Biofilm-based wound care with cadexomer iodine

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Introduction

Evidence suggests that biofilms are present in most, if not all, chronic, non-healing wounds with a recent *in vivo* study suggesting prevalence could be at least 78% (Malone et al, 2017a). This Made Easy informs clinicians about the role of cadexomer iodine, an effective antimicrobial dressing, as an early intervention within the T.I.M.E (Schultz, 2003) continuum of wound bed preparation.

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Wound bed preparation

Standard of care in wound management from the late 1990s has regarded wound bed preparation (WBP) as best practice. The T.I.M.E (Schultz, 2003) continuum provides a framework for WBP with T standing for tissue, understanding non-viable and unhealthy tissue should be removed. I is for inflammation and infection, with the practitioner identifying and managing both, M is for moisture management, keeping the balance of moisture for assisting replication and migration of healing cells and concluding with the E, which is for the edge of wound, keeping the wound edges clean, moist and attached for optimal healing. Biofilm-based wound care was coined by Wolcott et al in 2010 and encompasses the principles of WBP, but emphasises the following principles:

- **Cleansing, debridement and cleansing again with antiseptics**
- **Debridement that is aggressive in opening up tunnels and treating with one or multiple types of debridement**
- **Application of topical antimicrobials with proven anti-biofilm efficacy post-debridement**
- **Systemic antibiotics that are appropriate to the type and length of treatment.**

Biofilm: the hidden barrier to healing

A biofilm is a cluster of bacteria that reside within a matrix that offers protection from host defences and antimicrobials (Box 1). A biofilm forms with attachment of single planktonic bacteria (free-floating) within a protective matrix (extracellular polymeric substance [EPS]) (Stoodley et al, 2002; Burmølle et al, 2010; Flemming et al, 2010), which creates coherent clusters of cells (Stoodley et al, 2002). A growing consensus is that a non-healing wound status is the best indicator of biofilm presence (Malone et al, 2017a).

Biofilms delay healing by causing a chronic immune response, which in turn leads to a chronic cycle of inflammation and tissue damage produced by elevated levels of proteases and reactive oxygen species (ROS) (Costerton et al, 1999; Bjarnsholt et al, 2008). Biofilms are persistent and prone to reformation because:

- **The EPS of the biofilm matrix protects bacteria within it against systemic antibiotics or topical antiseptics**
- **Many of the bacteria in biofilms are metabolically dormant, which may result in tolerance to antibiotics**
- **Many antimicrobial agents can be neutralized by the biofilm's EPS components, even if they penetrate the matrix (Bianchi et al, 2016; Schultz et al, 2017).**

Box 1: Mechanisms of bacteria and biofilm

Microorganisms are commonly perceived to be free-floating and solitary, also known as planktonic. However, bacteria rarely present as single cells. In the air, on water, on surfaces including skin and our entire human microbiome, bacteria are present as aggregates. Many different types of bacteria are commonly found on the skin of healthy people. When these bacteria aggregate and become embedded within the wound they become sessile (immobile). In the early stages, this is reversible and the body's natural immune response can eradicate the bacteria, particularly in acute, vascularized wounds. However, when the immune system is compromised or the effectiveness of antibiotics and wound care treatments are reduced, the environment can favour development of biofilm.

Biofilm detection, diagnosis and treatment

The microorganisms within biofilms are microscopic structures, rendering them impossible to see with the naked eye. When the wound is not responding to 'optimal care', the best indicator of the presence of a biofilm is non-healing. All wounds that are determined healable and non-malignant but exhibit delayed healing despite optimal care in the context of the specific patient – including appropriate management of host factors – should be regarded as having biofilm present (Bianchi et al, 2016; Schultz et al, 2017). Currently, no routine method of identification or detection can discriminate between planktonic and biofilm-growing bacteria or identify organisms responsible for delayed healing; however, various clinical features have been proposed as surrogate markers:

