A route to more effective infection management: The Infection Management Pathway

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Local infection and biofilm management continue to be clinical challenges faced by clinicians caring for people with wounds. It is well-established that management and treatment of local infection and biofilm require different approaches. The innate immune response, which can successfully attack free-living bacteria, has been shown to have limited efficacy against biofilm communities, which provides challenges for resolving chronic infections caused by biofilm communities. While there is increasing recognition of the different nature of biofilm and local infection with results of an international survey identifying that although more than 50% of clinicians differentiate between local infection and biofilm in diagnosis – only 40% manage the wounds differently in practice. It is proposed that a comprehensive, succinct, expert-endorsed, evidence-based pathway can assist clinicians in the translation of evidence into daily practice. The Infection Management (IM) Pathway is one of the first tools that combines the diagnosis and treatment of local infection and biofilm, and offers a means to achieve a consistent approach.

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At its foundation, local infection is caused by microbial proliferation that overwhelms the host response and has the potential to cause tissue destruction. Local infection is triggered by the planktonic form of bacteria — these are single, free-floating, fast-growing organisms that, if not managed effectively locally, can spread systemically with an increased risk of morbidity and mortality. As bacteria colonise the wound bed and begin to attach, biofilms of poly-microbial organisms develop and embed in an extracellular matrix of proteins and sugars, which offers protection and tolerance from host defences and antimicrobials (Schultz et al, 2017).

The differences between planktonic bacteria and biofilm-based bacterial communities result in varying clinical challenges that require different treatment interventions. Biofilm-based wound care (BBWC) differs from local infection management in its aggressive step-down/step-up approach of multiple therapies to address underlying aetiologies and bacterial burden (Schultz et al, 2017).

While there is an evidence base that supports multiple diagnostic approaches of local infection and biofilm, a large percentage of chronic wounds lack proper assessment (Guest et al, 2015). Lack of a comprehensive patient and wound assessment leads to inappropriate diagnosis and care. Correct, prompt initial diagnosis of infection can save time, reduce infection escalation and prevent incorrect treatment use and costly interventions. Failing to intervene early with appropriate antimicrobial treatment can lead to more serious progression of infection; for example, nearly a quarter of patients with venous leg ulcers (23%) develop systemic infection (Guest et al, 2018a), and 17% of patients with infected diabetic foot ulcers ultimately require amputation (Guest et al, 2018b). The average management costs are three times higher for infected wounds than for non-infected wounds, so early identification and management of infection is clinically and economically beneficial (Guest et al, 2018a; 2018b).

INTERNATIONAL SURVEY: IDENTIFYING CLINICAL CHALLENGES

In an effort to better understand the challenges of clinicians globally, an international survey was conducted to investigate how local infection and suspected biofilm are diagnosed and managed. The survey built on work conducted by Swanson et al (2017), who identified a continuing need to

educate and increase clinical knowledge in the recognition and treatment of biofilm and the efficacy of antimicrobial treatments.

The survey was conducted in February 2020, and data were collected from 418 respondents. There was a completion rate of 82% and data from all participants were included in the analysis, irrespective of whether they answered all the questions. Most respondents came from Australia/New Zealand, Europe or North America; these three regions amounted to approximately 77% of all responses. Of the respondents, just under 75% were nurses (including specialist wound care nurses, community nurses and hospital nurses), 7% were doctors and 3.5% were surgeons. The remainder of the responders were a mix of podiatrists and academics. Based on their job role, the responders were grouped into "wound care specialists" (71.6%) and "non-wound care specialists" (28.4%). Respondents reported treating a range of wound types, including arterial ulcers, venous leg ulcers, pressure ulcers, diabetic foot ulcers and surgical dehisced wounds.

A total of 360 respondents (86%) specified that the three biggest challenges in their day-to-day practice related to accurate diagnosis of wound infection were:

1. Distinguishing between local infection and biofilm
2. Selecting the right treatment according to diagnosis
3. Fear of rapid deterioration due to systemic and spreading infection *[Figure 1]*.

