BIOBURDEN-BASED WOUND MANAGEMENT: A NEW PARADIGM

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Contamination

• Presence of non-replicating microorganisms on the wound surface that evoke no clinical host response

- All chronic wounds are contaminated
- Bacterial colony counts low
  - Planktonic
- Wound healing occurs in spite of bacteria presence

1. AWMA. Bacterial impact on wound healing: From contamination to infection. 2011.
Colonization

• Bacteria that have adhered to superficial tissue (sessile)

• Have begun to form colonies without generating a host immune response

• Not typically associated with a delay in healing

Critical Colonization

• The inability of the wound to maintain a balance between altered bioburden and an effective immune system

• Results in unexplained delay in healing - prolongation of the inflammatory phase

• No overt signs of clinical infection or wound deterioration

Biofilm

• Densely packed communities of microbial cells that grow on surfaces and surround themselves with Extracellular Polymeric Substance (EPS)

• Biofilms develop defenses from topical agents, and impair wound healing
  - Inflammatory immune response
  - Impairs granulation tissue formation
  - Impairs epithelialization

How quickly do biofilms form?

• Strongly attached micro-colonies
  - 2-4 hours

• Develop initial EPS
  - 6-12 hours

• Evolve into fully mature biofilm colonies
  - 2-4 days

• Rapidly recover from mechanical disruption (debridement)
  - Within 24 hours

Prevalence and Impact

• >90% of chronic wounds possess biofilm

• Biofilm may delay and impair the healing process

  - Each year, as many as 17 million new biofilm infections occur in the US

  - 65%-80% of all human infectious disease is caused by biofilm

1. Wolcott. The role of biofilms: are we hitting the right target? 2011
2. Wolcott. Understanding Wound Infection and the Role of Biofilms. AAWC. 2008
Principles of Biofilm Based Wound Care

1. Frequent debridement of wounds to physically remove biofilm communities

2. Use an effective microbicidal dressing after debridement to prevent reformation of biofilms

3. Alter topical & systemic antimicrobial treatments to prevent emergence of dominant bacteria from polymicrobial populations; utilize DNA bacterial identification techniques

4. Biofilm Based Wound Care is part of Wound Bed Preparation (TIME)

## TIME – Wound Bed Assessment

<table>
<thead>
<tr>
<th>Clinical observations</th>
<th>Wound bed preparation</th>
<th>Developments in wound care which can be used in clinical practice</th>
<th>Factors to consider when applying in clinical practice</th>
<th>Clinical outcome</th>
</tr>
</thead>
</table>
| **Tissue**            | Debridement           | • Debridging wipes  
• Larvae  
• Autolytic (honey and Hydrogels)  
• Chemical (antiseptics dressings and solutions) | • Knowledge  
• Skills  
• Competence  
• Evidence and efficacy | Viable wound bed |
| **Infection/inflammation** | Wound cleansing  
Bacterial balance  
Persistent inflammation  
Managing infection/Inflammation | • Microbial irrigation solutions  
• Biofilms: Improved understanding, management and detection  
• Improved understanding of the role of persistent inflammation in chronic/stalled wounds  
• Increased role of antimicrobial agents  
• Negative Pressure Wound Therapy in combination with microbical solutions to reduce levels of planktonic and biofilm bacteria | • Increased bacterial tolerance to topical/systemic agents  
• Diagnostic for biofilm detection needed  
• Diagnostic tests: when and how often? | Bacterial balance and reduced inflammation |
| **Moisture**           | Moisture balance  
Exudate | • Moist wound healing  
• Emphasis on moisture management  
• Negative Pressure Wound Therapy for management of large exudate volumes | Dressing selection: what needs to be considered  
• Absorption  
• Retention  
• Patient comfort  
• Bacterial pool  
• Sensitivity/allergy | Moisture balance |
| **Edge of wound/Epidermal advancement** | Epithelial edge advancement  
Improved state of surrounding skin | • Revisiting existing therapies  
• Advanced therapies such as Negative Pressure Wound Therapy | | Advancing wound edges |
Treatment Strategy
Treatment strategy

Treatment challenges

Systemic antibiotics
• Fail to reach adequate local tissue levels
  - Topical antiseptics in conjunction with systemic therapy may be more effective

Debridement
• Frequent debridement allows for treating agents to be most effective—Effective in the clinic setting?
  - Biofilm rapidly reconstitutes itself on the surface within 24 hours

Topical Antimicrobials
• Tissue compatibility? Broad spectrum? Resistance?

Facing this “New Problem”…do we need a New Paradigm?

- We need to be able to suppress Biofilm formation in chronic wounds
  - Barrier Dressings?
  - NPWT
    - Instillation?
  - Synthetic Graft products with antimicrobial properties?
Barrier Dressings

- Passive Antimicrobial Defense
  - Protecting the wound or the dressing?
- Tissue Compatibility?
- Efficacy
Can Dressings Disrupt & Kill Mature Biofilms?

