection, tolerance to treatment, and the mechanisms of delayed wound healing.[3] As a result, many experts believe that biofilm is present in most wounds and that treatment strategies should adjust accordingly.[4,5] Here we discuss the advantages of a comprehensive biofilm-based management approach, a proactive approach in which all chronic wounds are considered at risk for biofilm.

Biofilm is a risk in all wounds

Biofilm is a community of microbes encased within a protective proteinaceous matrix. Biofilm can be made of a single species of bacteria or fungi, but it is more often polymicrobial.[3] Biofilm has been reported in a variety of medical, dental, and industrial settings.[6] Biofilm phenotype is thought to be the more common state of bacteria in natural environments; 99.9% of microbes are attached to surfaces (sessile) rather than free-floating (planktonic).[6] In fact, within minutes of surface attachment, changes in gene expression can occur in bacteria that trigger initiation of the biofilm phenotype, including production of an exopolymeric matrix (EPM) and some bacteria downregulating metabolic activity (dormant persister cells).[6]

Based on the prevalence of the biofilm phenotype, it has been proposed that all wounds may be at risk for developing biofilm. James et al originally reported that 60% of chronic wounds in their study contained biofilm. In contrast, only 6% of acute wounds sampled contained biofilm.[7] More recently, a meta-analysis performed by Malone et al reported the presence of biofilm in 80% of chronic wounds.[8] Although the biofilm risk may differ, it is clear that neglected bioburden can progress to biofilm in any wound type.

Biofilm is hard to detect and impairs healing

Diagnosing biofilm is a significant challenge for wound care specialists. First, biofilm is not typically visible on the wound surface and classic signs of infection are often absent.[3] Thus, clinical assessment often results in an underestimated prevalence of biofilm. Only specialized imaging such as scanning electron microscopy (SEM) or immunohistochemistry (IHC) can identify biofilm, but even these techniques rely on obtaining a thorough sample from the wound bed.[7] A second confounding factor is the lack of specific biomarkers that allow laboratory testing for biofilm. In fact, culturing samples from the wound may be misleading, because standard cultures are designed to detect planktonic microbes, not biofilm.

Biofilm is a direct cause of delayed wound healing and is responsible for 80% of chronic human infections in at least 18 different clinical pathologies.[1,2,9] Biofilm impairs healing by stalling wounds in the inflammatory phase.[1] During normal wound healing, neutrophils and macrophages migrate to the wound where they secrete enzymes (proteases) that break down the damaged tissues and reactive oxygen species (ROS) that kill planktonic bacteria.[3] Eventually, these inflammatory cells die

off (apoptosis) and inflammation subsides. In contrast, biofilm continuously stimulates immune-mediated inflammation within the wound as the host fights the biofilm. The bacteria and host immune cells both produce high levels of proteolytic enzymes, resulting in degradation of growth factor receptors and extracellular matrix components that are essential for healing.[3]

Explaining BBWM™

Based on the prevalence of biofilm and its detrimental effects on wound healing, many experts believe that wound treatment strategies should adjust to directly address biofilm.[4,5] Here, we discuss BBWM™, which is a proactive approach that includes 2 key elements: physically removing biofilm through debridement and preventing re-formation with a broad-spectrum, noncytotoxic, antimicrobial product.

Debridement is a critical element for BBWM™

Debridement has been standard protocol in chronic wound care for decades. Aggressive and frequent debridement is necessary to remove surface biofilm and, importantly, colonies of biofilm that reside below the wound surface.[3] Standard wound care practice incorporates debridement regularly, often on a weekly basis, to clear necrotic tissue as well as biofilm.[3] However, it is clear that debridement alone is not sufficient for managing biofilm due to rapid re-formation beginning within 24 hours.[10] In fact, biofilm can fully mature within 3 days following debridement.[10] Thus, debridement is necessary but not sufficient for managing the re-formation of wound biofilm.

A broad-spectrum, noncytotoxic, antimicrobial product is essential for BBWM™

A broad-spectrum, noncytotoxic, antimicrobial product is essential following debridement for BBWM™.[3] However, not all antimicrobials are well suited for managing bioburden.[11] Research has shown that some topical antimicrobials are actually detrimental to wound healing. For example, some silver dressings demonstrate nonspecific cytotoxicity to both pathogenic bacteria and host cells required for healing, resulting in delayed epithelialization.[12]

Antibiotics often rely on metabolically active bacteria. However, frequently some bacteria in biofilm are metabolically inactive (dormant), rendering many antibiotics ineffective.[3]

Characteristics of an ideal antimicrobial[11]

