Hydro-responsive wound dressings for treating hard-to-heal wounds: a narrative review of the clinical evidence

Abstract: A break in skin integrity must be repaired as quickly as possible to avoid excess blood and fluid loss, and to minimise the onset of infection. Hard-to-heal wounds, in which the progression of the wound healing response is compromised, present several challenges to healing (for example, the presence of devitalised tissue acting as a physical barrier to healing and as a focus for bacterial contamination with the potential for subsequent infection). The objective of this article is to present, as a narrative review, the clinical evidence supporting the use of a unique hydro-responsive wound dressing (HydroClean, HRWD1, PAUL HARTMANN AG, Germany). The dressing provides a simple treatment option to address a number of clinical challenges clinicians must overcome in order to facilitate wound healing progression. These studies demonstrated that this product supported successful debridement/cleansing of a wide variety of wounds, including hard-to-heal wounds, enabled wound bed preparation, and lead to positive healing outcomes, including in wounds that previously had failed to heal. The simplicity of using HRWD1 as a single dressing can help clinicians overcome a variety of challenges when treating both acute and hard-to-heal wounds, which, with the benefit of proven patient outcomes, could make it an ideal choice for a first-line treatment.

Declaration of interest: This work was funded by PAUL HARTMANN AG, Germany.

Recent analysis of NHS statistics has shown that in 2017/2018 in the UK there were an estimated 3.8 million patients with either acute or hard-to-heal wounds and of these 89% acute but only 49% hard-to-heal wounds healed.1 The large number of patients with acute/hard-to-heal wounds is reflected globally and presents a huge challenge across the world.2 This is exacerbated by the development of antimicrobial resistance (of wound pathogens) which makes treatment of wound infections even more challenging.3

As a consequence and as an attempt to improve patient outcomes in terms of wound healing, standard practices and guidelines have been introduced.4 This has led to a more informed and simplified dressing selection based upon the specific wound/patient requirements. Examples of these frameworks include the TIME (tissue, infection, moisture, edge) and DIME (devitalised tissue, infection/inflammation, moisture balance, edge preparation) protocols that have been developed to support healing progression. In the first instance, this requires debridement (removal of devitalised tissue) and enabling wound bed preparation such that the normal progression of wound healing can occur.5,6

An open wound must be closed as quickly as possible in order for the skin’s barrier function to be restored and for the underlying tissues to be protected from the external environment. When left exposed, wound tissue dries out and forms a dry crust (a scab) over the wound surface.7 This process, together with the biochemical cascade of haemostasis, ensures that blood and additional fluid loss is halted, and the open wound is sealed off from exposure to potential contaminants (for example, bacteria). However, in hard-to-heal wounds the vital tissue required for regrowth of the skin is prohibited and, instead, devitalised tissue (slough and eschar) develops.8 This devitalised tissue, can prevent or delay a wound’s normal healing process, and provide a nidus for bacteria (and biofilm formation). Hence, it increases the risk of infection that may become deep seated in the tissues/bone or become systemic and life-threatening.8,10–12

A basic tenet therefore in the treatment of hard-to-heal (or acute) wounds is that it is imperative that any or all devitalised tissue must be removed, and the wound prepared for healing, according to the TIME management process.13 There are a number of ways in which a clinician may remove this devitalised tissue.14

Autolytic debridement is one such method. It is a natural mechanism by which devitalised tissue is removed from the wound and this removal can be supported using moist wound management protocols, including the use of moisture-donating and/or moisture-retentive dressings.15 In the process of

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A high proportion (up to 80%) of patients with hard-to-heal wounds suffer a high level of pain that impacts on their quality of life. By having a negative impact on psychological well-being, with depression, anxiety and decreased socialisation often rendering these patients immobile or unable to carry out their daily activities. Investigations suggest that the underlying disease processes that cause hard-to-heal wounds, such as venous leg ulcers, pressure ulcers and DFUs, disturb the normal progression of wound healing, halting the healing response in the inflammatory phase. Most wounds carry a level of bioburden that does not interfere with the healing process and some commensal skin bacteria may even be beneficial to the healing process. When the bioburden reaches a certain level or specific wound pathogens prevail then infection occurs. Wound infection can severely impact the progress of healing and in some cases (in patients with diabetes with a DFU) lead to amputation and an increase in mortality. A key cause of delayed healing in ulceration is the increased levels of protein–degrading enzyme activity within the wound. This leads to uncontrolled and elevated levels of inflammatory cells in non-healing wound tissues and results in disruptive tissue degradation. A moist wound environment allows the tissue’s own enzymes (for example, elastases, collagenases (MMPs), myeloperoxidase, acid hydrolases and lysosomal enzymes) to soften, digest and liquefy devitalised tissue. The initial breakdown of this devitalised tissue then allows further digestion of the tissue by specialised inflammatory cells (macrophages) via normal phagocytic processes.

Hydro-responsive wound dressings (HRWDs) are moisture balance-oriented wound dressings that aim to simplify wound dressing choice when applying the TIME concept in the management of wounds. HydroClean (HRWD1, PAUL HARTMANN AG, Germany), the focus of this review, enables moisture delivery and/or moisture absorption depending on the environmental fluid balance, providing hydration to soften and detach devitalised tissues, such as necrosis and slough, as well as absorbing bacteria- and proteinase-laden exudate into its absorbent core. Thus, the wound bed is prepared for the development of granulation tissue, re-epithelialisation and healing progression. These latter stages of wound progression are supported by another HRWD, HydroTac (HRWD2, PAUL HARTMANN AG, Germany), and will be the subject of a future review.

Consequently, the treatment of hard-to-heal wounds must address a number of different challenges in terms of removing devitalised tissue, overcoming the pathology that has delayed healing progression, reducing the level of infection (inherent in hard-to-heal wounds), managing the levels of exudate and associated pain observed in these wound types (Table 1).

