

Hydro-responsive wound dressings simplify T.I.M.E. wound management framework

Karen Ousey, PhD, Professor and Director for the Institute of Skin Integrity and Infection Prevention, School of Human and Health Sciences, University of Huddersfield, Queensgate, West Yorkshire. HD1 3DH. Tel: 01484-473462 E-mail: k.j.ousey@hud.ac.uk

Alan A Rogers, BSc (Hons), Independent Wound Care Consultant, Flintshire, UK

Mark G. Rippon, PhD, Visiting Clinical Research Fellow, School of Human and Health Sciences, University of Huddersfield, Queensgate, West Yorkshire, HD1 3DH

## **ABSTRACT**

The development of wound management protocols and guidelines such as the T.I.M.E. acronym are useful tools to aid wound care practitioners deliver effective wound care. The T.I.M.E. framework provides a systematic approach for the assessment and management of the majority of acute and chronic wounds. The debridement of devitalised tissue from the wound bed, the reduction in wound bioburden and effective management of wound exudate – i.e., wound bed preparation – are barriers to wound healing progression that are targeted by T.I.M.E. There are a large number of wound dressings available to experienced wound care practitioners to aid in their goal of healing wounds. Despite the systematic approach of T.I.M.E., the large number of wound dressings available can introduce a level of confusion when dressing choices need to be made. Any simplification in dressing choice, for example by choosing a dressing system comprising of a limited number of dressings that are able to address all aspects of T.I.M.E., would be a valuable resource for delivering effective wound care. This article reviews briefly the principles of T.I.M.E. and describes the evidence for the use of a two-dressing, moisture balance-oriented dressing-based wound management system for the treatment of wounds and that addresses principle requirements of delivering T.I.M.E.

Chronic wounds present a challenge to wound care practitioners. Normal wound healing is a complex process that relies on the progression of a series of interdependent phases that repairs tissue damage and, ideally, returns structure and function to the tissue defect. Unlike acute wounds, chronic wounds have impaired healing responses, where they appear to have become stuck in the inflammatory phase of the healing response.<sup>1</sup> The challenge faced by clinicians is to ‘convert’ these chronic wounds into healing wounds by resolving the signals responsible for the delayed healing profile and stimulating/optimising the healing response.

Alongside a better understanding of the mechanisms responsible for delayed wound healing in ulcers (e.g., leg ulcers, pressure ulcers), advanced wound dressings have been developed – based upon an improving understanding of healing – that are designed to support the healing of chronic wounds.<sup>2</sup> These wound dressings allow for optimal moisture balance at all stages of the healing process. The establishment of a moist wound healing environment is known to promote effective healing.<sup>3,4</sup> Wound bed preparation<sup>5</sup> is a necessary early step in wound care as it prepares the wound tissue for subsequent healing; this tissue preparation is supported by advanced wound dressings that promote a moist healing environment and autolytic debridement.

The development of wound management protocols such as T.I.M.E. (an acronym for a process of achieving wound bed preparation) aides wound care providers by detailing a practical guide for use when treating patients with problematic wounds.<sup>6</sup> Advanced wound dressings play a major role in delivering effective wound care within the T.I.M.E. framework. However, there are a large number of dressings available and it can be difficult for practitioners to identify which dressings are appropriate to promote which part of the healing response. This is in part due to the observation that there is “no single dressing suitable for the management of all wounds, and there are few dressings that are ideally suited for the treatment of a single wound during all stages of the healing process” (p66).<sup>7</sup>

This article briefly reviews the T.I.M.E. framework highlighting a dressing wound management system that focuses on delivering optimal moisture balance across all phases of healing while delivering benefits of the T.I.M.E. framework.

## **T.I.M.E. WOUND MANAGEMENT**

Wound care has advanced at a rapid pace in recent years. Advanced wound dressings and updated wound care guidelines are designed to assist healthcare practitioners in ensuring that optimal treatment is used for the wide range of wounds encountered. Since its introduction in 2002, the T.I.M.E framework has played an important role in aiding wound care practitioners to promote effective wound healing.<sup>6,8</sup> Figure 1 summarises the sections of the T.I.M.E framework.

