Hydro-Responsive Wound Dressings for the Treatment of Chronic Wounds: A Narrative Review of the Clinical Evidence (Part 1)

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ABSTRACT

A break in the integrity of the skin must be repaired as quickly as possible to avoid excess blood and fluid loss and to minimise the onset of infection. Chronic wounds, where the progression of the wound healing response is compromised, presents several challenges to healing (e.g., the presence of devitalised tissue acting as a physical barrier to healing and being a focus for bacterial contamination and 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) which provides a simple treatment option that addresses a number of clinical challenges clinicians must overcome in order to facilitate wound healing progression. These studies demonstrated that this product supports successful debridement/cleansing of a wide variety of wounds, including chronic wounds, enables wound bed preparation, and leads to positive healing outcomes including in wounds that previously had failed to heal. The simplicity of using HRWD1 as a single dressing that can overcome a variety of challenges that present to the clinician when they are treating both acute and chronic wounds make it an ideal choice for a first line treatment, with the benefit of proven patient outcomes.

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

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Recent analysis of NHS statistics has shown that in the UK 2017/2018 there were an estimated 3.8 million patients with either acute or chronic wounds and of these 89% acute but only 49% chronic wounds healed.[1] The large number of patients with acute/chronic 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 the development of 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 T.I.M.E and D.I.M.E. protocols that have been developed to support healing progression. In the first instance this requires debridement (removal of devitalized tissue) and enabling wound bed preparations 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, ensure that blood and additional fluid loss is halted, and the open wound is sealed off from the exposure to potential contaminants (e.g., bacteria). However, in chronic wounds the vital tissue required for re-growth of the skin is prohibited and instead devitalised tissue (slough and eschar) develops.[5] This devitalised tissue, can prevent or delay a wound's normal healing process,[8,9] provides a nidus for bacteria (and biofilm formation) hence increases the risk of infection that may become deep seated in the tissues/bone or become systemic and life threatening.[8,10-12]

In light of this, a basic tenant therefore in the treatment of chronic (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 T.I.M.E. (Tissue, Infection, Moisture, Edge) management process.[13] There are a number of ways in which a clinician may remove this devitalised tissue.[14] One method, autolytic debridement, 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 autolysis enzymes (e.g., matrix metalloproteinases (MMPs)) play a key role in tissue breakdown. These enzymes require a certain level of moisture within their molecular structure for them to maintain their correct shape and to deliver their full specific activities.[16] A moist wound environment allows the tissue's own enzymes (e.g., elastases, collagenases (MMPs), myeloperoxidase, acid hydrolases and lysosomal enzymes) to soften, digest and liquefy devitalised tissue.[17-19] 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 aims to simplify wound dressing choice when applying the concept of T.I.M.E. in the management of wounds.[20] The first dressing, HydroClean® (HRWD1), 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 and absorbing bacteria- and proteinase-laden exudate into its absorbent core.[21] Thus, the wound bed is prepared for the next stages of the healing processes, the development of granulation tissue, reepithelialisation and healing progression. These latter stages of wound progression are supported by another HRWD, HydroTac (HRWD2), and will be the subject of a future review. Consequently, the treatment of chronic wounds must address a number of different challenges in terms of removing devitalized tissue, overcoming the pathology that has delayed healing progression, reducing the level of infection (inherent in chronic wounds) managing the levels of exudate and associated pain seen in these wound types (Table 1).

AIM

The aim of this narrative review is to present clinical evidence supporting the use of the unique Hydro-Responsive Wound Dressings HRWD1 that provides simple treatment options to address a number of different clinical challenges that fall within the standard wound care frameworks. Removal of devitalised tissue and wound bed preparation using HRWD1 (HydroClean®) will be discussed in Part 1 of this narrative review.

METHOD

The PubMed/MEDLINE database was searched between January 1970 and July 2021, on the use of hydro-responsive wound dressings 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 HWRD1 as possible. In addition, a manual search of wound care/management-related peer-reviewed journals and conference proceedings not indexed in PubMed/MEDLINE 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

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 wounds that required removal of devitalized tissue to promote healing. Generally, the results from 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 pre-requisite for wound progression, specifically for wounds with devitalised tissue which is a major barrier to healing progression.[8,23,24] WBP can be summarised by T.I.M.E., an acronym for a now well-established and widely-used systematic approach to the management of wounds into four major principles.[25]

The first step in WBP is the removal of that devitalised tissue using various methods of debridement.[24] 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.[8,26,27] 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.[28] The establishment of this moist healing environment promotes the cleansing of the wound via autolytic debridement[29] and the conditioning of the wound bed, optimising the conditions for subsequent healing according to the T.I.M.E. principles.[20,30,31]

Clinical studies have shown that using HRWD1 has enabled successful and rapid autolytic debridement of wounds that have high levels of devitalised tissue (Table 2 and 3). For example, a study of the effectiveness of HRWD1 in the debridement and wound bed preparation of pressure ulcers, diabetic foot ulcers, surgical wounds, traumatic wounds, burns (n=100) was investigated in a clinical, prospective, non-comparative, multi-centre 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%.[32] The clinical evidence provided in this study supports the position that there is a necessity to clean and debride instead of using an antimicrobial on devitalised tissue as set out in the Health Improvement Scotland Health Technology Assessment (https://tinyurl.com/yuseab7p). A sub-population analysis on 10 patients with pressure

ulcers (PU) showed that the use of HRWD1 on patients with long-standing PU enabled removal of substantial elements of devitalised tissue within the wound (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 correspondingly reduction in wound area (by 50%), showing a clinically relevant healing response was seen upon treatment with HRWD. An example of this clinically-relevant debridement by HRWD1 is exemplified by the case study presented in Fig 1.