1. Distinguishing between local infection and biofilm

A large proportion of responders (67%; *n*=201/300) answered that they could differentiate between biofilm and local infection. A third (33%) either did not distinguish or did not know the different clinical presentations of local infection and biofilm. Three quarters (75%) of the total responders (*n*=230/306) followed a standardised pathway for local infection diagnosis *[Figure 2]*.

2. Treatment decision-making

Although 67% of clinicians could differentiate between local infection and biofilm in diagnosis – only 40% manage wounds differently and

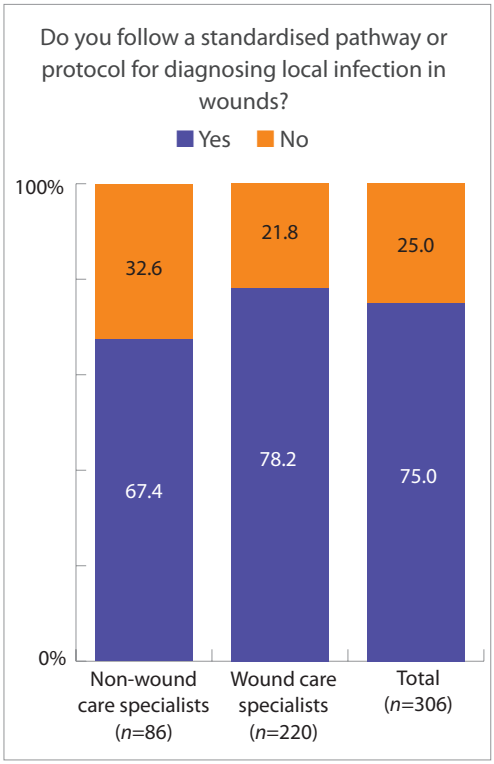


Figure 2. % of responders who do and do not use a protocol or pathway for the diagnosis of local infection in wounds.

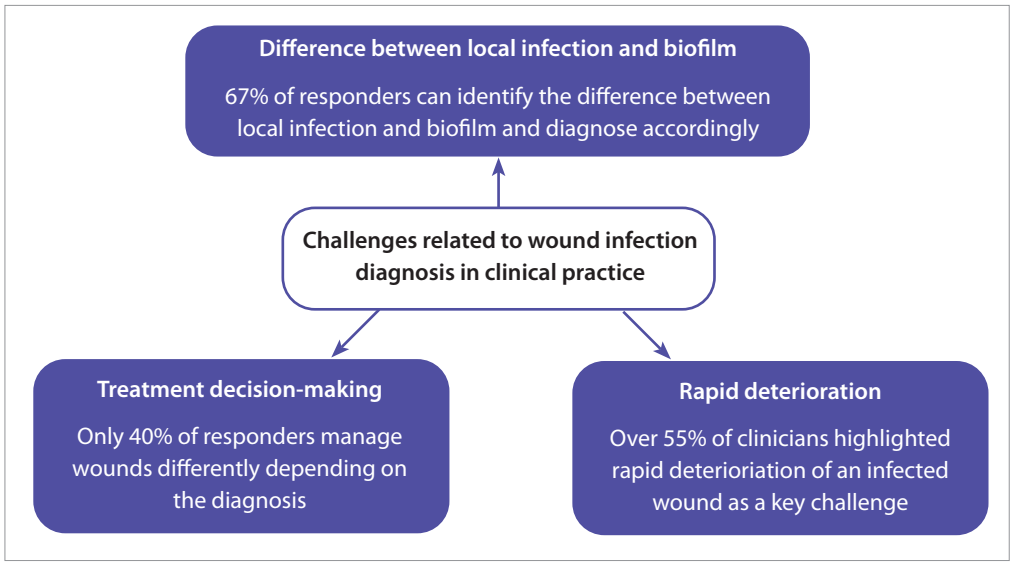


Figure 1. Challenges clinicians face in relation to infection diagnosis and management identified in an international survey.

followed a biofilm-specific pathway (*n*=119/298) *[Figure 3]*.