- **Failure of a wound to respond to appropriate systemic antibiotics or antiseptics (i.e. with selection guided by culture), since biofilm bacteria are inherently tolerant to both, unlike planktonic bacteria phenotypes**
- **Recurring inflammation/infection in the wound and an increased level of exudate related to this inflammation**
- **Presence of gelatinous material on the wound that reforms quickly after its removal, possibly a down stream product of biofilm presence (Schultz et al, 2017).**

Since the presence of biofilm is very different from planktonic (acute) infection, clinicians must understand that protocols based on planktonic infections are not effective in the treatment of chronic, non-healing wounds where biofilm is suspected or present. Sustained action that effectively disrupts and kills biofilm bacteria and reduces inflammation is required to promote healing. An antimicrobial must be able to penetrate the EPS, attack the bacteria within the protective matrix (Stoodley et al, 2002), and provide sustained action that prevents the biofilm from reforming (Kirketerp-Moller et al, 2008; Fazli et al, 2009).

Antimicrobial agents and biofilm: research and evidence

Many claims relating to reduction or total killing of biofilm bacteria are based on evidence from *in vitro* studies (i.e. in a controlled environment outside of a living organism); however, an over-reliance on *in vitro* research can lead to results with limited practical relevance. Other evidence derives from animal models or clinical evaluations; the former tends to be short-term and may not closely replicate low-grade chronic infection, while clinical evaluations (where available) are commonly tested with small patient numbers, lack of control and no clear interventions (Schultz et al, 2017).

A well-designed *in vitro* study that identifies an effective treatment strategy could form the premise for undertaking an appropriate and relevant *in vivo* study. These *in vitro* tests should:

- **Reproduce a chronic wound environment with clinically relevant test conditions – problems may occur with use of immature or young biofilm**
- **Show how biofilm becomes more tolerant to antibiotics/antiseptics at maturation**
- **Show a measurable reduction in biofilm bacteria over a clinically relevant time period (Schultz et al, 2017).**

IODOSORB◊ and biofilm-based wound care within the T.I.M.E (Schultz, 2003) continuum

IODOSORB◊ (Smith & Nephew) is a sterile antimicrobial dressing with cadexomer iodine (Figure 1) that removes barriers to healing. As a dual action wound management product it offers the benefits of a broad-spectrum, antimicrobial agent in combination with desloughing and fluid handling properties making it particularly effective against biofilm (Zhou et al, 2002; Akiyama et al, 2004; Hill et al, 2010; Philips et al, 2015).

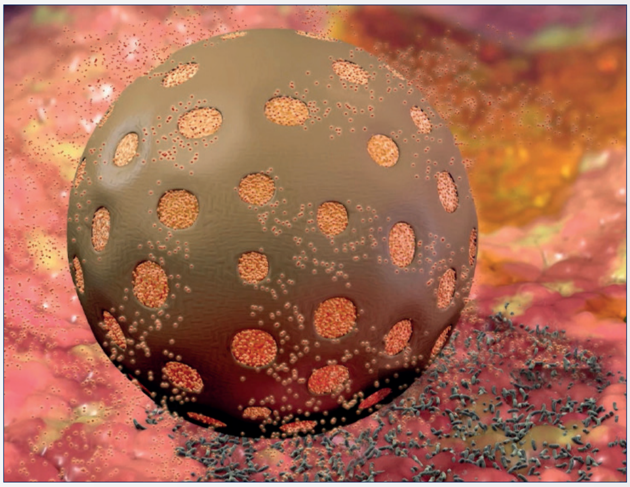


Figure 1 | Key features of IODOSORB◊ cadexomer (Smith & Nephew, 2017a; 2017b)

- **The cadexomer particle is a 3D cross-linked polysaccharide starch matrix**
- **The 0.9% iodine is physically enclosed in the cadexomer matrix and is released into the dressing only when it is in contact with wound fluid.**