Similarly, another study evaluating the use of HRWD1 with both acute and chronic wounds (n=86) showed a decrease in the percentage of predominantly fibrinous/necrotic wounds from the start to completion of the treatment (84.7% to 11.8%, respectively) that led to a positive wound healing response.[33] Further evidence that supporting the premise that HRWD1 enables wound bed preparation was demonstrated in an open, prospective, randomised, controlled trial evaluating the wound bed preparation ability of HRWD1 (n=34) versus an amorphous gel (n=41) in with venous leg ulcers (VLU) of greater than 4-weeks duration. The results showed that ulcer area covered by slough and necrosis decreased by 37.6% and 16.8% (HRWD1 vs. hydrogel, respectively) compared to the baseline (P=0.004). Additionally, granulation tissue increased by 36.0% and 14.5% (HRWD1 vs. hydrogel, respectively) compared to the baseline (p=0.005).[34] In a multi-centre, 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 wound bed preparation (by the promotion of autolytic debridement to remove devitalised tissue, and wound progression), the results showed that two patients progressed to healing, and there was a reduction in wound size was seen in a further nine patients.[35] In another study, a photographic wound assessment tool[36] was used to assess the status of 41 wounds based upon digital photos taken during the study. There was a significant decrease in the revPWAT total score from 19.5 ± 4.8 (median = 21, range 3-28) to 11.8 ± 6.3 (median = 13, range 0-25). Thirty-four 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.[37]

Delayed wound healing

Chronic wounds have become stuck at an early stage of the normal wound healing process and require active promotion to progress and achieve complete healing.[38,39] Two basic tenets for the treatment of chronic wounds are 1) debridement and removal of devitalised tissue – a focus of infection and a barrier to healing,[40,41] and 2) the management of wound exudate levels with the optimization of the wound environment moisture balance.[42] Hence, wound dressings that promote debridement and the creation of a moist wound healing environment encourages wound healing, particularly in more complex wounds such as leg ulcers.[28] HRWD1s can help manage both points 1 and 2 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 the 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). But, evidence that supports the position that HRWD1 enables wound healing progressions 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 chronic wounds. The majority (51.4%) of these patients had chronic wounds that showed no signs of wound progression within 4 weeks prior to study. After treatment with HRWD1, there was a positive healing trajectory (e.g., reduction in mean wound area versus baseline) over the treatment period of treatment (Fig 2). Additionally, a high level (93%) of chronic wounds demonstrated wound progression upon treatment with HRWD1.[32]

Another multi-centre clinical evaluation (n=86) of both acute and chronic wounds of varying severity and duration were evaluated after treatment with HRWD1.[33] The results showed that wounds were successfully cleansed/debrided with a corresponding statistically significant increase 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 reepithelialization 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[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 ± 59.3 cm² to 12.4 ± 36.7 cm ($p<0.0069$)). These results indicated that there was excellent wound progression when these previously recalcitrant wounds were treated with HRWD1. Additionally, it was reported in a multi-centre, two-arm parallel-group study in patients (n=75) with non-healing VLU's that were treated either with a HRWD1 or an amorphous gel that HRWD1-treated wounds demonstrated a larger reduction in fibrin slough/necrotic tissue compared to 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 to the baseline ($p=0.005$).[34] Fig 3 highlights a case study that indicating the effectiveness of the HRWD1 facilitating the healing of a serious burn.

The evidence presented here compare favorably with that presented by other authors that have reviewed the effectiveness of the wound healing support by both traditional[44-46] and advanced[47,48] (smart) dressings. The transition from a static wound to one that reverts to a healing trajectory as shown by the high number of chronic wounds with a population at any one time.[2] Evidence based

medicine must play a part in identifying wound dressings that can enable this transition and the evidence supplied here supports the use of HRWD1 in doing so.[49]

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 pathogenic and subsequent development of biofilm.[50] The association between wound bioburden and chronicity is a well-recognised but complex problem[51] that is worsened by the presence of devitalised tissue in the wound bed that acts as a focus for microorganism growth and possible infection.[8] Hence, the removal of this tissue is an 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.[29] There have been numerous antimicrobial approaches to aid in the reduction of this bioburden,[52] by for example the use of antiseptics[53] and antibiotics.[54] However, the use of these have significant disadvantages, not least the growth of antimicrobial resistance to antimicrobial agents.[55,56] The development of Non-Medicated Wound Dressings (NMWD) has, however, provided alternate treatment options without the downside of inducing antimicrobial resistance.[57] This potential for wound bioburden-modulation has been identified as related to the microorganisms-binding properties of such dressings, as has demonstrated in a number of laboratory-based studies for HRWD1.[57,58] HRWD1 has been classified as a Non-Medicated Wound Dressing and the mechanism of action by which this dressing enables a reduction of infection is “physical” not an “active” (see Table 4).[59] It is also noteworthy that NMWDs such as HRWD1 have been shown to be successful in treating superficial wound infections caused by microorganisms showing antimicrobial resistance (AMR) and, therefore, will be useful in supporting antimicrobial stewardship (AMS) strategies.[60]