24 hr Continuous Exposure of Mature PAO1 Biofilm on Porcine Explants

NPWT

- Utilization of existing NPWT modality with instillation
- Wound Lavage
  - “Wound Chemotherapy”
  - Saline
  - PVP
  - PHMB

*Figure 2. Biofilm bacteria concentration at (A) predebridement day 0; (B) postdebridement day 0; (C) predebridement day 7; and (D) postdebridement day 7. CFU: colony forming unit; NPWT: negative pressure wound therapy; NPWTi: negative pressure wound therapy with instillation*
Assessment of NPWT+ Instillation on Biofilms Grown on Pig Skin Explants


Check for leaks, NP pressure, Instillation, Saturation of ‘wound’ and foam before NPWT and final collection canister volume to verify completion of 6 cycles.
Effects of 6-Cycles of NPWT-Instill Treatments Over 24 Hours on *P. aeruginosa* Biofilm Grown on Pig Skin Explants

* P-Value <0.005 compared to saline control

Phillips P, Yang Q, Schultz G. unpublished
Advanced Tissue Products

- Dermal regenerative scaffolds
  - Collagen Matrix

- Antimicrobial Elements
  - Silver
  - Copper
  - PHMB
Importance of Collagen

- Collagen is the main structural protein in the extracellular space of connective tissue.

- ECM controls many cellular functions, including cell shape and differentiation, migration and protein synthesis.

- 28 types of collagen identified so far.

- Type 1 collagen
  - most common (80%-90%) and found in all tissues
  - the primary collagen in a healed wound.
Importance of Retaining Native Structure

- ECMs that retain native tissue structure were found to inhibit a wider range of MMPs, including collagenases, gelatinase and neutrophil elastase.

- Oxidized regenerated cellulose/collagen shown only to inhibit gelatinases.

- **Conclusion** – Native biomaterials that are capable of inhibiting both upstream (i.e. collagenases) and downstream (i.e. gelatinases) proteases are more likely to halt collagen proteolysis.

PriMatrix Ag Antimicrobial

Releases Ionic Silver, a broad spectrum antimicrobial to prevent microbial colonization of the graft

- Draining wounds
- Colonized wounds
- Wounds that have previously failed bioactive tissue therapies

*Reduction in colonization or microbial growth on the device has not been shown to correlate with a reduction in infections in patients. Clinical studies to evaluate reduction in infection have not been performed.*
Purified Collagen Matrix with PHMB

The first and only purified collagen matrix plus PHMB antimicrobial

- Purified Type 1 collagen matrix coated with broad-spectrum antimicrobial PHMB\(^1\)\(^a\)

- Acute and chronic wound management across a variety of wound types\(^1\)

\(^a\)PHMB = polyhexamethylenebiguanide hydrochloride

PHMB: mechanism of action

- Interacts with negatively charged phospholipids in the bacterial membrane (leading to disruption)
- Inhibits bacterial cell metabolism
- Shown to effectively remove biofilm through blocking microbial attachments to surfaces
- Binds to cellular surfaces for sustained effect over hours

**In vitro scientific data**¹

PHMB Antimicrobial effectively inhibited microorganisms¹

<table>
<thead>
<tr>
<th>Microorganism</th>
<th>Data on file. Organogenesis, Inc.</th>
<th>Zone of inhibition test demonstrated efficacy in vitro</th>
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</thead>
<tbody>
<tr>
<td><strong>Aspergillus niger</strong>ᵃ</td>
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<tr>
<td><strong>Candida albicans</strong>ᵃ</td>
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<td><strong>Staphylococcus aureus</strong>ᵃ</td>
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<td><strong>MRSA</strong>ᵇ</td>
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<td><strong>Pseudomonas aeruginosa</strong>ᵃ</td>
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<td><strong>Escherichia coli</strong>ᵃ</td>
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</table>

¹ United States Pharmacopeia Antimicrobial Effectiveness Test showed reduced concentrations at days 7, 14, and 28

ᵃ Zone of inhibition test demonstrated efficacy in vitro
Preclinical partial thickness wound model

Natural Collagen with PHMB Antimicrobial demonstrated greater reduction in MRSA vs other products

Bioburden Based Wound Management!
CASE PRESENTATIONS
• 67-year-old African American male presented with a pressure ulcer on the left heel at the site of a previously closed wound—likely due to shearing in a Crow Boot while walking on prosthesis on the right.
• Wound present for 2 months and was previously treated with negative pressure wound therapy (NPWT)
• PMH: includes diabetes, peripheral vascular disease, hypertension, neuropathy, gout, ESRD, hyperlipidemia, anemia, osteomyelitis (right heel)
• Surgical history includes partial calcanectomy bilaterally
• (May 6, 2014), right BKA (May 9, 2014), and surgical resection of left heel (May 13, 2014)
Pressure Ulcer (heel) closed after 9 applications

Before

After
PuraPly Antimicrobial Initiated

Week 1

Wound with significant slough, devitalized tissue and edema.