**Aim**

The aim of this narrative review is to present clinical evidence supporting the use of HRWD1 in providing a simple treatment option to address a number of different clinical challenges that fall within the standard wound care frameworks (for example, TIME). Removal of devitalised tissue and wound bed preparation using HRWD1 will also be discussed in this narrative review.

**Method**

The PubMed/Medline database was searched between January 1970 and July 2021 on the use of HRWDs as treatment options for wound debridement and/or cleansing, to identify published articles describing the clinical evidence in support of the use of HRWD1. The keywords search strategy included ‘HydroClean’, ‘debridement’, ‘wound cleansing’, and ‘hydro-responsive’. Although the HRWD1 dressing was not available as early as 1970, we wanted to search for as many potential dressings using the same principles as HRWD1 as possible. In addition, a manual search of wound care/management-related, peer-reviewed journals and conference proceedings not indexed in PubMed was also undertaken.

This review of the evidence for HRWD1 was limited to studies within the Oxford Centre of Evidence-based Medicine guidelines’ level of evidence (LoE) groups 1–4.22

**Results and discussion**

A total of 29 studies were included in the review. The results of the review are discussed in alignment with the headings set out in Table 1. A number of clinical studies (clinical trials, Table 2) and clinical evaluations (case series and case reports, Table 3) have been undertaken to ascertain the effect of the application of HRWD1 on

### Table 1. Challenges of treating hard-to-heal wounds

<table>
<thead>
<tr>
<th>Challenges</th>
<th>Comments</th>
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<tbody>
<tr>
<td>Presence of devitalised tissue</td>
<td>Both acute and hard-to-heal wounds can develop areas of devitalised tissue (for example, eschar and slough) that occurs because of various factors that cause localised tissue death, for example, poor blood supply, excessive levels of wound exudate (that contains MMPs) leading to infected tissue and ultimately delays in healing.</td>
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<tr>
<td>Delayed wound healing</td>
<td>Well-established that dermal wound healing progresses through a series of distinct but overlapping, interdependent steps (phases) to ensure that any disruption in skin integrity is repaired as quickly as possible. Any disruption of the normal progression of any phase of healing leads to delayed healing. Investigations suggest that the underlying disease processes that cause hard-to-heal wounds, such as venous leg ulcers, pressure ulcers and DFUs, disturb the normal progression of wound healing, halting the healing response in the inflammatory phase.</td>
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<tr>
<td>Presence of wound bioburden</td>
<td>Most wounds carry a level of bioburden that does not interfere with the healing process and some commensal skin bacteria may even be beneficial to the healing process. When the bioburden reaches a certain level or specific wound pathogens prevail then infection occurs. Wound infection can severely impact the progress of healing and in some cases (in patients with diabetes with a DFU) lead to amputation and an increase in mortality.</td>
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<tr>
<td>Exudate</td>
<td>A key cause of delayed healing in ulceration is the increased levels of protein–degrading enzyme activity within the wound. This leads to uncontrolled and elevated levels of inflammatory cells in non-healing wound tissues and results in disruptive tissue degradation.</td>
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<tr>
<td>Pain</td>
<td>A high proportion (up to 80%) of patients with hard-to-heal wounds suffer a high level of pain that impacts on their quality of life. By having a negative impact on psychological well-being, with depression, anxiety and decreased socialisation often rendering these patients immobile or unable to carry out their daily activities. Additionally, a systematic review reported that the pooled prevalence of wound-related background pain was 80% (95% CI: 65–92%) and the mean pain intensity score was 4 (95% CI: 3.4–4.3).</td>
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MMPs—matrix metalloproteinases; DFU—diabetic foot ulcer; CI—confidence interval.
Table 2. Clinical studies of hydro-responsive wound dressing (HRWD1) on hard-to-heal wounds