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 chronic wounds.[32] 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 binding properties of the HRWD1 for microorganisms. In an open-label non-comparative study in patients with a variety of acute and hard-to-heal wounds treatment with HRWD1 for up to 25 weeks that resulted in a decrease in the percentage of wounds with devitalised tissue and a 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 multi-centre observational study in 170 patients with a variety of chronic wounds.[61] The number of wounds showing clinical signs of infection reduced from 53% to 9% in a study of patients (n=221) with chronic wounds treated with HRWD1 for 1 month.[62] And, in a prospective, non-comparative multi-centre observational study in 403 patients with a variety of chronic 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 chronic wounds where wound exudate can be damaging to tissue, requires that any dressing maintains a moist wound environment (hydration management) whilst at the same time manages excessive production of wound exudate (exudate management).[63]

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.[64] Wound hydration and maintenance of a moist wound has been the basis for modern wound care since George Winter's landmark pre-clinical studies[65] and Hinman & Maibach's clinical[66] 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 wound bed preparation and enables progression of healing in both acute and chronic wounds.[67] HRWD1 is responsive to the wound environment in that it can be both donating or draw moisture under different wound conditions. HRWD1 is pre-activated with Ringer's solution that is donated to the wound environment,[35] whilst at the same time, bacteria and tissue 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 solution salts.[61] This effect produces a continuous rinsing effect for supporting effective wound bed preparation.

Exudate management

Wound exudate is a normal component of healing in acute wounds and is the result of the inflammatory process.[68] Acute wound fluid is mainly water but also contains salts, proteins, protein-digesting enzymes (including matrix metallopeptidases (MMPs)), growth factors, cells types (e.g.,

inflammatory cells, platelets), and microorganisms.[63,69] 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.[70] However, it is generally accepted that chronic wound exudate is detrimental to tissues contains elevated levels of protein-degrading enzymes such as MMPs that can degrade the wound tissue and peri-ulcer skin.[71,72] If this wound exudate is managed by dressings inappropriate for the management of exudate (i.e., they 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 costs of treatment.[69] Tissue maceration due to the prolonged exposure of tissue – particularly peri-wound skin – to exudate has been a concern in particular, the clinical observations of peri-wound damage and tissue maceration around more complex wounds where management of wound exudate has been shown to be lacking using inappropriate dressings.[42] 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.[32,35,61,73] In a multi-centre clinical evaluation (n=86), acute and chronic wounds of varying severity and duration were evaluated after treatment with HRWD1 using the PUSH assessment tool to monitor healing progression.[33] One 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 randomized controlled study on VLU.[45] After treatment with HRWD1 there was an improvement in peri-wound skin condition, with an increase in the percentage of patients with healthy wound margin skin (from 25% to 55%) suggesting that 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 which facilitates the progression of the wound towards healing.[74-76] However, in difficult-to-heal wounds such as chronic wounds (e.g., leg ulcers and pressure ulcers), there is an elevated and sustained level of these destructive enzymes. These enzymes now 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 chronic wounds showed that MMPs bound to the superabsorbent material of the dressing reducing the excess levels of these degrading enzymes.[77]

Pain management

Pain is a major concern for patients with a wide range of both acute and chronic 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).[78] In wounds that do not heal, persistent pain may develop and become a chronic pain condition affecting the patient's overall healtha.[79,80] If wound pain is not addressed, recalcitrant pain develops, which is associated with impaired mobility, insomnia, depression, and suicidal considerations.[81,82] 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.[83] 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,[84] while non-cyclic nociceptive pain results from one-off procedures such as sharp wound debridement.[85] An important aspect relates to pain at wound dressing change, whereby the actual dressing may be responsible for causing pain upon traumatic removal.[86] Alongside the direct pain resulting from the wound, infection may also increase wound-associated pain.[87] The majority of clinical studies we reviewed have demonstrated pain/pain reduction after application of HRWD1 (Tables 2 and 3). Some cases have suggested a "soothing effect" of the dressing.[32,88] With regards to the pain management effect of the HRWD1, this has been related to (in part) the Ringers solution component within the dressing that could effectively have a number of pathways for pain reduction.[89]

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/chronic wounds reported that the number of patients reporting "intermediate" or "high" levels of wound pain perception decreased from 64% to 19%.[62] A multi-centre 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.[61] In a single-centre observational study in patients with VLUs, 89% (33/37) of patients reported no or "slight" pain at HRWD1 dressing

changes.[90] And in a multi-centre, non-comparative clinical evaluation of HRWD1 in a variety of acute and chronic wounds, it was found that no patients experienced pain at dressing changes.[35] A case study presents evidence related to a reduction in wound pain, this 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 peri-wound 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.[91]