***T: Tissue Management – wound bed preparation & removal of devitalised tissue***

Wound bed preparation is vital to progressing a difficult-to-heal wound on the path to healing. The presence of devitalised tissue (e.g., necrosis and/or slough) is a barrier to healing responses and is a focus for bacterial growth and potential infection. Devitalised wound tissue also contributes to the heightened inflammatory status of these wounds.<sup>9</sup> In addition, the presence of devitalised tissue over the wound also obscures the wound bed from clinical assessment and its removal is required. Debridement of these wounds is necessary for the restoration of a viable wound bed for wound healing support.<sup>9,10</sup>

***I: Infection control & Inflammation – reduce bacterial load & minimise inflammation***

High levels of wound bacteria and uncontrolled inflammation are detrimental to wound healing. The host defence mechanisms of patients with chronic wounds are often compromised and results in these patients being more prone to wound infections.<sup>9</sup> As a consequence of wound infection, wounds may take longer to heal than expected.<sup>11–13</sup> Although critical for a healing wound, when the inflammatory response becomes elevated and sustained (as it does in chronic wounds), a delay in wound healing may be witnessed. There may be elevated inflammation due to high levels of wound bacteria and the high inflammatory status of chronic wounds due to the underlying wound aetiology<sup>14</sup> may have a negative impact on wound healing progression. Advanced wound dressings are one option for influencing infection control and inflammation, acting as barriers to wound contamination while maintaining a clean wound environment via cleansing some wound dressings will include antibacterial agents.<sup>15</sup>

***M: Moisture balance – exudate management & optimise hydration environment***

Through all phases of normal wound healing, moisture levels are balanced and maintained to optimise the healing response.<sup>16</sup> In chronic wounds, however, the disruption of the normal healing response results in a disturbance in hydration levels; for example, elevated levels of chronic wound exudate leads to problems.<sup>17</sup> Studies have identified that elevated hydration levels, per se, are not damaging and have demonstrated the benefits of a moist wound healing environment.<sup>3,4,18</sup> As mentioned above, elevated chronic wound tissue-based inflammation leads to high levels of damaging exudate components (e.g., proteinases) that can damage the wound bed and peri-wound skin if not effectively managed, leading to delayed healing.<sup>16,19,20</sup> Advanced wound dressings must balance moisture levels such that wounds are hydrated enough to promote a moist environment but tissues are not exposed to the elevated level of damaging components as discussed by Junker et al.,<sup>3</sup> Ousey et al.,<sup>4</sup> and Rippon et al..<sup>18</sup>

### ***E: Optimisation of wound Edge – promotion of epithelialisation***

When there is a lack of epidermal closure of a wound the wound bed and peri-wound skin must be optimised in order for healing opportunity to be maximised. Consideration of 'T', 'I' and 'M' parts of the T.I.M.E. framework must be completed.<sup>9</sup> Peri-wound epidermal cells are 'primed' to migrate across the wound bed<sup>21</sup> remove devitalised tissue from the wound bed ('T'). The modulation of wound bioburden and wound/peri-wound inflammatory status to pro-healing levels ('I' and 'M') and the establishment of a moist healing environment ('M') provides an optimised environment for wound coverage to progress.

Implementation of each of the four steps of T.I.M.E. (or similar frameworks, such as the US Wound Registry's D.I.M.E. (Debriement/devitalised tissue, Infection or inflammation, Moisture balance and wound Edge preparation/wound depth)<sup>22</sup>), can involve many different pathways and processes and a large number of wound dressings and products. For example, the treatment of a chronic wound can involve the use of a specific wound care product to promote wound debridement/removal of devitalised tissues such as necrosis and slough to prepare the wound bed, followed by application of a dressing to control infection/inflammation (with application of other products as necessary) and finally use of a secondary dressing for moisture control.