<table>
<thead>
<tr>
<th>Study type</th>
<th>Sample size, n</th>
<th>Wound type(s)</th>
<th>Main outcome measures</th>
<th>Main results</th>
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<tbody>
<tr>
<td>Hodgson et al., 2017</td>
<td>100</td>
<td>Acute and hard-to-heal wounds including venous leg ulcers, arterial ulcers,</td>
<td>• Debridement</td>
<td>• Effective, rapid and painless debridement of wounds</td>
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<td></td>
<td></td>
<td>diabetic foot ulcers, and pressure ulcers</td>
<td>• Wound healing</td>
<td>• Positive healing outcomes and an increase in healthy granulation tissue</td>
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<td></td>
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<td>• Pain</td>
<td>• The number of patients with infected wounds reduced</td>
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<td></td>
<td>• Infection</td>
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<tr>
<td>Scholz et al., 1999</td>
<td>37</td>
<td>Venous leg ulcers</td>
<td>• Level of fibrinous coatings</td>
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<td>• Level of necrotic tissue</td>
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<td>• Granulation tissue formation</td>
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<td>• Exudate levels</td>
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<td>König et al., 2005</td>
<td>42</td>
<td>Venous leg ulcers</td>
<td>• Levels of eschar, slough and necrotic tissue</td>
<td>• Significant reduction in fibrous and necrotic tissue and wound coatings</td>
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<td></td>
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<td></td>
<td>• Levels of granulation tissue formation</td>
<td>• Promotion of granulation tissue formation</td>
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<td>• Wounds showing ‘moderate/severe’ exudate decreased from 28 (75.7%) to 8 (21.6%)</td>
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<td>• 33 patients reported ‘no’ or ‘slight’ pain at dressing change</td>
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<td>Humbert et al., 2014</td>
<td>75</td>
<td>Venous leg ulcers</td>
<td>• Levels of slough and necrotic tissue</td>
<td>• Greater reduction in HRWD1 group of proportion of ulcer area covered by slough and necrotic tissue</td>
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<td></td>
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<td></td>
<td>• Granulation tissue formation</td>
<td>• Greater proportion in HRWD1 group of proportion of ulcer covered by granulation tissue</td>
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<td></td>
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<td></td>
<td>• Cost-benefit analysis</td>
<td>• Response rates of hard-to-heal ulcers of &gt;6 months’ duration higher in HRWD1 group</td>
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<td>• Cost-benefit analysis favoured HRWD1 group</td>
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<td>Kaspar et al., 2008</td>
<td>221</td>
<td>Hard-to-heal wounds including venous leg ulcer, arterial ulcers, mixed aetiology ulcers, diabetic foot ulcers and burns</td>
<td>• Level of fibrinous slough</td>
<td>• Number of wounds completely or partially (&gt;50% surface area) covered in fibrinous slough decreased from 54% to 9%</td>
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<td></td>
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<td>• Number of wounds showing granulation tissue formation</td>
<td>• Number of wounds showing granulation tissue (&gt;50% surface area) increased from 5% to 74%</td>
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<td></td>
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<td>• Clinical signs of infection</td>
<td>• Number of wounds showing clinical signs of infection reduced from 53% to 9%</td>
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<td>• Wounds with high exudate levels</td>
<td>• Number of wounds with high exudate levels reduced from 74% to 10%</td>
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<td></td>
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<td></td>
<td>• Wound pain</td>
<td>• Number of patients reporting ‘intermediate’ to ‘high’ levels of wound pain perception decreased from 64% to 19%</td>
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<tr>
<td>Mwipatayi et al., 2005</td>
<td>10</td>
<td>Hard-to-heal wounds including venous leg ulcer, diabetic foot ulcer and arterial ulcers</td>
<td>• Assessment of wound bed Monitor reduction in wound area</td>
<td>• Rate of wound debridement estimated as an average of 6% per day</td>
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<td>• Wound area reduction measured during HRWD1 application</td>
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<td>• Two patients showed no wound bed debridement</td>
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<td>• Three patients noted pain during dressing change, No follow-up was noted</td>
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<tr>
<td>König et al., 2005</td>
<td>42</td>
<td>Venous leg ulcers</td>
<td>• Levels of eschar, slough and necrotic tissue</td>
<td>• Slough within the groups reduced by almost 19% (HRWD1) compared with 9% (enzyme)</td>
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<td></td>
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<td>• Levels of granulation tissue formation</td>
<td>• Granulation tissue area increased by 26% (HRWD1) compared with 10% (enzyme)</td>
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<td>• Dressing and enzymatic agent equally effective at reducing levels of necrotic tissue and wound coatings</td>
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<td>• HRWD1 promoted moist wound environment</td>
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<td>• HRWD1 managed excessive exudate and tissue debris</td>
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### Table 2. Clinical studies of hydro-responsive wound dressing (HRWD1) on hard-to-heal wounds (continued)