CONCLUSION

HRWD1 is designed for the management of wounds that requiring cleansing/debridement (to remove devitalized tissue) and good exudate management both of which are needed to encourage an optimal wound environment and to 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 shows that HRWD1 can promote wound cleansing and removal of devitalised wound tissue in poorly healing or infected wounds via autolytic debridement. They have been shown to achieve wound progression and to promote granulation tissue formation in more complex wounds along with excellent fluid-handling properties, to be easy to use, and to be comfortable for the patient. This dressing has also been shown reduce levels of wound pain and pain experienced at dressing changes. In addition, that these dressings (defined now as NMWD) have a “physical” anti-microbial action, which makes their use crucial in supporting an AMS strategy.

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 e.g., biased towards HydroClean) this ultimately affects the way the studies are analysed, and the conclusions drawn. But the premise of the aim of the study is clinical review of HydroClean therefore in this respect this is an accepted methodology.

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Table 1. Challenges of treating chronic wounds

Challenges	Comments
Presence of devitalised tissue	• Both acute and chronic wounds can develop areas of devitalised tissue (e.g., eschar and slough) that occurs because of various factors that cause localised tissue death e.g., poor blood supply, excessive levels of wound exudate (that contains MMPs) leading to infected tissue and ultimately delays healing[92]
Delayed wound healing	• Well-established that dermal wound healing progresses through a series of distinct but overlapping, inter-dependent steps (phases) to ensure that any disruption in skin integrity is repaired as quickly as possible[93] • Any disruption of the normal progression of any phase of healing leads to delayed healing • Investigations suggest that the underlying disease processes that cause non-healing wounds such as venous leg ulcers, pressure ulcers and diabetic foot ulcers disturb the normal progression of wound healing, halting the healing response in the inflammatory phase[94]
Presence of wound bioburden	• Most wounds carry a level of bioburden that do not interfere with the healing process[95] and some commensal skin bacteria may even be beneficial to the healing process[96] • When the bioburden reaches a certain level or specific wound pathogens prevail then infection occurs[97] • Wound infection can severely impact the progress of healing and in some cases (in diabetic patients with DFU) lead to amputation and an increase in mortality[98]
Exudate	• One of the key causes of the delayed healing in ulceration is the increased levels of protein-degrading enzyme activity within the wound.[99,100] This leads to uncontrolled and elevated level of inflammatory cells in non-healing wound tissues and results in disruptive tissue degradation[74,75]
Pain	• A high proportion (up to 80%) of patients with chronic 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.[101] 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 3.4-4.5)[78]

Table 2. Clinical studies of HRWD1 on chronic wounds

	Study type	Sample size	Wound type(s)	Main Outcome Measures	Main Results
Hodgson et al, 2017[32]	Open-labelled, non-comparative study	100	Acute and hard-to-heal wounds including venous leg ulcers, arterial ulcers, diabetic foot ulcers, and pressure ulcers	Debridement, wound healing pain infection	Effective, rapid and painless debridement of wounds Positive healing outcomes and an increase in healthy granulation tissue The number of patients with infected wounds reduced
Sterpione et al, 2021[33]	Open-labelled, non-comparative study	86	Acute and hard-to-heal wounds including venous leg ulcers, arterial ulcers, diabetic foot ulcers, and pressure ulcers	- Assessment of wound healing progression (as measured by PUSH score) - Pain experienced at dressing change - Assessment of wound severity - Wound response to treatment - Clinical signs of infection - Ease of use of dressing - Performance of dressing (ease of use, patient acceptability)	- Wound progression as measured by a decrease in PUSH score from a mean of 11.9 ± 2.9 to 7.0 ± 4.5 ($p<0.0001$) - Decrease in wound size (median 12.0 cm^2 to 2.8 cm^2, $p=0.0069$) - Decrease in wounds with exudate (95.3% to 59.3%, $p<0.0001$) - Decrease in percentage of wounds with predominantly devitalised tissue (84.7% to 11.8%) - Increase in granulation tissue (15.3% to 88.2%) ($p<0.0001$) - Only 20% (62/310) of dressing removals resulted in pain (>30 mm, VAS) - Proportion of infected wounds decreased over study period (19.3% to 3.6%, $p<0.01$) - Ease of use rated very good/good by >95% clinicians
Humbert et al, 2014[34]	Open, multi-centre, prospective, randomised, controlled study	75	Venous leg ulcers	- Levels of slough and necrotic tissue - Granulation tissue formation - Cost-benefit analysis[64]	- Greater reduction in HRWD1 group of proportion of ulcer area covered by slough and necrotic tissue - Greater proportion in HRWD1 group of proportion of ulcer covered by granulation tissue - Response rates of hard-to-heal ulcers of >6 months duration higher in HRWD1 group - Cost-benefit analysis favoured HRWD1 group[64]
Kaspar et al, 2008[62]	Open, prospective observational study	221	Chronic wounds including venous leg ulcers, arterial ulcers, mixed aetiology ulcers, diabetic foot ulcers and burns	- Level of fibrinous slough - Number of wounds showing granulation tissue formation - Clinical signs of infection - Wounds with high exudate levels - Wound pain	- Number of wounds completely or partially (>50% surface area) covered in fibrinous slough decreased from 54% to 9% - Number of wounds showing granulation tissue (>50% surface area) increased from 5% to 74% - Number of wounds showing clinical signs of infection reduced from 53% to 9% - Number of wounds with high exudate levels reduced from 74% to 10% - Number of patients reporting “intermediate” to “high” levels of wound pain perception decreased from 64% to 19%
Mwipatayi et al, 2005[102]	Prospective non-controlled case series study	10	Chronic wounds including venous leg ulcer, diabetic foot ulcer and arterial ulcers	- Assessment of wound bed - Monitor reduction in wound area	- Rate of wound debridement estimated as an average of 6% per day - Wound area reduction measured during HRWD1 application - Two patients showed no wound bed debridement - Three patients noted pain during dressing change. No follow-up was noted
König et al, 2005[73]	Prospective, randomised study	42	Venous leg ulcers	- Levels of eschar, slough and necrotic tissue - Levels of granulation tissue formation	- Slough within the groups reduced by almost 19% (HRWD1) compared with 9% (enzyme) - Granulation tissue area increased by 26% (HRWD1) compared with 10% (enzyme) - Dressing and enzymatic agent equally effective at reducing levels of necrotic tissue and wound coatings - HRWD1 promoted moist wound environment - HRWD1 managed excessive exudate and tissue debris
Scholz et al, 1999[90]	Single centre observational study	37	Venous leg ulcers	- Level of fibrinous coatings - Level of necrotic tissue - Granulation tissue formation - Exudate levels	- Significant reduction in fibrinous and necrotic tissue - Promotion of granulation tissue formation - Wounds showing “moderate/severe” exudate decreased from 28 to 8 - 33 patients reported no or “slight” pain at dressing change