If active encouragement of epithelialisation is needed, another dressing may need to be applied. It is apparent that there are a plethora of products available to choose when managing a wound through the various stages of healing. Tissue viability teams need to fully understand the complex nature of the wound healing trajectory to be able to effectively identify appropriate wound care products.<sup>23</sup> It can therefore be assumed that simplification of product choice could assist practitioners with implementation of the T.I.M.E. framework in the assessment and management of wounds would prove beneficial.

### **A MOISTURE BALANCE-ORIENTATED DRESSING-BASED WOUND MANAGEMENT SYSTEM**

In an attempt to reduce the number of wound dressings required to deliver effective wound care, and reduce confusion when choosing a product,<sup>24-27</sup> a recently developed moisture balance-oriented dressing-based wound management system has been developed. This system aims to simplify wound dressing choice when applying the concept of T.I.M.E. in the management of chronic wounds. It is based upon two dressings (Hydro-Responsive Wound Dressings, HRWDs) that complement one another, delivering rapid cleansing, early granulation tissue formation, epithelialisation while maintaining a balanced level of moisture at all phases of wound progression

to support effective wound healing.<sup>28</sup> A review of laboratory and clinical evidence (see below) indicates that these HRWDs can implement all the steps involved in the T.I.M.E. framework (Figure 1).

#### **HRWD #1: Hydro-Responsive Wound Dressing activated by Ringer's solution**

HRWD #1 cleanses the wound by encouraging autolytic debridement of devitalised tissues present in the wound. The fluid handling characteristics of the dressing absorbs wound exudate and removes the bacteria and damaging chronic wound exudate components that can potentially affect healing progression.<sup>28</sup> The high Ringer's solution content within the core of the dressing acts as a reservoir for wound cleansing promotion. The high pH buffering capacity of the HRWD superabsorber modifies the pH of exudate with the Ringer's solution diluting biological exudate components that cause wound bed damage.<sup>29</sup> These characteristics mean that HRWD #1 can address the first three steps of T.I.M.E.; cleansing the wound bed (T), removes factors involved in infection and assists with inflammation control (I), and provides an optimal moist wound environment (M).

#### **HRWD #2: Hydro-Responsive Wound Dressing with AquaClear Gel Technology**

HRWD #2 is a foam dressing that uses AquaClear Gel Technology and an active moisture-release system to maintain the beneficial moist environment established by HRWD #1. The AquaClear Gel Technology promotes effective moisture balance in the latter stages of the progressing wound whilst at the same time concentrating within the moist environment growth factors that help promote re-epithelialisation.<sup>30</sup> HRWD #2 is able to address a number of steps of T.I.M.E. The ability to maintain a moist wound environment allows the dressing to maintain the optimal moisture balance (M) established by HRWD #1 and extend the optimal wound environment to support epithelialisation (E).

This simple moisture balance-oriented dressing-based wound management system provides support for all four of the T.I.M.E. management strategy steps (Figure 2). Chronic wounds can be the most challenging for clinicians as by definition these are wounds that do not progress through healing in a timely manner.<sup>31</sup> Chronic wounds should be carefully classified according to validated classification systems.<sup>32</sup> allowing wound care practitioners to assess whether a moisture balance-oriented dressing-based wound management system is suitable for these wound types.

#### **CLINICAL EVIDENCE TO SUPPORT MOISTURE BALANCE-ORIENTED DRESSING-BASED WOUND MANAGEMENT SYSTEM IMPACT IN T.I.M.E.**

HRWD #1 and HRWD #2 are designed to optimise hydration levels in wounds. Although based upon the core technology of superabsorbent polymers, current HRWDs have a long history in treating wounds. Over the course of over 20 years, modifications have led to improvements in the design of

these HRWDs but the core technology and the mechanism of action has remained constant.<sup>4</sup> For the purpose of this discussion, clinical studies based upon previous dressing iterations are included alongside studies conducted using the most recent versions.