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<th>Wound type(s)</th>
<th>Main outcome measures</th>
<th>Main results</th>
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<tbody>
<tr>
<td>Spruce et al., 2016&lt;sup&gt;35&lt;/sup&gt;</td>
<td>20</td>
<td>Acute and hard-to-heal wounds</td>
<td>• Assessment of wound bed preparation&lt;br&gt;• Assessment of wound progression (wound area and wound depth)&lt;br&gt;• Performance of dressing (ease of application, removal)&lt;br&gt;• Cost-benefit analysis</td>
<td>• Two patients progressed to healing&lt;br&gt;• Reduction in wound size and/or depth in a further nine patients&lt;br&gt;• Two wounds were completely debrided and six wounds were debrided to 80–99% healthy tissue&lt;br&gt;• No patients experienced pain on dressing change&lt;br&gt;• Proportion of patients experiencing wound pain reduced from 95% to 35%&lt;br&gt;• Potential cost savings associated with using HRWD1</td>
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<tr>
<td>Mancini et al., 2017&lt;sup&gt;102&lt;/sup&gt;</td>
<td>28</td>
<td>Leg ulcers including venous leg ulcers, diabetic foot ulcers and mixed aetiology ulcers</td>
<td>• Assessment of wound bed&lt;br&gt;• Monitor levels of slough and granulation tissue</td>
<td>• Reduction in levels of slough&lt;br&gt;• Increase in levels of healthy granulation tissue</td>
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<tr>
<td>Rippon and Ousey, 2021&lt;sup&gt;37&lt;/sup&gt;</td>
<td>403</td>
<td>Hard-to-heal wounds including venous leg ulcers, arterial ulcers, decubitus ulcers, diabetic foot ulcers, mixed venous/arterial ulcers and burns</td>
<td>• Level of wound bed fibrous coatings&lt;br&gt;• Wound granulation&lt;br&gt;• Clinical signs of infection&lt;br&gt;• Wound pain&lt;br&gt;• Physician evaluation of effectiveness and handling&lt;br&gt;• Patient evaluation of tolerability, wearing comfort and pain during treatment</td>
<td>• Number of wounds with &gt;50% fibrous coating decreased from 56% to 6%&lt;br&gt;• Levels of necrotic tissue reduced from 32% to 5% of wounds&lt;br&gt;• Number of wounds with florid granulation tissue increased from 6% to 69%&lt;br&gt;• Significant reduction in wound pain&lt;br&gt;• Infections decreased&lt;br&gt;• Wound edge damage showed significant improvement&lt;br&gt;• &gt;90% of physicians evaluated HRWD1 ‘very good’ or ‘good’&lt;br&gt;• &gt;84% of patients evaluated HRWD1 ‘very good’ or ‘good’</td>
</tr>
<tr>
<td>Rippon and Ousey, 2021&lt;sup&gt;37&lt;/sup&gt;</td>
<td>170</td>
<td>Hard-to-heal wounds including venous leg ulcers, decubitus ulcers, arterial leg ulcers, diabetic foot ulcers and traumatic wounds</td>
<td>• Level of wound bed fibrous coatings&lt;br&gt;• Level of wound bed necrosis&lt;br&gt;• Wound granulation&lt;br&gt;• Clinical signs of infection&lt;br&gt;• Wound pain&lt;br&gt;• Physician evaluation of effectiveness&lt;br&gt;• Patient evaluation of tolerability, wearing comfort and pain during treatment</td>
<td>• Number of wounds with necrosis decreased from 17% to 10%&lt;br&gt;• Number of wounds with fibrous coatings decreased from 41% to 33%&lt;br&gt;• Proportion of granulation tissue increased from 35% to 46%&lt;br&gt;• Proportion of epithelial tissue increased from 6% to 11%&lt;br&gt;• Wound edge damage reduced from 71% to 62%&lt;br&gt;• Wounds with clinical signs of infection reduced from 24% to 17%&lt;br&gt;• Patients experiencing moderate to severe wound pain reduced from 35% to 19%&lt;br&gt;• Levels of moderate to severe wound pain at dressing change decreased from 26% to 11%&lt;br&gt;• Over 85% physicians evaluated dressing removability as ‘good’ or ‘very good’&lt;br&gt;• &gt;90% physicians evaluated HRWD1 ‘very good’ or ‘good’&lt;br&gt;• &gt;80% patients evaluated HRWD1 ‘very good’ or ‘good’</td>
</tr>
<tr>
<td>Rippon and Ousey, 2021&lt;sup&gt;37&lt;/sup&gt;</td>
<td>14</td>
<td>Hard-to-heal wounds including venous leg ulcers and mixed (venous/arterial) aetiology ulcers</td>
<td>• Level of fibrous coating&lt;br&gt;• Level of necrotic tissue&lt;br&gt;• Granulation tissue formation&lt;br&gt;• Patient tolerability of dressing&lt;br&gt;• Periwound skin condition</td>
<td>• Significant reduction in fibrous and necrotic tissue&lt;br&gt;• Promotion of granulation tissue formation&lt;br&gt;• Improvement in periwound skin condition; reduction in erythema (n=5) and reduction in desquamation (n=3)&lt;br&gt;• Wounds sufficiently cleansed for split-skin grafting within 7–10 days</td>
</tr>
<tr>
<td>Rippon and Ousey, 2021&lt;sup&gt;37&lt;/sup&gt;</td>
<td>130</td>
<td>Acute and hard-to-heal wounds including venous leg ulcers, diabetic foot ulcers, mixed aetiology ulcers, burns, and traumatic wounds</td>
<td>• Assessment of wound healing progression (as measured by the revised Photographic Wound Assessment Tool, revPWAT)&lt;br&gt;• Clinical signs of infection&lt;br&gt;• Periwound skin condition</td>
<td>• Reduction in mean wound area (25.1%, p=0.049) and wound volume (48.7%, p=0.046)&lt;br&gt;• Decrease in median revPWAT score from 21 to 13 indicating an improvement in wounds over the treatment period&lt;br&gt;• Decrease in levels of devitalised tissue and corresponding increase in granulation tissue levels&lt;br&gt;• Improvement in the status of both wound edge and periwound skin condition when treated with HRWD1 over the course of the study period</td>
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wounds that required removal of devitalised tissue to promote healing. Generally, the results of these studies have demonstrated success in that there was softening and removal of devitalised tissue that enabled autolytic debridement and/or removal by surgical techniques. This removal of devitalised tissue resulted in a corresponding increase in the presence of healthy granulation tissue within the wound bed which in turn enabled progression of wound healing. This review summarises the main findings from the clinical evaluations in relation to the various clinical challenges (identified above) for treatment of a variety of wounds.

**Devitalised tissue**
It is well established that wound bed preparation (WBP) is a prerequisite for wound progression, specifically for wounds with devitalised tissue, which is a major barrier to healing progression. WBP can be summarised by TIME, the acronym of a now well-established and widely-used systematic approach to the management of wounds into four major principles (Box 1).

The first step in WBP is the removal of devitalised tissue using various methods of debridement. This process removes a physical barrier to healing and a focus for wound tissue irritation and bacterial colonisation and/or proliferation that are likely to elevate the inflammatory status of the wound, and impair the progress to healing. To enable healing progression, a dressing that promotes a moist environment is required that will provide the wound surface with a moist environment without the presence of free water. The establishment of this moist healing environment promotes the cleansing of the wound via autolytic debridement and the conditioning of the wound bed, optimising the conditions for subsequent healing according to the TIME principles.

Clinical studies have shown that using HRWD1 has enabled successful and rapid autolytic debridement of wounds that have high levels of devitalised tissue (Tables 2 and 3). For example, the effectiveness of HRWD1 in the debridement and WBP of pressure ulcers (PUs), diabetic foot ulcers, surgical wounds, traumatic wounds and burns (n=100) was investigated in a clinical, prospective, non-comparative, multicentre observational study. The results showed that the levels of devitalised tissue (necrosis and slough) reduced from 85.5% to 26.3% and this was accompanied by an increase in wound bed granulation from 12.0% to 33.7%. The clinical evidence provided in this study supports the position that there is a necessity to clean and debride devitalised tissue instead of using an antimicrobial as set out in the Health Improvement Scotland Health Technology Assessment (https://tinyurl.com/yuseab7p). A subpopulation analysis of 10 patients with PUs showed that the use of HRWD1 on patients with long-standing PUs enabled removal of substantial elements of devitalised tissue within the wound (a reduction from 90% to 13%). This removal enabled easier assessment and grading of the PU which supported improved and, in some cases, more appropriate treatment choices. There was also a corresponding reduction in wound area (by 50%), showing a clinically-relevant healing response upon treatment with HRWD1. An example of this clinically relevant debridement by HRWD1 is presented in Fig 1.