Pre-debridement
Date: 6/29/15
Wound Size: 4.0 x 4.5 x 0.2 cm
Wound Area: 18.0 cm²

Wound Bed Prep: Sharp debridement
Primary Dressings: Restore
Secondary Dressings: Calcium alginate, Kling, Ace
Off-loading: Total contact cast (TCC)
Reduction in wound size with increased granulation tissue.

Pre-debridement
Date: 7/6/15
Wound Size: 3.7 x 4.2 x 0.2 cm
Wound Area: 15.54 cm²

Wound Bed Prep: Sharp debridement
Primary Dressings: Restore
Secondary Dressings: Calcium alginate, Kling, Ace
Off-loading: TCC
3rd Application

Week 3

Continued reduction in wound size—despite complete wound dressing change during the prior week.

Pre-debridement

Date: 7/13/15

Wound Size: 2.4 x 4.0 x 0.2 cm

Wound Area: 9.6 cm²

Wound Bed Prep: Sharp debridement
Primary Dressings: Restore
Secondary Dressings: Calcium alginate, Kling, Ace
Off-loading: TCC
Continued reduction in wound size.

**Pre-debridement**

**Date:** 7/20/15  
**Wound Size:** 2.3 x 4.0 x 0.2 cm  
**Wound Area:** 9.3 cm²

**Wound Bed Prep:** Sharp debridement  
**Primary Dressings:** Restore  
**Secondary Dressings:** Calcium alginate, Kling, Ace  
**Off-loading:** TCC
5th Application

Week 5

Continued reduction in wound size with some peri-wound maceration; additional nursing visits added to manage drainage.

Pre-debridement
Date: 7/27/15
Wound Size: 2.1 x 3.3 x 0.1 cm
Wound Area: 6.93 cm²

Wound Bed Prep: Sharp debridement
Primary Dressings: Restore
Secondary Dressings: Calcium alginate, Kling, Ace
Off-loading: TCC
6th Application

Week 6

Continued reduction in wound size and maceration improved.

Pre-debridement

Date: 8/3/15

Wound Size: 1.4 x 3.0 x 0.1 cm
Wound Area: 4.2 cm²

Wound Bed Prep: Sharp debridement
Primary Dressings: Restore
Secondary Dressings: Calcium alginate, Kling, Ace
Off-loading: TCC
7th Application
Week 7

Continued reduction in wound size.

Pre-debridement
Date: 8/10/15
Wound Size: 1.2 x 2.5 x 0.1 cm
Wound Area: 3.0 cm²

Wound Bed Prep: Sharp debridement
Primary Dressings: Restore
Secondary Dressings: Calcium alginate, Kling, Ace
Off-loading: TCC
8th Application

Week 8

Continued reduction in wound size with no signs of peri-wound maceration.

Pre-debridement
Date: 8/17/15
Wound Size: 0.7 x 2.1 x 0.1 cm
Wound Area: 1.47 cm²

Wound Bed Prep: Sharp debridement
Primary Dressings: Restore
Secondary Dressings: Calcium alginate, Kling, Ace
Off-loading: TCC
9th Application
Week 9

Continued reduction in wound size.

Pre-debridement
Date: 8/24/15
Wound Size: 0.2 x 0.7 x 0.1 cm
Wound Area: 0.14 cm²

Wound Bed Prep: Sharp debridement
Primary Dressings: Restore
Secondary Dressings: Calcium alginate, Kling, Ace
Off-loading: TCC
Wound Closed

Week 10

Patient received 9 Applications of PuraPly Antimicrobial.

Complete Wound Closure
Date: 8/31/15
Wound Size: closed

Wound Healed: Offloading continued
Off-loading: TCC
• 59 y/o female with a history of a puncture wound and subsequent ulceration sub 5th metatarsal wound which extends dorsally to a dorsal wound
• PMH: PAD, Peripheral neuropathy

Prior to first application
After 1st application
SH 01/04/16

Plantar

Dorsal

After 2\textsuperscript{nd} Application
After 3\textsuperscript{rd} Application
SUMMARY

• All wounds have some level of bioburden\textsuperscript{1}

• 90\% of chronic wounds have biofilm\textsuperscript{2}

• Excessive bioburden can adversely affect tissue repair and delay healing\textsuperscript{1,3}

• Excess protease activity in chronic wounds degrade the collagen matrix thereby inhibiting healing\textsuperscript{4}

SUMMARY

• A new paradigm that adds the management of biofilm and suppression of bioburden to pre-existing standard modalities

• Staged wound healing
  • Appropriate offloading
  • Wound bed preparation
  • Progression to closure