Of the 60% of responders who did not follow a biofilm-specific pathway for management (*n*=180), 70% were non-wound care specialists and 56.5% were wound care specialists (*p*=0.041), suggesting that non-specialists require support in the management of biofilm.

The most frequently used antimicrobial agents among responders were silver, polyhexamethylene biguanide (PHMB) and iodine. For managing local infection and resolution of the clinical signs of infection, silver (74.5%), iodine (47.1%) and PHMB (28.8%) were most frequently used *[Figure 4a]*. The most regularly used antimicrobial agents for managing suspected biofilm were silver (46.6%), PHMB (36.3%) and iodine (31.2%) *[Figure 4b]*.

Considering that biofilm-based communities are estimated to be present in 78% of wounds (Malone et al, 2017), there was low use of a biofilm-specific protocol in the survey (40%). The results also suggest that iodine is currently under-used in biofilm management, despite the strong evidence for the use of cadexomer iodine for the management of biofilm (Akiyama et al, 2004; Hill et al, 2010; Phillips et al, 2015; Malone et al, 2017; Fitzgerald et al, 2017; Roche, 2019; Schwarzer et al, 2020).

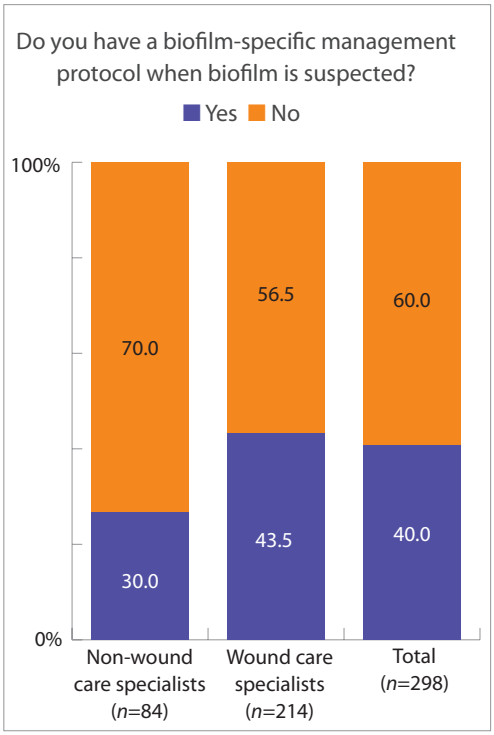


Figure 3. % of responders who do and do not use a biofilm-specific management pathway when biofilm is suspected.

3. Rapid deterioration of the patient and wound

Clinicians need to balance effective management of local infection and biofilm with concerns over inappropriate antimicrobial use and rapid deterioration of the wound; over 55% of clinicians highlighted rapid deterioration of an infected wound as a key challenge in the survey.

ROLE OF PATHWAYS TO SUPPORT CLINICAL DECISION MAKING

Perceived or actual knowledge deficits are an opportunity for pathways to facilitate best practice and enhance clinical confidence and skill in assessment, diagnosis and management of wounds (Blackburn et al, 2019). Responders (*n*=318) indicated that a new pathway that differentiates between local infection and biofilm would be useful for clinical practice if it was:

- Supported by international guidelines and evidence (73.2%)
- Endorsed by wound experts (53.0%)
- Applicable to local practice (55.6%).