- **Broad antimicrobial spectrum:** Biofilm is often polymicrobial, including gram-positive and gram-negative bacteria and fungi
- **No microbial resistance:** Has a mechanism of action that does not result in the development of microbial resistance
- **High tissue compatibility:** Does not negatively impact healthy cells or healing
- **Sustained barrier effect:** Prevents biofilm re-formation in the wound

BBWM™ has demonstrated encouraging clinical outcomes

As the problem of wound biofilm has become more appreciated, some experts evolved their wound care strategies to incorporate the principles of BBWM™. A report by Wolcott et al provided an indication that debridement resulted in only a temporary setback for biofilm rather than elimination.[10] Wolcott et al demonstrated that debridement opens a time-dependent window during which antimicrobial intervention is most effective in preventing biofilm re-formation. Following debridement, biofilm is often more susceptible to antimicrobial and antibiofilm agents.[10]

This led Wolcott et al to pursue a comprehensive biofilm-based management approach in the clinic. They observed a 77% healing rate in patients with critical limb ischemia. Though this was not a randomized controlled trial, the rates of healing observed were higher than reported elsewhere in the literature.[13] It is thought that optimizing the wound bed through a comprehensive BBWM™ approach will help to optimize the effectiveness of subsequent treatment with an advanced bioengineered cell therapy.

Various case reports provide additional support for a BBWM™ approach. Outcomes have been encouraging for BBWM™ on various chronic wounds, surgical dehiscence, an infected burn wound, and others. Overall, wound outcomes supported the use of BBWM™ as an effective approach to facilitate wound healing.[4,14]

New technologies are available to facilitate BBWM™

Debridement and proactive prevention of biofilm formation with a broad-spectrum, noncytotoxic, antimicrobial product are the foundation of BBWM™.[3] Many physicians have adopted BBWM™ and reported success in the clinic and the literature. Comprehensive BBWM™ requires technologies that both manage biofilm formation and support healing, striking a delicate balance between antimicrobial effectiveness and high tissue compatibility.[5,14]

One promising product is PuraPly™ Antimicrobial, a unique technology that enables a comprehensive BBWM™ approach in a wide range of wound types. PuraPly Antimicrobial combines the broad-spectrum, noncytotoxic antimicrobial PHMB (polyhexamethylene biguanide) with a purified native collagen matrix.[15] PHMB blocks microbial attachments, helping to prevent biofilm re-formation,[11] while the native collagen matrix forms a durable biocompatible scaffold that supports healing.[16] Biofilm management with PuraPly Antimicrobial following debridement may help provide the support required for wounds to proceed to closure.[14]

PURAPLY AM PRESCRIBING INFORMATION

Please see complete prescribing information at **www.puraplyam.com**.

Device Description: PuraPly Antimicrobial Wound Matrix (PuraPly AM) consists of a collagen sheet coated with 0.1% polyhexamethylene biguanide hydrochloride (PHMB) intended for the management of wounds. PuraPly AM is supplied dry in sheet form. The device is packaged in sterile, sealed single pouches.

Intended Use/Indications: PuraPly AM is intended for the management of wounds and as an effective barrier to resist microbial colonization within the dressing and reduce microbes penetrating through the dressing. PuraPly AM is indicated for the management of partial and full-thickness wounds, venous, diabetic, chronic vascular, and pressure ulcers, tunneled/undermined, surgical, trauma, and draining wounds.

Contraindications: PuraPly AM is derived from a porcine source and should not be used in patients with known sensitivity to porcine material. PuraPly AM is not indicated for use in third-degree burns. PuraPly AM should not be used on individuals with a known sensitivity to PHMB.

Warnings and Precautions: Do not resterilize. The device is intended for single patient use only. Do not reuse. Discard all open and unused portions. PuraPly AM is sterile if the package is dry, unopened and undamaged. Do not use if the package seal is broken. PuraPly AM must be used prior to the expiration date. Discard PuraPly AM if mishandling has caused possible damage or contamination. PuraPly AM should not be applied until excessive exudate, bleeding, acute infection and significant swelling are controlled. Do not freeze or expose PuraPly AM to excessive heat.

Prescription Only: PuraPly AM is restricted to use by or on the order of a physician or properly licensed practitioner.

Manufactured and Distributed by: Organogenesis Inc. Canton, MA 02021

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This paper features select topics and content adopted from a previously published, coauthored supplement to Wounds *June 2016 titled: Expert Recommendations for Optimizing Outcomes in the Management of Biofilm to Promote Healing of Chronic Wounds. This focused paper draws from the author's previous contributions to the published supplement and provides expanded discussion.*

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