				- Wound pain	
Spruce et al, 2016[35]	Multi-centre, non-comparative, clinical evaluation	20	Acute and chronic wounds	- Assessment of wound bed preparation - Assessment of wound progression (wound area & wound depth) - Performance of dressing (ease of application, removal) - Cost-benefit analysis	- Two patients progressed to healing - Reduction in wound size and/or depth in a further nine patients - Two wounds were completely debrided, and six wounds were debrided to 80-99% healthy tissue - No patients experienced pain on dressing change - Proportion of patients experiencing wound pain reduced from 95% to 35% - Potential cost savings associated with using HRWD1
Mancini et al, 2017[103]	Prospective, non-controlled case series study	28	Leg ulcers including venous leg ulcers, diabetic foot ulcers, and mixed aetiology ulcers	- Assessment of wound bed - Monitor levels of slough and granulation tissue	- Reduction in levels of slough - Increase in levels of healthy granulation tissue
Rippon and Ousey, 2016[61]	Prospective, non-comparative, multi-centre observational study	403	Chronic wounds including venous leg ulcers, arterial ulcers, decubitus ulcers, diabetic foot ulcers, mixed venous/arterial ulcers and burns	- Level of wound bed fibrinous coatings - Wound granulation - Clinical signs of infection - Wound pain - Physician evaluation of effectiveness and handling - Patient evaluation of tolerability, wearing comfort and pain during treatment	- Number of wounds with >50% fibrinous coating decreased from 56% to 8% - Levels of necrotic tissue reduced from 32% to 5% of wounds - Number of wounds with florid granulation tissue increased from 6% to 69% - Significant reduction in wound pain - Infections decreased - Wound edge damage showed significant improvement - >90% of physicians evaluated HRWD1 “very good” or “good” - >94% of patients evaluated HRWD1 “very good” or “good”
Rippon and Ousey, 2016[61]	Multi-centre observational study	170	Chronic wounds including venous leg ulcers, decubitus ulcers, arterial leg ulcers, diabetic foot ulcers and traumatic wounds	- Level of wound bed fibrinous coatings - Level of wound bed necrosis - Wound granulation - Clinical signs of infection - Wound pain - Physician evaluation of effectiveness - Patient evaluation of tolerability, wearing comfort and pain during treatment	- Number of wounds with necrosis decreased from 17% to 10% - Number of wounds with fibrinous coatings decreased from 41% to 33% - Proportion of granulation tissue increased from 35% to 46% - Proportion of epithelial tissue increased from 6% to 11% - Wound edge damage reduced from 71% to 62% - Wounds with clinical signs of infection reduced from 24% to 17% - Patients experiencing moderate to severe wound pain reduced from 35% to 19% - Levels of moderate to severe wound pain at dressing change decreased from 26% to 11% - Over 85% physicians evaluated dressing removability as “good” or “very good” - >90% physicians evaluated HRWD1 “very good” or “good” - >80% patients evaluated HRWD1 “very good” or “good”
Rippon and Ousey, 2016[61]	Single centre observational study	14	Chronic wounds including venous leg ulcers and mixed (venous/arterial) aetiology ulcers	- Level of fibrinous coating - Level of necrotic tissue - Granulation tissue formation - Patient tolerability of dressing - Peri-wound skin condition	- Significant reduction in fibrinous and necrotic tissue - Promotion of granulation tissue formation - Improvement in peri-wound skin condition; reduction in erythema (n=5) and reduction in desquamation (n=3) - Wounds sufficiently cleansed for split-skin grafting within 7-10 days
Sterpione et al, 2021[37]	Open-labelled, non-comparative study	130	Acute and hard-to-heal wounds including venous leg ulcers, diabetic foot ulcers, mixed aetiology ulcers, burns, and traumatic wounds	- Assessment of wound healing progression (as measured by revPWAT tool) - Clinical signs of infection - Peri-wound skin condition	- Reduction in mean wound area (25.1%, p=0.049) and wound volume (48.7%, p=0.046) - Decrease in median revPWAT score from 21 to 13 indicating an improvement in wounds over the treatment period - Decrease in levels of devitalised tissue and corresponding increase in granulation tissue levels - Improvement in the status of both wound edge and peri-wound skin condition when treated with HRWD1 over the course of the study period