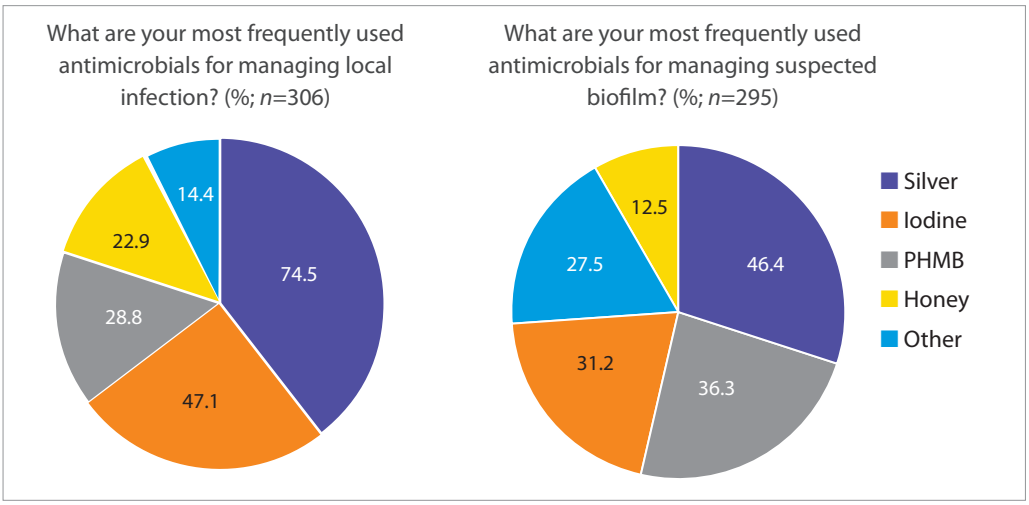


Figure 4. Most frequently used antimicrobials used by clinicians for (a) local infection (b) suspected biofilm.

DEVELOPMENT OF THE INFECTION MANAGEMENT PATHWAY

Based on the results of the international survey, the process of developing an Infection Management (IM) Pathway was commenced. An international multidisciplinary expert panel convened with the aim to simplify local and biofilm infection differentiation and diagnosis and to direct the clinician to appropriate management and antimicrobial selection. The IM Pathway is designed to provide a simple, easy-to-use guidance tool for clinical practice *[Figure 5]*. Other aims of the IM Pathway are to:

1. Promote comprehensive assessment of patients and their wounds with signs and symptoms of local infection or suspected biofilm
2. Guide management of patients and their wounds with local infection or suspected biofilm
3. Simplify clinical decision making and facilitate best practice among non-wound care specialists
4. Increase continuity and consistency in care
5. Encourage and support antimicrobial stewardship practices.

IM PATHWAY: EVIDENCE BASE

The cornerstone of evidence-based practice is the integration of high-quality research evidence into clinical-decision making (Moore et al, 2019).

Comprehensive assessment

Accurate and ongoing patient and wound assessment are the foundation of an effective wound management strategy (Edwards et al, 2018), and provides a common vocabulary to aid communication between clinicians around the status of all wounds. Given the importance of performing a holistic patient assessment and involving a multidisciplinary team as appropriate, the pathway guides the clinician to assess and regularly reassess the patient and their wound using the 'ABCD and E' approach developed by Moore et al (2019).

Clinical signs and symptoms of infection

The IM Pathway builds on the work by the European Wound Management Association (2006), International Wound Infection Institute (2016) and Schultz et al (2017) who defined the clinical presentations of suspected biofilm and overt (classic) wound infection. It is important to note that no single sign or symptom can reliably confirm the presence of infection, and those with immunosuppression or poor tissue perfusion may not exhibit signs and symptoms of clinical infection. The pathway also recognises that clinicians need to identify the spreading and systemic signs of infection and take action fast.

Infection management

The management plan following assessment is based on the patient and their concerns, treatment of the underlying conditions, local wound management and wound bed preparation (Dowsett, 2013). The IM Pathway incorporates the evidence that supports judicious use of effective topical antimicrobials, such as nanocrystalline silver (NCS; ACTICOAT®) and cadexomer iodine (IODOSORB®), alongside antibiotics within an antimicrobial stewardship approach. The antimicrobial stewardship approach includes:

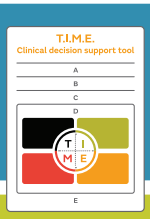
- Hand hygiene and improved infection prevention and control (Uchil et al, 2014).
- Identification of individualised patient need, i.e. not using antimicrobials prophylactically unless the patient is high-risk or it is indicated (Ayello et al, 2012).
- Early intervention with an effective antimicrobial agent.
- Reservation of antibiotics for spreading and systemic infections, i.e. targeting local infection with effective antimicrobial dressings as part of an infection management protocol has been shown to reduce antibiotic use and related resistance (Fong et al, 2005; Tonkin and Wood, 2005; Strand et al, 2010; Ayello et al, 2012; Glik et al, 2018).
- Appropriate duration of antimicrobial treatment following the two-week challenge (Ayello et al, 2012).