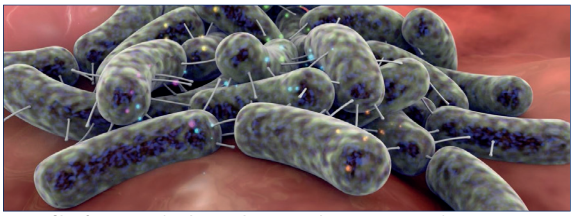
An emerging paradigm for biofilm-based wound care takes the form of a simple step-down approach, following initial aggressive debridement, then step-up to advanced therapies if needed to enhance healing (summarized in Figure 3). The paradigm:

- **Immediate action: Sharp debridement is a key component of removing necrotic, devitalized tissue and the presence of either planktonic or sessile microorganisms. Physical removal of biofilm leaves**

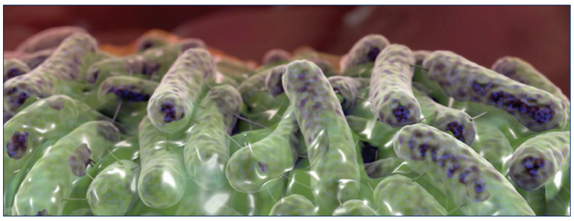
Challenges in biofilm identification

- Best practice techniques for detection (i.e. electron microscopy and confocal laser scanning microscopy) are highly specialized, may not be practical for use in a clinical setting and have limitations (World Union of Wound Healing Societies [WUWHS], 2016)
- Swab sampling methods may not identify biofilm since large amounts can reside in the deeper tissues, while single biopsies are not always successful, since biofilm tends to be distributed heterogeneously across a wound (Figure 2) (WUWHS, 2016)
- Wound biofilm can contain various bacterial species and many may contain multiple pathogens, so the search for specific biomarkers is challenging (Schultz et al, 2017).

Figure 2 | Biofilm formation and delayed wound healing (Smith & Nephew, 2017b)



1. Biofilm formation (early attachment and communication)



2. Mature biofilm (embedded in protective extracellular polymeric substance matrix)

	~Days 1 – 4	~Days 5 – 7	~Weeks 1 – 4	Until healed
Diagnose	Point-of-care diagnostics/ identification of microorganisms			
Assess	Assess inflammation and healing status	Assess inflammation and healing status	Assess inflammation and healing status	
Prepare	Aggressive debridement	Appropriate debridement	Maintenance debridement	
Treat	CONSIDER IODOSORB◊* Empiric topical antiseptics and systemic antibiotics	CONSIDER IODOSORB◊* Optimise topical antiseptics and systemic antibiotics	CONSIDER IODOSORB◊* Re-evaluate topical antiseptics and systemic antibiotics	Standard care
Manage	Management of host factors, such as diabetes, nutrition	Continue management of host factors	Continue management of host factors	Advanced therapies

**For its autolytic debridement and desloughing properties and its proven anti-biofilm efficacy (Phillips et al, 2015, Oates et al, 2016; Schultz and Yang, 2016; Fitzgerald et al, 2017; Malone et al, 2017b)*

Figure 3 | A step-down approach to biofilm treatment

Wound assessment and biofilm identification

1. Assessment of indirect clinical signs and symptoms
2. Biopsy and biofilm lab testing, however these might not be reliable given the non-homogeneous distribution of biofilm on the surface and within the deeper layers of the wound.

Aggressive debridement

Sharp debridement is a crucial and necessary step in the wound bed preparation continuum but it is often not enough to remove all biofilm. Moreover, biofilm is known to reform rapidly following debridement.

Initiate biofilm therapies

The selection of a proven and effective antimicrobial dressings, such as IODOSORB◊, is crucial to remove residual biofilm into the dressing following debridement and also ideal to address biofilm where sharp debridement is not possible.

Maintenance debridement and treatment optimization

Maintenance debridement is an important complementary step. Some dressings (such as cadexomer iodine) can assist autolytic debridement by absorbing slough and debris (Moberg et al, 1983; Ormiston et al, 1985; Lindsay et al, 1986; Holloway et al, 1989; Johnson et al, 1991; Sundberg et al, 1997; Troeng et al, 1997; Hansson et al, 1998) and promote effective wound bed preparation (Skog et al, 1983; Sundberg et al, 1997; Troeng et al, 1997; Holloway et al, 1989).