Similarly, another study evaluating the use of HRWD1 with both acute and hard-to-heal wounds (n=86) showed a decrease in the percentage of predominantly fibrinous/necrotic wounds from the start to completion of treatment (84.7% to 11.8%, respectively) that led to a positive wound healing response. Further evidence supporting the premise that HRWD1 enables WBP was demonstrated in an open, prospective, RCT evaluating the WBP ability of HRWD1 (n=34) versus an amorphous gel (n=41) in venous leg ulcers (VLU) of >4 weeks' duration. The results showed that ulcer area covered by slough and necrosis decreased by 37.6% and 16.8% (HRWD1 versus hydrogel, respectively) compared with the baseline (p=0.004). Additionally, granulation tissue increased by 36.0% and 14.5% (HRWD1 versus hydrogel, respectively) compared with the baseline (p=0.005).

In a multicentre, community-based product evaluation of HRWD1 in 20 patients with wounds of various aetiologies, and where the primary objective was to evaluate HRWD1 in facilitating WBP (by the promotion of autolytic debridement to remove devitalised tissue and enable wound progression), the results showed that two patients progressed to healing, and a reduction in wound size was observed in a further nine patients.

In another study, a photographic wound assessment tool (revPWAT) was used to assess the status of 41 wounds based upon digital photographs taken during the study. There was a significant decrease in the revPWAT total score from 19.5±4.8 (median: 21; range: 3–32) to 11.8±6.3 (median: 13; range: 0–25; p<0.05). A total of 34 wounds (34/41, 82.9%) decreased in revPWAT score, 4/41 (9.8%) remained unchanged and only 3/41 (7.3%) increased over the course of the study.

**Delayed wound healing**
Hard-to-heal wounds have become stuck at an early stage in the wound healing process and require a different approach to fast-track the healing process.

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**Box 1. Principles of TIME wound management**

<table>
<thead>
<tr>
<th>T</th>
<th>Tissue non-viable or deficient</th>
<th>Does the wound contain non-viable tissue such as necrotic tissue, slough, non-viable tendon or bone?</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Infection or inflammation</td>
<td>Does the wound have signs of bacterial contamination, infection or inflammation?</td>
</tr>
<tr>
<td>M</td>
<td>Moisture imbalance</td>
<td>Does the wound have excess exudate or is the wound too dry?</td>
</tr>
<tr>
<td>E</td>
<td>Edge of wound non-advancing or undermined</td>
<td>Are the edges of the wound undermined and is the epidermis failing to migrate across the granulation tissue?</td>
</tr>
</tbody>
</table>
Table 3. Clinical evaluations of hydro-responsive wound dressing (HRWD1) on hard-to-heal wounds

<table>
<thead>
<tr>
<th>Study type</th>
<th>Sample size, n</th>
<th>Wound type(s)</th>
<th>Main outcome measures</th>
<th>Main results</th>
</tr>
</thead>
</table>
| Ousey et al., 2016<sup>271</sup> | Case series 3 | Foot ulcer, mixed aetiology ulcer, pressure ulcer | • Wound debridement  
• Periwound skin condition | • Removal of devitalised tissue  
• Wound progression  
• Improvement of periwound skin  
• Reduced pain |
| Haycock and Chadwick, 2017<sup>103</sup> | Case series 3 | Diabetic foot ulcer | • Wound debridement  
• Granulation tissue formation | • Removal of devitalised tissue  
• Increase in granulation tissue  
• Wound progression  
• Reduced pain |
| Yeh et al., 2019<sup>104</sup> | Case series 6 | Diabetic foot ulcer, pressure ulcer, non-healing traumatic wound | • Wound debridement  
• Granulation tissue formation  
• Wound progression | • Removal of devitalised tissue  
• Wound progression (wound area reduction)  
• Increase in granulation tissue |
| Cara, 2018<sup>105</sup> | Case report 1 | Hard-to-heal wound | • Wound debridement  
• Wound progression  
• Pain | • Removal of devitalised tissue  
• Wound progression  
• Reduced pain |
| Cooper, 1998<sup>106</sup> | Case report 1 | Leg ulcer | • Wound debridement  
• Granulation tissue formation | • Removal of devitalised tissue  
• Increase in granulation tissue |
| Chadwick and Haycocks, 2016<sup>107</sup> | Case series 5 | Diabetic foot ulcer | • Assessment of wound bed | • Removal of devitalised tissue  
• Increase in granulation tissue |
| Rippon and Ousey, 2021<sup>107</sup> | Case series 5 | Pressure ulcer, diabetic foot ulcer, venous leg ulcer | • Wound debridement  
• Granulation tissue formation  
• Wound progression | • Removal of devitalised tissue  
• Increase in granulation tissue  
• Wound progression |
| Rippon and Ousey, 2021<sup>107</sup> | Case series 3 | Mixed aetiology ulcer, pressure ulcer | • Wound debridement  
• Granulation tissue formation | • Removal of devitalised tissue  
• Increase in granulation tissue |
| Rippon and Ousey, 2021<sup>107</sup> | Case report 1 | Pressure ulcer | • Wound debridement  
• Wound conditioning | • Removal of devitalised tissue  
• Wound progression |
| Rippon and Ousey, 2021<sup>107</sup> | Case series 3 | Venous leg ulcer, pressure ulcer | • Wound debridement  
• Wound progression  
• Pain | • Removal of devitalised tissue  
• Increase granulation tissue  
• Periwound skin improvement  
• Reduced pain and exudate levels |
| Rippon and Ousey, 2021<sup>107</sup> | Case report 1 | Venous leg ulcer | • Wound debridement  
• Granulation tissue formation  
• Wound progression  
• Pain  
• Periwound skin condition | • Removal of devitalised tissue  
• Increase in granulation tissue  
• Reduced pain and exudate levels  
• Wound progression |
| Rippon and Ousey, 2021<sup>107</sup> | Case series 7 | Pressure ulcer, venous leg ulcer, foot ulcer | • Wound debridement  
• Granulation tissue formation  
• Wound progression  
• Pain | • Removed devitalised tissue  
• Increase in granulation tissue  
• Wound progression  
• Reduced pain levels |
| Rippon and Ousey, 2021<sup>107</sup> | Case series 7 | Pressure ulcer, arterial ulcer, venous leg ulcer | • Wound debridement  
• Granulation tissue formation  
• Wound progression | • Removed devitalised tissue  
• Increase in granulation tissue  
• Wound progression |
| Knowles et al., 2016<sup>107</sup> | Case report 1 | Pressure ulcer | • Wound debridement  
• Wound size reduction | • Removed devitalised tissue  
• Reduction in wound size |
| Knowles et al., 2016<sup>107</sup> | Case report 1 | Pressure ulcer | • Wound debridement  
• Granulation tissue formation | • Removed devitalised tissue  
• Increase in granulation tissue |
| Knowles et al., 2016<sup>107</sup> | Case report 1 | Hard-to-heal wound | • Wound debridement  
• Granulation tissue formation  
• Pain  
• Wound progression | • Removed devitalised tissue  
• Increase in granulation tissue  
• Reduced pain levels  
• Wound progression |
stage of the normal wound healing process and require active promotion to progress and achieve complete healing.\textsuperscript{38,39} There are two basic tenets for the treatment of hard-to-heal wounds:

- Debridement and removal of devitalised tissue—a focus of infection and a barrier to healing,\textsuperscript{40,41}
- The management of wound exudate levels with optimisation of the wound environment moisture balance.\textsuperscript{42}

Hence, wound dressings that promote debridement and the creation of a moist wound healing environment encourage wound healing, particularly in more complex wounds such as leg ulcers.\textsuperscript{28} HRWD1s can help manage both points above in that they are indicated for use when the wound needs to be actively cleansed and the wound bed prepared for wound healing progression to occur. In addition, they can absorb high volumes of wound exudate and help maintain optimal fluid levels and balance at the wound surface, enabling healing progression.

A number of studies have been undertaken that have shown the importance of HRWD1 in providing a moist wound that enables healing progression (Tables 2 and 3). Evidence that supports HRWD1 as an enabler of wound healing progression is exemplified in the following clinical studies. A study was undertaken to evaluate the effectiveness of HRWD1 in the treatment of patients (n=100) with a variety of acute and hard-to-heal wounds. The majority (51.4\%) of these patients had hard-to-heal wounds that showed no signs of wound progression within the four weeks prior to the study. After treatment with HRWD1, there was a positive healing trajectory (for example, a reduction in mean wound area versus baseline) over the treatment period (Fig 2). Additionally, a high level (93\%) of hard-to-heal wounds demonstrated wound progression upon treatment with HRWD1.\textsuperscript{32}

Another multicentre clinical evaluation (n=86 patients) assessed both acute and hard-to-heal wounds of varying severity and duration after treatment with HRWD1.\textsuperscript{33} The results showed that wounds were successfully cleansed/debrided with a corresponding statistically significant increase in the level of wound granulation tissue present from start (15.3\%) to completion of the study (88.2\%) (p<0.0001), and a subsequent increase in re-epithelialisation of the wounds. Additionally, 93\% of the wounds demonstrated wound progression (as measured by an overall 40\% reduction in wound area). The study also used a Pressure Ulcer Scale for Healing assessment tool (PUSH score evaluation\textsuperscript{43}) that over the course of the evaluation period showed a decreased PUSH score (11.9±2.9 to 7.0±4.5; p<0.0001) and a reduction in mean wound area (28.1±59.3cm\textsuperscript{2} to 12.4±36.7cm\textsuperscript{2} (p=0.0069)). These results indicated wound healing progression when these previously recalcitrant wounds were treated with
HRWD1. Additionally, it was reported in a multicentre, two-arm parallel-group study in patients (n=75) with non-healing VLU's that were treated with either HRWD1 or an amorphous gel, that HRWD1-treated wounds demonstrated a larger reduction in fibrin slough/necrotic tissue compared with amorphous gel-treated wounds. The proportion of the ulcer covered by granulation tissue increased by 36.0% in the HRWD1 group and by 14.5% in the amorphous hydrogel group compared with the baseline (p=0.005). Fig 3 highlights a case study that indicates the effectiveness of HRWD1 in facilitating the healing of a serious burn.

The evidence presented here compares favourably with that presented by other authors that have reviewed the effectiveness of the wound healing support by both traditional and advanced (smart) dressings. Evidence-based medicine must play a part in identifying wound dressings that can enable this transition, and the evidence presented here supports the use of HRWD1 in doing so.

Wound bioburden
All open wounds are contaminated with bacteria, with the initial colonisation after wounding usually by commensal species from the skin and with subsequent colonisation by pathogens and development of biofilm. The association between wound bioburden and chronicity is a well-recognised but complex problem that is worsened by the presence of devitalised tissue in the wound bed acting as a focus for microorganism growth and possible infection. Hence, the removal of this tissue is imperative for preventing/reducing infection. This removal can be achieved, for example, by dressings that enable autolysis and the autolytic digestion of necrosis and slough.