Silver and local infection management

Silver dressings (such as NCS) are one of the most popular treatment modalities to manage local infection, as confirmed by the survey results *[Figure 4a]*. Silver has been demonstrated to be effective in reducing wound bioburden, treating local infection and preventing systemic bacterial spread (Ayello et al, 2012). Silver ions (Ag^+) have broad-spectrum antimicrobial activity against bacteria, fungi and viruses and can rapidly kill microorganisms (Woodmansey and Roberts, 2018). Silver may also prevent biofilm re-formation by reducing the number of planktonic bacteria (Driffield et al, 2007). Silver is now available in a variety of forms, such as mesh, foam, alginates and creams, and can be found added to many types of commonly used dressings.

A route to more effective infection management

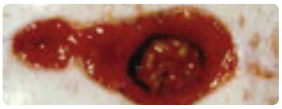
Improve patient outcomes[1] with accurate decision making, a fast response and effective treatment choices



Start with following steps to undertake a comprehensive assessment[2]

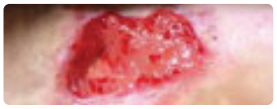
- **A** **Assess** patient, wellbeing and wound
- **B** **Bring in** a multi-disciplinary team and informal carers to promote holistic patient assessment
- **C** **Control** and treat the underlying causes and barriers to wound healing
- **D** **Decide** appropriate treatment
- **E** **Evaluate** and reassess the treatment and wound management outcomes

What clinical signs and symptoms of infection are present?



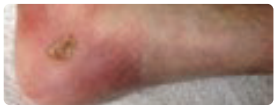
Biofilm[1,3-5]

- Antibiotic/antimicrobial treatment failure
- Recurrence of delayed healing on cessation of antibiotic treatment
- Delayed healing despite optimal wound/patient management
- Low level chronic inflammation
- Low level erythema
- Friable granulation
- Covert (subtle) signs of infection



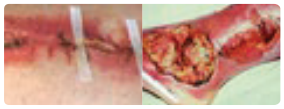
Covert (subtle)[1,3]

- Delayed wound healing
- Serous drainage with concurrent inflammation
- Hypergranulation
- Bleeding, friable granulation
- Epithelial bridging and pocketing in granulation tissue
- Wound breakdown & enlargement
- New or increasing pain
- Increasing malodour



Overt (classic)[1,3]

- Erythema
- Warmth
- Oedema/swelling
- Purulent discharge
- Pain
- Increasing malodour
- Delayed wound healing



Spreading or systemic infection[1,3]

- Spreading erythema, warmth
- May include cellulitis, crepitus
- Wound breakdown/dehiscence with or without satellite lesions
- Malaise/lethargy
- Loss of appetite
- Systemic inflammatory response
- Sepsis
- Organ dysfunction

Biofilm based wound care[4,5]

1. Repeated aggressive debridement and cleanse† as per local protocol
2. Manage suspected biofilm with **IODOSORB**◊ 0.9% Cadexomer Iodine Ointment / **IODOFLEX**◊ Cadexomer Iodine Dressing[7-9Ω]
3. Reassess at regular intervals as per local protocol and appropriate antimicrobials use. **Two weeks' minimum treatment – may need longer than overt local infection treatment due to persistent nature of biofilms**

Local wound infection management[1,3,6]

1. Debride and cleanse† as per local protocol
2. Manage local bioburden and infection with **ACTICOAT**◊ [10‡] Antimicrobial Barrier Dressing
3. Reassess at regular intervals as per local protocol and following **the two-week challenge principles[6]**

Spreading or systemic infection management

- Refer to appropriate specialist
- Tissue sample for culture and sensitivity
- Systemic antibiotics per local protocol

Have signs and symptoms of biofilm / covert infection resolved?