HRWD #1 and HRWD #2 offer a simple wound management regimen that provides solutions to the T.I.M.E. wound management framework ( Table 1). The effective removal of necrotic tissue, fibrinous slough and bacteria-laden wound exudates and the promotion of granulation tissue formation and epithelialisation using the moisture balance-oriented dressing-based wound management system is supported by a number of clinical studies. The following sections summarise some of the key clinical studies for each of the four sections of the T.I.M.E. wound management framework (Tables 2-5).

***T: Tissue Management – wound bed preparation & removal of devitalised tissue (Table 2)***

At the centre of tissue management is the removal of necrotic or compromised tissue that is commonly present in chronic wounds.<sup>33</sup> Acting as a barrier to re-epithelialisation and as a potential reservoir for bacterial growth and possible infection, the removal of this devitalised tissue is the first step in ‘kick-starting’ these chronic wounds along the pathway of healing. Hydro-responsive wound dressings, are important tools in preparing wound beds by promoting autolytic debridement.

Data from a number of clinical studies and additional case studies (Table 2) suggests that dressings of the moisture balance-oriented dressing-based wound management portfolio are associated with a significant reduction in necrotic and devitalised tissues (including slough) including venous leg ulcers, diabetic foot ulcers and pressure ulcers.. The promotion of autolytic debridement of fibrinous slough and necrotic tissue results in a reduction in the proportion of the wound bed covered by devitalised tissue and a corresponding increase on the presence of granulation tissue. Observational studies where HRWD #1 was applied to wounds partially and/or significantly covered by devitalised tissue, resulted in significant removal of necrotic/sloughy tissue.<sup>34–37</sup> In one particular study, a multi-centre, open, prospective and randomised two-arm study comparing HRWD with an amorphous gel treatment in venous leg ulcer patients; the hydro-responsive wound dressings resulted in a rapid debridement of these wounds and a more effective promotion of autolytic debridement compared with the amorphous gel preparation.<sup>38</sup>

A significant number of additional studies, including case series studies and case studies (Table 1), all indicate that moisture balance-oriented dressing-based wound management system treatment results in the removal of devitalised tissue from wounds of varying aetiologies.

The cleansing action of HRWD #1 promotes the removal of devitalised tissue through the enhancement of autolytic debridement of the wound. Debridement, together with the increase in healthy granulation tissue prepares the wound bed for subsequent healing.

***I: Infection control & Inflammation – reduce bacterial load & minimise inflammation (Table 3)***

As well as the underlying disease processes that may result in the formation and maintenance of chronic wounds leading to tissue inflammation, the presence of elevated levels of bacterial contamination may also contribute to the stimulation of a localised inflammatory response in the wound bed adjacent to any devitalised tissues. The presence of the bacteria themselves may stimulate inflammation but bacterial toxins, including bacterial proteinases, also contribute to this inflammatory stimulus. HRWDs, with their novel fluid management capabilities, offer the capability to reduce wound bioburden<sup>39,40</sup> and local tissue inflammatory stimuli,<sup>41</sup> and by modulating the local wound environment via affecting the “I” section of the T.I.M.E. framework.

Data from three open, prospective, observational studies where one clinical outcome was changes in clinical signs of infection all show reduced evidence of wound infection when treated with HRWDs ( Table 3). Clinical studies of patients with variety of chronic wounds including venous leg ulcers, diabetic foot ulcers and pressure ulcers treated with HRWDs consistently showed a reduction in the number of wounds exhibiting clinical signs of infection. Laboratory studies examining the interaction between these dressings and micro-organisms suggest that HRWDs have the ability to absorb and retain significant numbers of micro-organisms either when these organisms are in suspension or presented to the dressing as an agar-covering mat.<sup>39,40</sup>