There have been numerous antimicrobial approaches to aid in the reduction of this bioburden by, for example, the use of antiseptics and antibiotics. However, the use of these have significant disadvantages, not least the growth of antimicrobial resistance (AMR) to antimicrobial agents. The development of non-medicated wound dressings (NMWD) has, however, provided alternative treatment options without the downside of inducing AMR. This potential for wound bioburden-modulation has been identified as being related to the microorganism-binding properties of such dressings, as has been demonstrated in a number of laboratory-based studies for HRWD1. HRWD1 has been classified as a NWMD and the mechanism of action by which this dressing enables a reduction of infection is ‘physical’ not ‘active’ (Table 4). It is also noteworthy that NMWDs such as HRWD1 have been shown to be successful in treating superficial wound infections caused by microorganisms showing AMR and, therefore, will be useful in supporting antimicrobial stewardship (AMS) strategies.

The evidence for the use of HRWD1 to successfully treat wound infection is presented in Tables 2 and 3. The management of infection by HRWD1 has been demonstrated in an open-labelled, non-comparative study on 100 patients with a variety of acute and hard-to-heal wounds. In this study, 22 wounds were assessed as showing clinical signs of infection at the start of the evaluation period. By the end of the study, 13 (59.1%) of these previously infected wounds showed no signs of infection. The authors noted that the reduction in wound infection was due to the rapid removal of devitalised tissue and the microorganism-binding properties of HRWD1. In an open-labelled non-comparative study in patients with a variety of acute and hard-to-heal wounds, treatment with HRWD1 for up to 25 weeks resulted in a decrease in the percentage of wounds with devitalised tissue and a

### Table 4. Properties of a hydro-responsive wound dressing (HRWD1), a non-medicated wound dressing

<table>
<thead>
<tr>
<th>Property</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Debridement and removal of devitalised tissue</td>
<td>Removal of microorganisms with the dressing at routine dressing change</td>
</tr>
<tr>
<td>Absorption of microorganisms</td>
<td>Sequestration of microorganisms</td>
</tr>
<tr>
<td>Matrix metalloproteinases and bacterial endotoxins</td>
<td>Retention and immobilisation of microorganisms within the wound dressing matrix</td>
</tr>
<tr>
<td>Removal of microorganisms</td>
<td></td>
</tr>
</tbody>
</table>
corresponding increase in healthy wound granulation tissue. There was also a decrease in the proportion of infected wounds over the course of the study period (19.3% to 3.6%, \(p<0.01\)).33

A decrease in wound infections after treatment with HRWD1 was also observed in a multicentre observational study of 170 patients with a variety of hard-to-heal wounds.37 The number of wounds showing clinical signs of infection reduced from 53% to 9% in a study of patients (n=221) with hard-to-heal wounds treated with HRWD1 for one month.64 In a prospective, non-comparative multicentre observational study of 403 patients with a variety of hard-to-heal wounds, treatment with HRWD1 led to a reduction in the number of wounds, with >50% devitalised tissue and a corresponding increase in the number of wounds with healthy granulation tissue.37

**Exudate management**

The management of wound exudate, particularly in hard-to-heal wounds where wound exudate can be damaging to tissue, requires that any dressing maintains a moist wound environment (hydration management) while at the same time manages excessive production of wound exudate (exudate management).65

**Hydration management**

Having prepared the wound bed (see above), other factors must be taken into consideration to enable progression of wound healing. The balance of wound hydration has been shown to be a key element in supporting healing.63 Wound hydration and maintenance of a moist wound has been the basis for modern wound care since George Winter's landmark pre-clinical studies,64 and Hinman and Maibach's clinical65 work showing that the level of tissue hydration had a significant impact in the healing response. HRWDs have been developed with a super-absorbent core to aid in wound exudate management but also supply a level of moisture (in the form of Ringer's saline solution) that supports WBP and enables progression of healing in both acute and hard-to-heal wounds.66 HRWD1 is responsive to the wound environment in that it can both donate or draw moisture under different wound conditions. HRWD1 is pre-activated with Ringer's solution that is donated to the wound environment,35 while at the same time, bacteria and debris-laden wound exudate is absorbed into and retained by the polyacrylate core.57,58 This exchange occurs due to the higher affinity of the polyacrylate polymer for the protein in the wound exudate compared with the Ringer's saline solution.37 This produces a continuous rinsing effect to support effective WBP.

**Exudate management**

Wound exudate is a normal component of healing in acute wounds and is the result of the inflammatory process.67 Acute wound fluid is mainly water but it also contains salts, proteins, protein-digesting enzymes (including MMPs), growth factors, cells types (for example, inflammatory cells, platelets) and microorganisms.62,68 In acute wounds, growth factor-rich exudate stimulates the proliferation wound tissue cells such as fibroblasts and keratinocytes/ epithelial cells, which is beneficial to wound healing.69 However, it is generally accepted that hard-to-heal wound exudate is detrimental to tissues as it contains elevated levels of protein-degrading enzymes, such as MMPs that can degrade the wound tissue and peri-ulcer skin.70,71 If this wound exudate is managed by dressings that cannot absorb the required levels of exudate then the consequences are excessive or prolonged exposure of the wound and surrounding skin resulting in a number of conditions that can themselves delay healing, cause pain and suffering to the patient, and increase treatment costs.68 Tissue maceration due to the prolonged exposure of tissue—particularly periwound skin—to exudate has been a particular concern. Therefore, managing wound exudate is an imperative in obtaining good healing outcomes.

Some clinical studies have demonstrated the excellent fluid management capabilities of HRWD1 and, in particular, the prevention of maceration and damage to peri-ulcer wound skin.32,35,37,72 In a multicentre clinical evaluation (n=86 patients) both acute and hard-to-heal wounds of varying severity and duration were evaluated after treatment with HRWD1 using the PUSH assessment tool to monitor healing progression.33 A component of the PUSH score relates to exudate and the study showed that the presence of wounds with significant exudate decreased from 95.3% to 59.3%. PUSH-derived exudation scores also showed a reduction in the proportion of wounds with moderate/heavy exudate over the course of the study (44.2% to 9.3%) and an increase in the proportion of wounds with no exudate production over the course of the evaluation period (4.7% to 40.7%) (\(p<0.0001\)).33 Effective wound exudate management was also identified in an open multi-centre, prospective randomised controlled study on VLUs.45 After treatment with HRWD1, there was an improvement in periwound skin condition, with an increase in the percentage of patients with healthy wound margin skin (from 25% to 55%) suggesting effective exudate management by HRWD1.