Yes

No

Conduct comprehensive reassessment using the A B C D E approach, manage host factors and refer to an appropriate specialist

Have signs and symptoms of local infection resolved?

No

Yes

Is the wound still stalled?

Yes – suspect biofilm

No

Use standard wound care (i.e. non-antimicrobial dressings) or advanced therapies until healing (follow local protocol)[5]

TWO-WEEK CHALLENGE[1,6∞]

Antimicrobial dressings are recommended to be used for a minimum of two weeks' duration. After two weeks, re-evaluate and either:

1. discontinue if signs and symptoms of infection have resolved,
2. continue with antimicrobial if wound is progressing but there are still signs and symptoms, or
3. consider an alternative antimicrobial and refer to an appropriate specialist if no improvement.

* No one sign or symptom can reliably confirm the presence of infection, and those with immunosuppression may not exhibit signs and symptoms of clinical infection.
† Cleanse wound and periwound skin thoroughly. Should an antiseptic cleanser be selected, the product's Instructions for Use (IFU) and soak time should be followed.
‡ Consider the use of **DURAFIBER**◊ **Ag Silver Gelling Fibre Dressing** for deep infected wounds.
Ω Unless iodine contraindicated.
∞ For very-high risk patients and wounds (e.g. osteomyelitis), it may be appropriate to use antimicrobial treatment for longer than the two-week challenge.

For detailed product information, including indications for use, contraindications, precautions and warnings, please consult the product's Instructions for Use (IFU).

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Photographs (from left to right) courtesy of Kerlyn Carville, Kevin Woo, and Henri Post.

Figure 5. The Infection Management Pathway.

NCS antimicrobial dressings have a unique nanocrystalline silver structure that provides increased silver surface area, allowing rapid and sustained availability of bactericidal levels of Ag^+ ions. This sustained availability provides continuous replenishment of silver to overcome neutralisation of Ag^+ ions due to exudate and other proteins in the wound, whilst supporting rapid and sustained antimicrobial activity and successful clinical outcomes (Woodmansey and Roberts, 2018).

After 2 weeks of use, NCS dressings have been shown to reduce the clinical signs of infection in 60% of chronic wounds – leading to reduced healing time and reduced number of dressing changes (Gago et al, 2008). Further analysis of the data found NCS dressings were not only the most clinically effective (in terms of resolution of infection), but also the least costly of three silver dressings evaluated (Searle and Bielby, 2010). In addition, early intervention with NCS dressings as part of a care bundle in wounds can help minimise progression of local infection to more serious systemic issues. Newton (2010) showed a reduction in wound-related methicillin-resistant *Staphylococcus aureus* (MRSA) bacteraemia cases following introduction of an NCS dressing-containing care bundle to manage MRSA contamination of wounds. Therefore, using NCS dressings for a short 2-week period following the two-week challenge principles illustrates that rapid effective intervention leads to positive clinical and economic outcomes and identifies that antimicrobials need only be used for a short amount of time (Ayello et al, 2012).

Silver and biofilm

Whereas silver dressings are an effective antiseptic in the management and treatment of local infection, they are less effective against biofilm since charged ions are more easily neutralised by the extracellular polymeric substances (EPS) matrix (Stewart et al, 2001).

The bactericidal concentration of silver required to eradicate the bacterial biofilm is 10–100 times higher than that used to eradicate planktonic bacteria in local infection, and the concentration of silver in currently available wound dressings is too low for the treatment of chronic biofilm wounds (Bjarnsholt et al, 2007). Despite this, silver is still popular in the management of suspected biofilm as identified in the international survey – 31% of responders use silver in the management of biofilm *[Figure 4b]*, supporting the aims of the IM Pathway to guide differential management for suspected biofilm and local infection.

