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 anti-biofilm 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; Burmelle 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 neutralised by the biofilm’s EPS components, even if they penetrate the matrix (Bianchi et al, 2016; Schultz et al, 2017).**

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.

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, vascularised 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.
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).

**Anti-biofilm agents: 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, slow-release 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).

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 (summarised in Figure 3). The paradigm:

- Immediate action: Sharp debridement is a key component of removing necrotic, devitalised tissue and the presence of either planktonic or sessile biofilm.

**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 only when it is in contact with wound fluid.

**Challenges in biofilm identification**

- Best practice techniques for detection (i.e. electron microscopy and confocal laser scanning microscopy) are highly specialised, 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)
**Figure 3** | A step-down approach to biofilm treatment

<table>
<thead>
<tr>
<th>~Days 1 – 4</th>
<th>~Days 5 – 7</th>
<th>~Weeks 1 – 4</th>
<th>Until healed</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Diagnose</strong></td>
<td>Point-of-care diagnostics/ identification of microorganisms</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Assess</strong></td>
<td>Assess inflammation and healing status</td>
<td>Assess inflammation and healing status</td>
<td>Assess inflammation and healing status</td>
</tr>
<tr>
<td><strong>Prepare</strong></td>
<td>Aggressive debridement</td>
<td>Appropriate debridement</td>
<td>Maintenance debridement</td>
</tr>
<tr>
<td><strong>Treat</strong></td>
<td>CONSIDER IODOSORB◊ Empiric topical antibiotics and systemic antibiotics</td>
<td>CONSIDER IODOSORB◊ Optimise topical antibiotics and systemic antibiotics</td>
<td>CONSIDER IODOSORB◊ Re-evaluate topical antibiotics and systemic antibiotics</td>
</tr>
<tr>
<td><strong>Manage</strong></td>
<td>Management of host factors, such as diabetes, nutrition</td>
<td>Continue management of host factors</td>
<td>Continue management of host factors</td>
</tr>
</tbody>
</table>


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

- **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 anti-biofilm treatment, such as IODOSORB◊, is crucial to remove residual biofilm following debridement and also ideal to address biofilm where sharp debridement is not possible.

- **Maintenance debridement and treatment optimisation**
  Maintenance debridement is an important complementary step. Some dressings (such as cadexomer iodine) can also promote autolytic debridement throughout application and promote effective wound bed preparation.

- **Step-up to advanced therapies to kick-start healing**
  Once biofilm has been disrupted and removed the clinician may choose 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-based dressing, such as ACTICOAT◊).

- **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 address accordingly, advanced therapies such as negative pressure wound therapy (NPWT) could be applied to the wound to kick start healing.

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

**Microorganisms.** Physical removal of biofilm leaves 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.

- **Personalisation:** The use of antimicrobials should be followed by personalised, optimised 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.
improve the healing trajectory in a large cohort study. Implementation of personalised, 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 (Johnson, 1991; Akiyama et al, 2004) within the biofilm community, via sustained, gentle release 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 delivers it 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 neutralised 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)

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

<table>
<thead>
<tr>
<th>Feature</th>
<th>Silver</th>
<th>Surfactants</th>
<th>Honey</th>
<th>PHMB</th>
<th>Povidone iodine</th>
<th>IODOSORB†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-toxic</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
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<tr>
<td>Sustained release for up to 72 hours</td>
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<tr>
<td>Modulated release in response to healing</td>
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<tr>
<td>Mechanical action against biofilm</td>
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<tr>
<td>Antimicrobial efficacy in mature biofilm in vitro</td>
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<tr>
<td>Measured biofilm reduction in vivo in patients</td>
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<tr>
<td>Positive Cochrane review</td>
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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)
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).

**Biofilm efficacy across multiple models***

<table>
<thead>
<tr>
<th>Treatment (hours)</th>
<th>Model 1†</th>
<th>Model 2‡</th>
<th>Model 3§</th>
<th>Model 4§</th>
<th>Model 5‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>24</td>
<td>24</td>
<td>24</td>
<td>48¥</td>
<td>72*</td>
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</tr>
</tbody>
</table>

*Model 1: Colony (Fitzgerald et al, 2017)
Model 2: DripFlow (Fitzgerald et al, 2017)
Model 3: Lubbock (Oates et al, 2016)
Model 4: Mouse (Fitzgerald et al, 2017)
Model 5: Porcine explant (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

<table>
<thead>
<tr>
<th>Log reduction (Log10 CFU/sample)</th>
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<tr>
<td>0</td>
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<tr>
<td>2</td>
</tr>
<tr>
<td>4</td>
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<tr>
<td>6</td>
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<tr>
<td>8</td>
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<tr>
<td>10</td>
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**IODOSORB®:**

**Practical tips**

- Can breach the biofilm’s protective matrix and kill the bacteria within (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 (Log10 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).

**Box 2. Case Study: Patient with a diabetic foot ulcer**

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

**Figure 5** Summarised representation of the efficacy of IODOSORB® in five clinically relevant, challenging biofilm models
References


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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 an intrinsic anti-biofilm, dual mode of action that meets all the criteria of an effective biofilm agent, with appropriately robust evidence to support effectiveness claims versus alternative options.

Available from: www.woundsinternational.com