As well as the presence of elevated levels of bacteria in the wound bed, the presence of elevated levels of protein-degrading enzymes (from both bacterial contamination sources and from tissue-derived inflammatory cells) will potentiate local inflammation levels. Modulation of proteinase activity levels in and around the wound is likely to reduce the level of inflammatory stimuli experienced by the tissue. Studies examining the interaction between matrix metalloproteinases (MMPs) and the superabsorbent particles (SAPs) contained within moisture balance-oriented dressing-based wound management system dressings have indicated a significant effect on proteinase activities.<sup>41</sup> The SAPs contained within these dressings inhibited MMP activity from wound fluid from chronic venous leg ulcers by >87%. Interestingly, MMPs were inhibited via two mechanisms: 1) direct binding of MMPs by dressing materials, and 2) binding of co-factors necessary for MMP activity. The effective binding of proteinases by these dressings is likely to reduce the inflammatory stimuli affecting chronic wounds and its surroundings.

Cleansing the wound bed of devitalised tissue (necrotic and/or slough) by HRWD #1 reduces the wound's bacterial load via effective absorption and retention of micro-organisms. This action, together with the dressing's ability to retain damaging and irritant wound-derived components such as proteinases (MMPs), reduces and minimises additional inflammatory stimulus that is likely to be harmful to wound healing progression.

***M: Moisture balance – exudate management & optimise hydration environment (Table 4)***

Balancing skin hydration levels is important for the normal functioning of this important organ and disruption of moisture levels when skin wounding occurs upsets this fine balance.<sup>28</sup> Re-optimising moisture balance is a key requirement for the tissue and appropriate dressing choice is key to aiding wound management. HRWDs, with their innovative fluid absorption/moisture release 'pre-activated' superabsorbent technology, are important tools for balancing the moisture levels necessary for optimal healing.<sup>4</sup> The absorbing and rinsing effect, as well as the absorption of protein- and bacteria-laden wound exudate, have been demonstrated in laboratory studies.<sup>42</sup> As well as donating pre-absorbed Ringer's solution to its surroundings, the wound dressing is capable of absorbing and binding proteins and bacteria as fluid is absorbed into the dressing pad. These laboratory studies offer an insight into the mechanism by which moisture balance-oriented dressing-based wound management system aids absorption of exudate and provide good exudate management.

Data from a number of clinical studies offer evidence of the excellent moisture management capabilities of the HRWDs (Table 4). When questioned about effectiveness of HRWDs in the management of wound exudate during the treatment of chronic wounds, clinicians responded positively and expressed satisfaction with the moisture absorption and retention capacity of HRWDs.<sup>35-37</sup> The balancing of moisture levels in and around the wound by HRWDs translated to improvements in the peri-wound skin of chronic wound patients: use of HRWD led to a reduction in peri-wound skin irritation.<sup>37</sup>

A number of clinical studies have shown improvements in peri-ulcer skin condition, an indication of effective exudate management and the optimisation of hydration levels in and around the wound. Two large observational studies where HWRD and HRWD #2 (with AquaClear Gel Technology) was used to treat a number of difficult-to-heal wounds with a variety of aetiologies (e.g., VLU, diabetic foot, pressure ulcer, burns) showed significant improvements in peri-wound skin conditions when treated with HRWDs.<sup>37,43</sup> Additional case study reports also provide evidence for the moisture balance-oriented dressing-based wound management system providing effective moisture balance control when used in the treatment of problematic wounds.<sup>44,45</sup>



The current moisture balance-oriented dressing-based wound management system offers two complementary approaches to wound healing therapy. HRWD #1 debrides and cleanses wounds by balancing of wound environment moisture levels leading to effective wound progression through “T”, “I” and the “M” compartments of the T.I.M.E. framework. HRWD #2 builds on the solid foundation for wound progression by continuing to optimise moisture levels of the granulating wound in order to promote the final stages of healing.

***E: Optimisation of wound Edge – promotion of epithelialisation (Table 5)***

Wound re-epithelialisation requires a number of elements of the wound and surrounding tissue to be optimised for wound coverage to proceed. A healthy granulation tissue free of devitalised tissue is required for migrating epithelium to provide wound coverage. In addition, the peri-wound epidermis must be in an optimal state – e.g., minimally inflamed – for epithelial migration to proceed efficiently. The complimentary dressings of the moisture balance-oriented dressing-based wound management system promote the optimal wound base and peri-wound skin environments for achieving positive re-epithelialisation responses.