During the progression of a normally-healing wound, proteolytic enzymes such as MMPs are released by inflammatory cells into the wound environment (including wound exudate) and play a role in the breakdown of devitalised tissues and other debris present in the wound, facilitating the progression of the wound towards healing.73-75 However, in hard-to-heal wounds (for example, leg ulcers and PUs), there is an elevated and sustained level of these destructive enzymes. These enzymes then have a negative impact on the healing response due to the sustained and elevated levels of proteolytic activity. A study examining the interaction of HRWDs and wound exudate from patients with hard-to-heal wounds showed that MMPs
bound to the superabsorbent material of the dressing reducing the excess levels of these degrading enzymes.76

Pain management
Pain is a major concern for patients with a wide range of both acute and hard-to-heal wounds, with pain in the latter group—particularly if unresolved—resulting in a considerable amount of suffering and a reduction in quality of life (QoL).77 In wounds that do not heal, persistent pain may develop and become a chronic condition affecting the patient’s overall health.78,79 If wound pain is not addressed, recalcitrant pain develops, which is associated with impaired mobility, insomnia, depression and suicidal considerations.80,81

Pain has been divided into two categories: ‘nociceptive pain’, a normal physical response to a painful stimulus, and ‘neuropathic pain’, pain caused by damaged nerves.82 Wound-related neuropathic pain may involve persistent pain that is usually associated with the underlying wound aetiology. Cyclic acute (nociceptive) pain is induced by repeated wound care interventions such as wound cleaning and dressing change,83 while non-cyclic nociceptive pain results from one-off procedures such as sharp wound debridement.84 An important aspect relates to pain at wound dressing change, whereby the actual dressing may be responsible for causing pain upon traumatic removal.85

Alongside the direct pain resulting from the wound, infection may also increase wound-associated pain.86 The majority of clinical studies we reviewed demonstrated pain/pain reduction after application of HRWD1 (Tables 2 and 3). Some cases have suggested a ‘soothing effect’ of the dressing.22,87 With regards to the pain management effect of the HRWD1, this has been related to (in part) the Ringer’s solution component within the dressing that could effectively have a number of pathways for pain reduction, such as diluting irritant exudate components including MMPs and pain-inducing mediators (for example, pro-inflammatory cytokines).88

A number of clinical studies have reported improvements in the levels of wound pain experienced by patients when treated with HRWD1. An open, prospective observational study of patients (n=221) with acute/hard-to-heal wounds reported that the number of patients reporting ‘intermediate’ or ‘high’ levels of wound pain perception decreased from 64% to 19%.61 A multicentre non-comparative clinical evaluation of HRWD1 in patients with similar wounds reported the proportion of patients experiencing wound pain reduced from 95% to 35%.35 Studies using HRWD1 have also reported reduced pain at dressing removal. For example, an observational study reported only 20% of patients (n=86) with a variety of acute and hard-to-heal wounds treated with HRWD1 experiencing pain (>30mm VAS) at dressing removal.33 Another study that measured pain throughout the study demonstrated a decrease in moderate pain experienced at dressing change from 28% of patients at the commencement of the study to 11% at the end of study.37 In a single-centre observational study in patients with VLUs, 89% (33/37) of patients reported ‘none’ or ‘slight’ pain at HRWD1 dressing changes.89 In a multicentre, non-comparative clinical evaluation of HRWD1 in a variety of acute and hard-to-heal wounds, it was found that no patients experienced pain at dressing changes.35

A case study presented by Jones and McCracken80 evidence related to a reduction in wound pain, in which a 44-year-old patient with systemic lupus erythematosus (SLE) and a previous deep vein thrombosis presented with bilateral circumferential leg ulcers to the gaiter region (Fig 4). The left leg wound had 100% necrotic tissue, low exudate and high pain levels. The periwound skin was inflamed with no maceration. The patient had not been able to tolerate many dressings due to the pain. HRWD was applied and the wound evaluated after 14 days. There was a 70% reduction in necrotic tissue with the remaining tissue being significantly softened. At the final examination, the wound showed 20% granulation tissue and 80% slough, and the patient reported a reduction in pain levels.80

Limitations
This is a narrative review rather than a systematic review and is designed to provide a comprehensive overview of the clinical evidence available for the treatment of wounds with HRWD1. The nature of this method is that it is subjective (in the determination of which studies to include, for example, biased towards HRWD1); this ultimately affects the way the studies are analysed and the conclusions drawn. However, the premise of the aim of the study is a clinical review of HRWD1, therefore, in this respect, this is an accepted methodology.
Conclusion
HRWD1 is designed for the management of wounds that require cleansing/debridement and good exudate management, both of which are needed to encourage an optimal wound environment and support wound healing progression. This focused review has demonstrated that there is extensive evidence that supports the clinical effectiveness of this dressing in the management of a wide range of wound types. The evidence presented in this paper showed that HRWD1 can promote wound cleansing and removal of devitalised wound tissue in poorly healing or infected wounds via autolytic debridement. It has been shown to achieve wound progression and promote granulation tissue formation in more complex wounds along with possessing excellent fluid-handling properties, ease of use and comfort for the patient. This dressing has also been shown to reduce levels of wound pain and pain experienced at dressing changes. In addition, these dressings (defined now as NMWD) have demonstrated a ‘physical’ antimicrobial action, which makes their use crucial in supporting an AMS strategy. JWC

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What is the first step in wound bed preparation?
What type of wound dressing promotes progression of healing?
What are the properties of a non-medicated wound dressing?
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