Step-up to advanced therapies to kick-start healing

Once biofilm has been disrupted and removed the clinician may chose a move to standard care using a non-antimicrobial dressing or ***step-up*** to advanced therapies such as negative wound pressure therapy (e.g. PICO◊) - this can be used in conjunction with dressings that are able to prevent biofilm reformation, e.g. silver dressings.

Figure 4 | Pathway for biofilm treatment using IODOSORB◊ as part of good wound bed preparation practice

it vulnerable to antimicrobials (Wolcott et al, 2010). The use of antimicrobials or antiseptics proven to be effective against biofilms after debridement help to manage residual biofilm and also reformation. The aim of this is to rapidly reduce biofilm levels and subsequently reduce inflammation, ROS and protease activities.

- **Personalization: The use of antimicrobials should be followed by personalized, optimized treatment based on healing status. The wound should be re-evaluated regularly (i.e. weekly) for 2 to 4 weeks until the wound shows signs of improvement (e.g. a reduction in size, exudate levels, pain), at which point treatment can be stepped down to standard of care.**
- **Step-up to advanced therapies: If the wounds does not show evidence of infection (and biofilm has been addressed accordingly), advanced therapies such as negative pressure wound therapy (NPWT) could be applied to the wound to kick start healing (Schultz, 2017).**

Figure 3 shows this systematic approach while Figure 4 proposes a pathway within which IODOSORB might be used as part of the T.I.M.E (Schultz, 2003) WBP continuum.

Why choose IODOSORB?

Mature biofilm exhibit an enhanced tolerance to treatment and this has resulted in a shift towards sharp debridement and adjunctive use of antimicrobial and other anti-biofilm compounds (Dowd et al, 2011).

This biofilm-based wound care approach promotes a multifaceted attack on biofilm (Wolcott et al, 2010) and has been shown to improve the healing trajectory in a large cohort study (Wolcott and Rhoads, 2008). Implementation of personalized, topical therapeutics, guided by molecular diagnosis of bacterial species, resulted in statistically and clinically significant improvements in healing (Dowd et al, 2011).

Clinicians are encouraged to take an initial aggressive approach to treating biofilm: one that is then revised through on-going assessment. This may result in stepping down to standard care or referral to specialist services where advanced therapies may be considered if current treatment is not progressing the wound to healing. Frequent debridement is central to this approach, with physical removal of microbial aggregates being key to opening up a therapeutic 'window' during which the bacteria are most susceptible to antimicrobials, such as IODOSORB (Wolcott et al, 2010).

High absorptive property

IODOSORB's cadexomer micro-beads promote autolytic debridement and desloughing actions (Ormiston et al, 1985; Hansson et al, 1998), and can dehydrate and directly disrupt the biofilm structure (Akiyama et al, 2004).

Antimicrobial 0.9% cadexomer iodine

Once the cadexomer micro-beads have physically disrupted the biofilm matrix, the iodine can then kill the exposed bacteria within the dressing (Johnson, 1991; Akiyama et al, 2004), via sustained availability of iodine (Cooper, 2007; Harrow, 2009; Smith & Nephew, 2009). With its broad-spectrum antimicrobial efficacy (Gottardi, 1991; Smith & Nephew, 2017a), IODOSORB's smart micro-bead technology harnesses the effectiveness of iodine as a broad-spectrum antimicrobial and is available in effective, sustained low concentrations, rather than high and short-burst doses (as with older formulations such as povidone iodine). There have been no reports of acquired resistance with iodine.

Superior to other topical antimicrobials

IODOSORB has comparatively superior results versus topical antimicrobials such as PHMB, silver and povidone iodine (Table 1) *in vitro* and *in vivo*. Silver dressings, in particular, are less effective against biofilm since charged ions are more easily neutralized by the EPS matrix (Stewart et al, 2001), while the concentration of silver needed to eradicate biofilm bacteria is estimated to be 10 to 100 times higher than that needed to eradicate planktonic bacteria (Bjarnsholt et al, 2007). These concentrations are generally not available in a silver dressing.