For re-epithelialisation to occur the wound bed must be able to sustain epidermal migration. In chronic wounds, evidence suggests that the wound bed matrix is ‘immature’ in terms of its ability to support epidermal migration.<sup>46</sup> The establishment of a moist wound environment and an optimal moisture balance of the wound that progresses the chronic wound along the healing pathway results in the development of healthy granulation tissue that is able to support migrating epidermis. Studies have shown that the epidermis at the wound margin expresses a migratory phenotype and is able to migrate but cannot until healthy granulation tissue is present.<sup>46</sup> Inflamed peri-wound skin (including epidermis) is unlikely to be in the optimal state required for effective migration. The moisture balance-oriented dressing-based wound management system are able to promote the development of the healthy granulation tissue and optimised peri-ulcer skin necessary for effective re-epithelialisation to occur (Table 5).

A number of clinical studies have shown HRWDs associated with the development of healthy granulation tissue. Proportions of healthy granulation tissue increased significantly as a result of the increased debridement of devitalised necrotic and sloughy tissues covering wounds of different aetiologies.<sup>35,37,38,47</sup> Together with improvements in peri-wound skin condition when wounds were treated with HRWDs (Table 6),<sup>35,36</sup> the development of healthy granulation tissue corresponded with re-epithelialisation of chronic wounds<sup>37,47,48</sup> and an increase in the number of chronic wounds progressing to healing.<sup>36</sup>

In vitro studies have suggested that the HRWD #2's moisture management system, AquaClear Gel Technology, may influence epidermal migration directly and complement the beneficial moisture balance effects of HRWD #2 and HRWD #1. HRWD #2's hydrated polyurethanes have been shown to concentrate proteins from complex solutions.<sup>49</sup> When exposed to these hydrated polyurethanes, platelet releasate growth factor activity is increased (as measured by keratinocyte cell growth). Supplementary experiments showed a concentration of epidermal growth factors (e.g., hepatocyte growth factor) and the stimulation of epidermal cell migration, as measured by enhanced closure of an in vitro scratch wounding model.<sup>30</sup> A 270-patient prospective, observational study of the treatment of a variety of granulating chronic wounds with HRWD #2 showed a reduction in perilesional skin irritation and an accompanying increase in the proportion of wound epithelialisation.<sup>43</sup>

A number of clinical case studies also reported re-epithelialisation of wounds treated with HRWD (Table 1).

The combination of the complimentary benefits of HRWD #1 and HRWD #2 leads to the optimisation of the wound bed granulation tissue and to the peri-wound skin and maximises the opportunity for wound re-epithelialisation and closure of the tissue defect. Figure 3 highlights a number of clinical examples where the two-dressing, moisture balance-oriented dressing-based wound management system has been used effectively in the treatment of wounds with a variety of aetiologies.

## **CONCLUSION**

Modern wound care has a myriad of wounds dressings (traditional and advanced) that aid wound care practitioners deliver effective wound care. The concept of wound bed preparation has become a cornerstone in the efforts to heal problematic wounds and the development of protocols such as T.I.M.E. provide a systematic approach for treating wounds, and the appropriate use of wound dressings is key to optimising wound healing treatments. The two-dressing, moisture balance-oriented dressing-based wound management system approach to wound care offers a valuable tool in delivering effective wound management, simplifying which wound dressing to use from the large number of dressings currently available that addresses the requirements set out in T.I.M.E..

## **REFERENCES**

1. Enoch, S., Harding, K. Exudate levels in chronic wounds. *Wounds* 2003; 15: 7, 213-229.
2. Petruyte, S. Advanced textile materials and biopolymers in wound management. *Dan Med Bull* 2008; 55: 1, 72-77.