Topical wound antimicrobials vary widely in their ability to kill microorganisms within a mature biofilm and their efficacy is influenced by time of exposure, number of applications, moisture level and agent formulation (Phillips et al, 2015). *In vitro* biofilm models have elucidated that the physiology and structure of biofilm define its ability to withstand many topical antimicrobial treatments *[Box 1]*.

Antimicrobial failure and recurrence of delayed healing on cessation of antimicrobial treatment are therefore well-established clinical indicators of the presence of biofilm (Schultz et al, 2017) and indicate that a different management approach is required.

Biofilm based wound care (BBWC)

Due to the challenges of biofilm, treatment approaches should be altered to effectively disrupt protective coating and kill associated microbes. This growing understanding combined with the evidence linking biofilm to delayed healing has led to the introduction of BBWC as a multi-faceted, step-down/step-up approach (*[Figure 6]*; Malone and Swanson, 2017; Schultz et al, 2017).

BBWC incorporates multiple therapies:

- Repeated aggressive debridement to physically disrupt biofilm communities and expose the microorganisms to make them vulnerable to the effects of topical antiseptics and systemic antibiotics (Wolcott et al, 2010; Schultz et al, 2017).
- Cleansing to remove any residual debris and antimicrobial intervention against exposed bacteria and residual biofilm. Antimicrobial wound cleansers with short exposure durations (i.e. 15 minutes) have been shown to remove surface bacteria, but are not necessarily effective at killing biofilms communities unless exposed for 24 hours (Johani et al, 2018).
- Use of an antimicrobial with proven effect against mature biofilms in clinical practice (Schultz et al, 2017).

Iodine is a highly effective topical antimicrobial with a broad spectrum of antimicrobial activity against bacteria, mycobacteria, fungi, protozoa and viruses (McDonnell and Russell, 1999). The two most commonly used iodophors in modern wound dressings are povidone iodine (PVP-I) and cadexomer iodine (IODOSORB®/ IODOFLEX®). The latter format is an antimicrobial dressing/ ointment/powder with cadexomer iodine; 0.9% iodine is physically enclosed in the

Box 1. Key features of biofilm physiology that impact of antimicrobial tolerance.

- Reduced growth/ metabolism - most antibiotic agents act on metabolic pathways in active bacterial cells. Therefore, in the case of slow-growing or dominant microorganisms, antibiotics can be less effective.
- The extracellular polymeric substance matrix encapsulates and protects the biofilm microorganisms from antimicrobials.