Scientific and clinical evidence for IODOSORB

Biofilm treatments should be supported by both *in vitro* and *in vivo* tests against mature biofilm. This evidence shows that IODOSORB:

- **Is highly effective in the removal of biofilms (Schultz and Yang, 2016; Fitzgerald et al, 2017)**

Table 1. Comparison of potential biofilm agents based on published evidence.

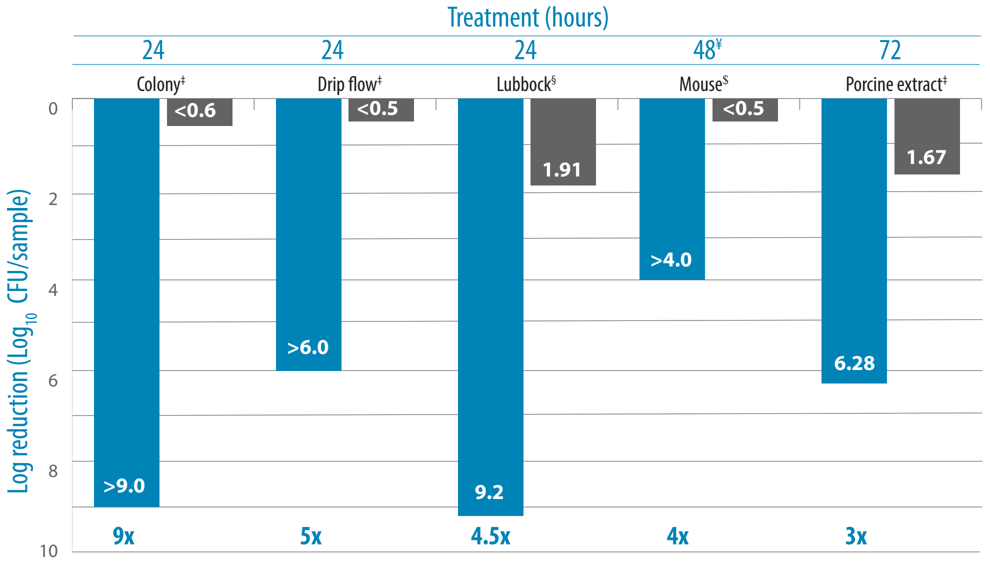
	Silver	Surfactants	Honey	PHMB	Povidone iodine	IODOSORB◊
Non-toxic	✔ In lower concentrations required to kill planktonic microbes	✔ (Kramer et al, 2004; Franz and Vögelin, 2012)	✔ (Du Tout and Page, 2009)	✔ (Müller and Kramer, 2008; Romanelli, 2010)	✖ (Balin and Pratt, 2002; Van den Broek et al, 1982)	✔ (Zhou et al, 2002)
Sustained release for up to 72 hours	Variable reports	✖	✖	✖ (Phillips et al, 2015)	✖ (Harrow, 2009)	✔ (Skog, 1983; Harrow, 2009; Smith & Nephew, 2009)
Modulated release in response to healing	✖	✖	✖	✖	✖ (Harrow, 2009)	✔ (Zhou et al, 2002; Smith & Nephew, 2009)
Mechanical action against biofilm	✖	More evidence required (Yang et al, 2016)	Limited (Cooper et al, 2002; Lu et al, 2004)	✖	✖	✔ (Akiyama et al, 2004)
Antimicrobial efficacy in mature biofilm *in vitro*	✖ High concentration required (Bjarnsholt et al, 2007) currently not available in any known silver-based dressing	✖	Variable reports (Merckoll et al, 2009; Brackman et al, 2013; Phillips et al, 2015)	Limited (Phillips et al, 2015)	Limited (Phillips et al, 2015)	✔ (Phillips et al, 2015, Oates et al, 2016; Schultz and Yang, 2016; Fitzgerald et al, 2017)
Measured biofilm reduction *in vivo* in patients	✖	✖	✖	✖	✖	✔ (Malone et al, 2017b)
Positive Cochrane review	✖ No Cochrane review	✖ No Cochrane review	✖ (Jull et al, 2015)	✖ No Cochrane review	✖ No Cochrane review	✔ (O'Meara et al, 2017)