3. Junker, J.P., Kamel, R.A., Caterson, E.J., Eriksson, E. Clinical impact upon wound healing and inflammation in moist, wet, and dry environments. *Adv Wound Care (New Rochelle)* 2013; 2: 7, 348-356.
4. Ousey, K., Cutting, K.F., Rogers, A.A., Rippon, M.G. The importance of hydration in wound healing: reinvigorating the clinical perspective. *J Wound Care* 2016; 25: 3, 122-130
5. Gokoo C. A primer on wound bed preparation. *Journal of the American College of Certified Wound Specialists* 2009; 1: 1, 35-39.
6. Schultz, G., Sibbald, G., Falanga, V. et al. Wound bed preparation: a systematic approach to wound management. *Wound Repair Regen* 2003; 11: Suppl. 1, S1–S28.
7. Bell, D., Hyam, D. Choosing an appropriate dressing for chronic wounds. *Prescriber* 2007; 18: 11, 65-70.
8. Leaper, D.J., Schultz, G., Carville, K., Fletcher, J., Swanson, T., Drake, R. Extending the TIME concept: what have we learned in the past 10 years? *Int Wound J* 2012; 9: 2, 1-19.
9. Dowsett, C., Newton, H. Wound bed preparation: TIME in practice. *Wounds UK* 2005; 1: 3, 58-70.
10. Milne, J. Wound-bed preparation: the importance of rapid and effective desloughing to promote healing. *Br J Nurs* 2015; 24: 20, S52-S58.
11. Falanga, V. The chronic wound: impaired healing and solutions in the context of wound bed preparation. *Blood Cells Mol Dis* 2004; 32: 1, 88-94.
12. Scotton, M.F., Miot, H.A., Abbade, L.P. Factors that influence healing of chronic venous leg ulcers: a retrospective cohort. *An Bras Dermatol* 2014; 89: 3, 414-422.
13. Brothers, K.M., Stella, N.A., Hunt, K.M. et al. Putting on the brakes: Bacterial impediment of wound healing. *Sci Rep* 2015; 5: 14003.
14. Martin, P., Leibovich, S.J. Inflammatory cells during wound repair: the good, the bad and the ugly. *Trends Cell Biol* 2005; 15: 11, 599-607.
15. Dabiri, G., Damstetter, E., Phillips, T. Choosing a wound dressing based on common wound characteristics. *Adv Wound Care (New Rochelle)*. 2016; 5: 1, 32-41.
16. Spear, M. Wound exudate - the good, the bad, and the ugly. *Plast Surg Nurs* 2012; 32: 2, 77-79.
17. Tickle, J. Wound exudate assessment and management: a challenge for clinicians. *Br J Nurs* 2015; 24: 20, S38-S43.
18. Rippon, M.G., Ousey, K., Cutting, K.F. Wound healing and hyper-hydration: a counterintuitive model. *J Wound Care*. 2016; 25: 2, 68-75.