Table 3. Clinical evaluations of HRWD1 on chronic wounds

	Study type	Sample size	Wound type(s)	Main Outcome Measures	Main Results
Ousey et al, 2016[21]	Case series	3	Foot ulcer, mixed aetiology ulcer, pressure ulcer	- Wound debridement - Per-wound skin condition	- Removal of devitalised tissue - Wound progression - Improvement of peri-wound skin - Reduced pain
Haycocks and Chadwick, 2017[104]	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[105]	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[106]	Case report	1	Hard-to-heal wound	- Wound debridement - Wound progression - Pain	- Removal of devitalised tissue - Wound progression - Reduced pain
Cooper, 1998[107]	Case report	1	Leg ulcer	- Wound debridement - Granulation tissue formation	- Removal of devitalised tissue - Increase in granulation tissue
Chadwick and Haycocks, 2016[108]	Case series	5	Diabetic foot ulcer	- Assessment of wound bed	- Removal of devitalised tissue - Increase of granulation tissue
Rippon and Ousey, 2016[61]	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, 2016[61]	Case series	3	Mixed aetiology ulcer, pressure ulcer	- Wound debridement - Granulation tissue formation	- Removal of devitalised tissue - Increase in granulation tissue
Rippon and Ousey, 2016[61]	Case report	1	Pressure ulcer	- Wound debridement - Wound conditioning	- Removal of devitalised tissue - Wound progression
Rippon and Ousey, 2016[61]	Case series	3	Venous leg ulcer, pressure ulcer	- Wound debridement - Wound progression - Pain	- Removal of devitalised tissue - Increase granulation tissue - Peri-wound skin improvement - Reduced pain and exudate levels
Rippon and Ousey, 2016[61]	Case report	1	Venous leg ulcer	- Wound debridement - Granulation tissue formation - Wound progression - Pain - Peri-wound skin condition	- Removal of devitalised tissue - Increase in granulation tissue - Reduced pain and exudate levels - Wound progression
Rippon and Ousey, 2016[61]	Case series	7	Pressure ulcer, venous leg ulcer, foot ulcer	- Wound debridement - Wound conditioning - Wound progression - Granulation tissue formation - Pain	- Removed devitalised tissue - Increase in granulation tissue - Wound progression - Reduced pain levels
Rippon and Ousey, 2016[61]	Case series	7	Pressure ulcer, arterial ulcer, venous leg ulcer	- Wound debridement - Granulation tissue formation	- Removed devitalised tissue - Increase in granulation tissue

				- Wound progression	- Wound progression
Knowles et al, 2016[108]	Case report	1	Pressure ulcer	- Wound debridement - Wound size reduction	- Removed devitalised tissue - Reduction in wound size
Knowles et al, 2016[108]	Case report	1	Pressure ulcer	- Wound debridement - Granulation tissue formation	- Removed devitalised tissue - Increase in granulation tissue
Knowles et al, 2016[108]	Case report	1	Hard-to-heal wound	- Wound debridement - Granulation tissue formation - Pain - Wound progression	- Removal of devitalised tissue - Increase in granulation tissue - Reduced pain levels - Wound progression

Table 4. Properties of HRWD1, a Non-Medicated Wound Dressing (NMWD)[59]
• Debridement and removal of devitalised tissue and break-up of wound surface biofilm
• Absorption of microorganisms (planktonic and biofilm-associated), MMPs and bacterial endotoxins
• Sequestration of microorganisms
• Retention and immobilization of microorganisms within the wound dressing matrix
• Removal of microorganisms with the dressing at routine dressing change

Fig 1. Case study demonstrating wound debridement/cleansing and wound bed preparation by HRWD1 (adapted from Hodgson et al, 2017[32])

A female patient with a sacral pressure ulcer presented with 100% wound bed coverage with black necrotic tissue and inflamed peri-wound skin. Exudate levels were low and there was no sign of clinical infection.