IODOSORB has been tested and shown to be effective across five challenging and clinically relevant biofilm models*

*Colony (Fitzgerald et al, 2017)
DripFlow (Fitzgerald et al, 2017)
Lubbock (Oates et al, 2016)
Mouse (Fitzgerald et al, 2017)
Porcine extract (Schultz and Yang, 2016)
¥Treatment every 24 hours for 48 hours total.
‡*Staphylococcus aureus* mature biofilms
§Mixed bacterial cultures: *Pseudomonas aeruginosa* PA01, *Staphylococcus aureus* Mu50, and *Enterococcus faecalis* V583.
$MRSA biofilms.

IODOSORB◊ (Smith & Nephew)

Aquacel® Ag+ (ConvaTec)



N.B. Values in **blue** indicate the number of times more effective IODOSORB was demonstrated to be compared to Aquacel Ag+ in that test model.

Figure 5 | Summarized representation of the effect of IODOSORB◊ against *in vitro* and in animal biofilm models

- **Can breach the biofilm's protective matrix and kill the bacteria within the dressing (Zhou et al, 2002; Akiyama et al, 2004; Hill et al, 2010)**
- **Impacts on biofilm populations in patients (Lantis et al, 2016; Malone et al, 2017a).**

In five clinically relevant, challenging biofilm models (Figure 5), IODOSORB was shown to be more effective than a comparative silver dressing in terms of log reduction (Log_{10} CFU/sample) over 24 hours (three models), 48 hours and 72 hours (one model each). Clinically, Malone et al (2017b) showed cadexomer iodine to reduce the microbial load of chronic non-healing diabetic foot ulcers complicated by biofilms. In addition, a Cochrane meta-analysis highlighted the role of cadexomer iodine on a faster rate of healing in venous leg ulcers (VLUs) compared to standard care (O'Meara, 2014). Further analysis of healing data has shown use of IODOSORB can lead to cost savings in treatment of VLUs (Nherera et al, 2016).

Using IODOSORB in practice

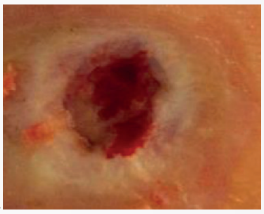
A number of real-life case examples have also explored the use of cadexomer iodine in patients with chronic wounds. An example is provided below of a patient with a diabetic foot ulcer who received IODOSORB (Box 2).

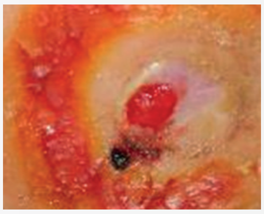
IODOSORB◊: Practical tips

- **Frequency of dressing change: Frequency will depend on the amount of exudate. The dressing will change from brown to yellow/grey when the iodine has been released indicating the time to change. On average, dressings are changed 3 times a week but clinical judgment can dictate frequency based on assessment.**
- **Wound cleansing: Upon dressing removal, clinicians may observe that the dressing is granular with residue on the wound. The wound can be irrigated to remove remaining dressing.**

Box 2. Case study: Patient with a diabetic foot ulcer

1. 

2. 

3. 

1. Pre-debridement
2. Post-debridement
3. +17 days using IODOSORB◊ and total contact casting

Supported by Smith & Nephew. The views expressed in this Made Easy do not necessarily reflect those of Smith & Nephew.

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Summary

A systematic, simple and clear approach to biofilm-based wound care is increasingly important, with biofilm thought to be present in up to 78% of chronic wounds and conflicting evidence often leading to uncertainty in their treatment. IODOSORB is a unique antimicrobial with a dual mode of action, supported by appropriately robust evidence.