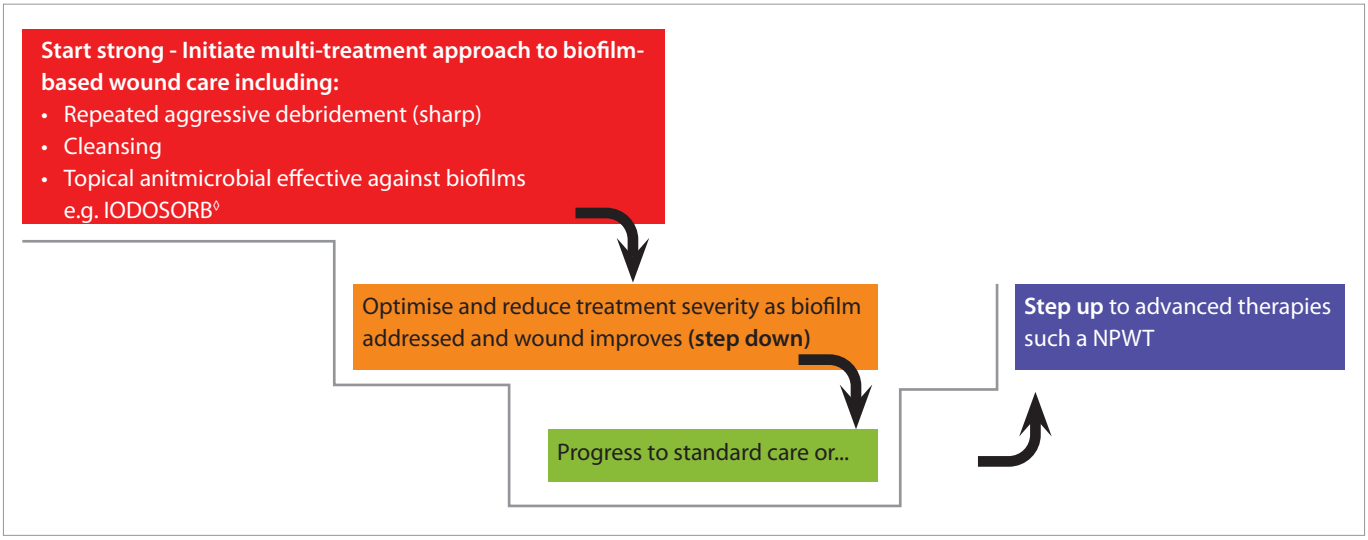

Figure 6. Step-down/step-up approach modified from Schultz et al (2017).

cadexomer beads and is released in a sustained manner only when the dressing is in contact with wound fluid. The cadexomer beads provide effective exudate management and desloughing properties (Harcup and Saul, 1986; Hansson, 1998; Skog et al, 1983) in combination with the benefits of a broad-spectrum, sustained antimicrobial activity (Harrow, 2009; Forest, 2018).

In vivo and *in vitro* evidence suggests that sustained-release iodine can penetrate biofilms more effectively than silver (including those formulations with special additives to enhance biofilm activity), PHMB and PVP-I (Phillips et al, 2015; Fitzgerald et al, 2017; Roche, 2019). In addition to the antimicrobial effects, cadexomer iodine dressings have been shown to physically disrupt biofilm structure and subsequently kill biofilm bacteria (Akiyama et al, 2004; Fitzgerald et al, 2017; Forest et al, 2019; Malone et al, 2017). Furthermore, a meta-analysis considered data from *in vitro* animal and clinical cases concluded that iodine, particularly cadexomer iodine, is a key treatment focus for biofilms (Schwarzer et al, 2019).

Step-down/step-up approach

Following initiation of a multi-faceted approach to remove biofilm, as the wound improves and the clinical indicators of local infection or biofilm resolve, treatment is stepped-down to a non-antimicrobial dressing (as per local protocol), or standard care as indicated (Schultz et al, 2017; Moore et al, 2019). Alternatively following optimal wound bed preparation, faster healing of larger, complex wounds may be supported using a step-up approach, with the introduction of advanced products such as NPWT (Schultz et al, 2017; Moore et al, 2019). The step-down/step-up approach is incorporated within the IM Pathway.

CONCLUSION

The IM Pathway is designed to guide clinicians in the assessment and management of local wound infection or suspected biofilm, and to promote consistency of care among wound care specialist and non-specialist (WUWHS, 2020). It is a support tool with the aim to simplify the complexities of wound infection assessment and diagnosis of the causes of delayed healing associated with local infection and biofilm. Furthermore, if the wound is not responding to treatment, then the IM Pathway will lead to prompt referral and facilitate communication among the multidisciplinary team.

The pathway will help wound specialist and non-specialist clinicians to consistently communicate the difference between local, spreading and biofilm infection and encourage early detection and differentiated treatment. It can be used by specialists as an educational tool to train non-specialists, and it will help provide confidence to non-specialist team members.

The IM Pathway will aim to standardise assessment and provide a treatment plan based on the signs and symptoms present to stop unnecessary treatment and avoid delays in the patient receiving the correct care. This should lead to better patient outcomes, appropriate use of products and reduced cost if wound complications are prevented, and wound healing is achieved.

The next steps are to validate the IM Pathway in clinical practice to measure its impact in supporting clinicians to deliver improved patient outcomes.

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