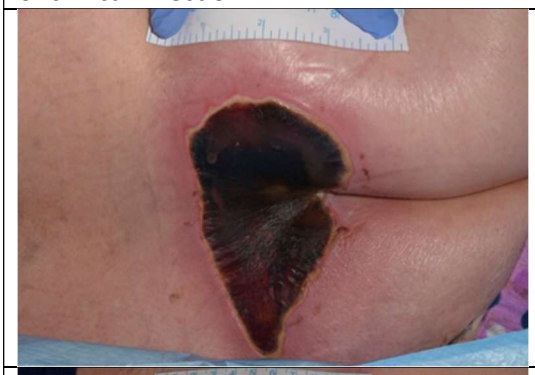
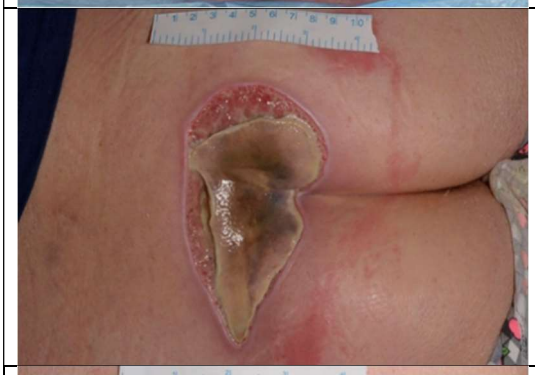
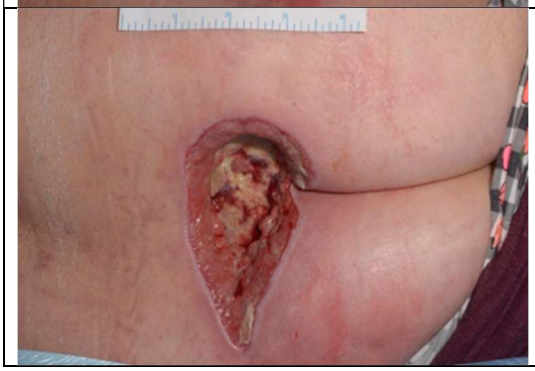
	Wound at presentation. Note complete coverage of wound with black devitalised tissue and reddened peri-wound skin. HRWD applied and the dressing was changed every three days.
	Eight days after commencement with HRWD1 treatment black devitalised tissue debridement seen and leaving a layer of yellowish slough that had begun to detach from wound margins. Wound margins appeared less inflamed. Healthy-looking granulation tissue could also be observed where devitalised tissue had lifted from wound bed.
	As HRWD1 treatment continued slough levels decreased and there was a corresponding increase in visible granulation tissue. Sharp debridement was applied to clean wound of the remaining devitalised tissue.

Fig 2. Change in normalised mean wound area over the course of the study evaluation period (adapted from Hogdson et al, 2017[32])

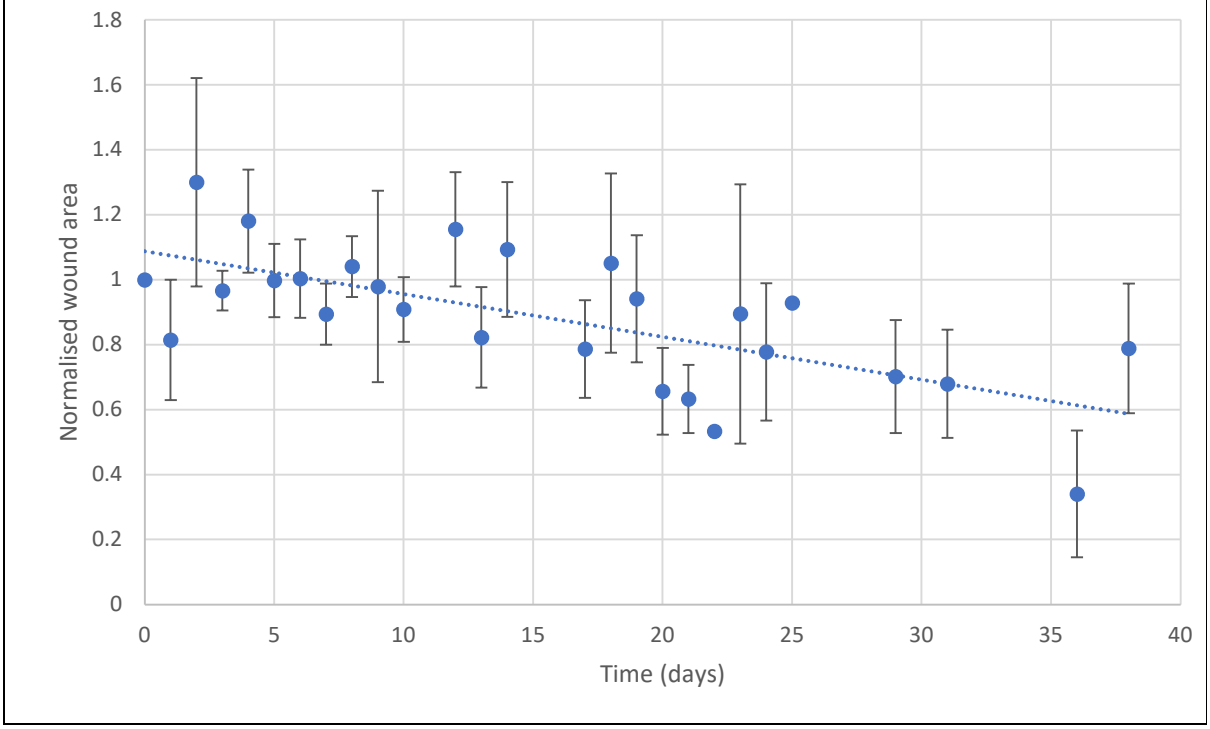
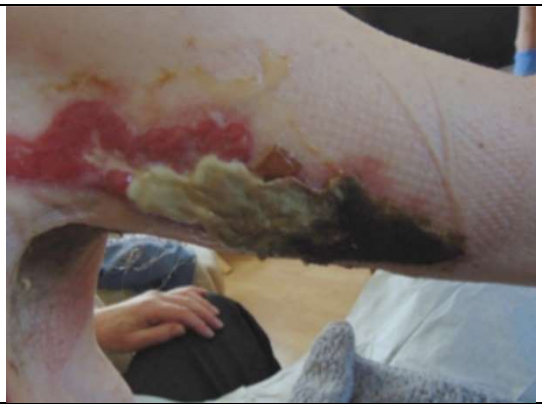


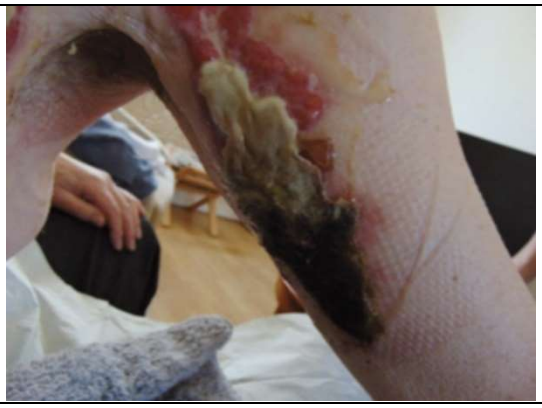
Fig 3. Case report of patient with serious burn wound before and after treatment with HRWD1 (adapted from Butters et al, 2019[88])

A 72-year-old male who burnt himself with hot water and porridge. Wound duration was seven weeks. The wound showed slow autolytic debridement over the previous seven weeks with conventional wound dressings. The wound had a slight odour. The wound was treated with HRWD1.

The wound bed desloughed within fourteen days and the condition of the peri-wound skin was good. The dressing hydrated the area well and enabled the use of some sharp debridement to show a clean wound bed. The wound showed excellent wound progression during HRWD1 treatment.



12-Apr-2017



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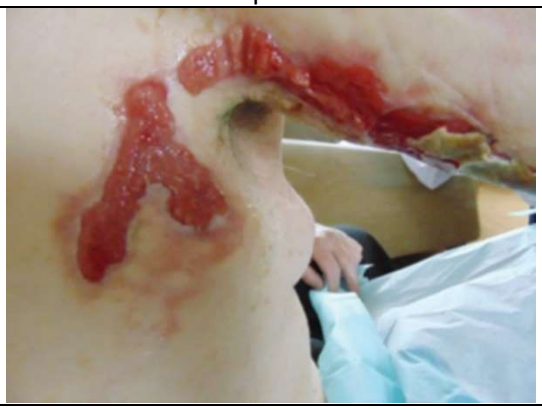

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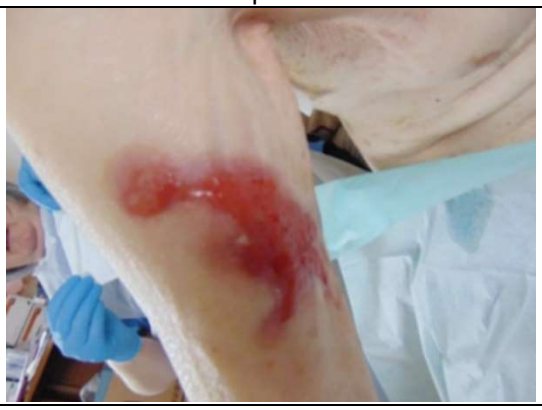

12-May-17

Fig 4. Promotion of wound cleansing of a leg ulcer in a patient with systemic lupus erythematosus (SLE) by HRWD1[61]

A 44-year-old female with SLE and bilateral leg ulcers presented with sepsis of bilateral circumferential ulcers. Application of compression was problematic and the patient had a history of cellulitis over a period of 18 months. At presentation, the wound had 100% devitalised tissue, low wound exudate, and a high level of pain. The peri-wound area was inflamed with no maceration. HRWD1 was applied and the dressing was changed every three days. After fourteen days the level of black necrosis had reduced and there were areas of granulation tissue visible. At the final examination, the wound showed continuing improvement. The patient reported reduced pain levels.

At presentation	Day 14	End of assessment