19. McCarty, S.M., Percival, S.L. Proteases and delayed wound healing. *Adv Wound Care (New Rochelle)* 2013; 2: 8, 438-447.
20. Hollinworth, H. Challenges in protecting peri-wound skin. *Nurs Stand* 2009; 24: 7, 53-58.
21. Pastar, I., Stojadinovic, O., Yin, N.C., et al. Epithelialization in wound healing: a comprehensive review. *Adv Wound Care (New Rochelle)* 2014; 3: 7, 445-464.
22. Snyder, R.J., Fife, C., Moore, Z. Components and quality measures of DIME (Devitalized tissue, Infection/inflammation, Moisture balance, and Edge preparation) in wound care. *Adv Skin Wound Care* 2016; 29: 5, 205-215.
23. Carville, K Which dressing should I use? It all depends on the 'TIMEING'. *Aust Fam Physician* 2006; 35: 7, 486-489.
24. White, R., Cowan, T., Glover, D. Evidence-based dressing selection. *J Wound Care* 2011; 20: Suppl. 1, 4-8.
25. Burton, F. An evaluation of non-adherent wound-contact layers for acute traumatic and surgical wounds. *J Wound Care* 2004; 13: 9, 371-372.
26. van Rijswijk, L. Ingredient-based wound dressing classification: a paradigm that it passé and in need of replacement. *J Wound Care* 2006; 15: 1, 11-14.
27. Norris, R., Staines, K., Vogwill, V. Reducing the cost of lower limb wound management through industry partnership and staff education. *J Wound Care* 2012; 21: 5, 216-222.
28. Ousey, K., Rogers, A.A., Rippon, M.G. HydroClean plus: a new perspective to wound cleansing and debridement. *Wounds UK* 2016; 12: 1, 94-104.
29. Colegrave, M., Rippon, M.G., Richardson, C. The effect of Ringer's solution within a dressing to elicit pain relief. *J Wound Care* 2016; 25: 4, 184-190.
30. Smola, H. Simplified treatment options require high-performance dressings – from molecular mechanisms to intelligent dressing choice. Presented at the European Wound Management Association (EWMA) Congress, Bremen, Germany, 2016.
31. Powers, J.G., Higham, C., Broussard, K., Phillips, T.J. Wound healing and treating wounds: Chronic wound care and management. *J Am Acad Dermatol.* 2016; 74: 4, 607-625.
32. Frykberg, R.G., Banks, J. Challenges in the treatment of chronic wounds. *Adv Wound Care (New Rochelle)* 2015; 4: 9, 560-582.
33. EWMA (European Wound Management Association) Position document: wound bed preparation in practice. MEP Ltd., London, 2004.
34. Kaspar, D., Dehiri, H., Tholon, N. et al. [Clinical efficacy of a polyacrylate superabsorbent containing wound pad (HydroClean® active) in the treatment of chronic wounds – observational study on 221 patients.] *J Plaies Cicatrisations* 2008; 13: 63, 21-24.

35. HARTMANN (2010) Effective wound cleansing with TenderWet active – observational study with 403 patients. Available at:  
[http://nl.hartmann.info/images/20140219\\_observatie\\_studie.pdf](http://nl.hartmann.info/images/20140219_observatie_studie.pdf) (accessed July 2016)
36. Spruce, P., Bullough, L., Johnson, S., O'Brien, D. Benefits of HydroClean plus in wound bed preparation: a case study series. *Wounds International* 2016; 7: 1, 26-32.
37. Kaspar D (2011) TenderWet plus. Therapeutic effectiveness, compatibility and handling in the daily routine of hospitals or physician's practices. Published by HARTMANN
38. Humbert, P., Faivre, B., Véran, Y. et al. Protease modulating polyacrylate-based hydrogel stimulates wound bed preparation in venous leg ulcers – a randomized controlled trial. *J Eur Acad Dermatol Venereol* 2014; 28: 12, 1742-1750.
39. Bruggisser, R. Bacterial and fungal absorption properties of a hydrogel dressing with a superabsorbent polymer core. *J Wound Care* 2005; 14: 9, 438-442.
40. Courderot-Masuyer, C., Robin, S., Bertrand, X. et al. [Behaviour of normal fibroblasts and venous leg ulcer fibroblasts in contact with *Pseudomonas aeruginosa* and HydroClean active dressing.] *J Plaies Cicatrisations* 2005; 9: 51, 3-7.
41. Eming, S., Smola, H., Hartmann, B. et al. The inhibition of matrix metalloproteinase activity in chronic wounds by a polyacrylate superabsorber. *Biomaterials* 2008; 29: 19, 2932-2940.
42. Knestele, M. The treatment of problematic wounds with TenderWet – tried and tested over many years in clinical practice. *WundForum* 2004, Special Issue: 3
43. Zöllner, P., Ellermann, J., Kaspar, D, Smola, H. From material science to clinical application – a novel foam dressing for the treatment of granulating wounds. Presented at the European Wound Management Association meeting, Belgium, 2011.
44. Kapp, H. Effective cleansing, better handling - clinical observations using new TenderWet active. *HARTMANN WundForum* 2004; Special Issue.
45. Nemegeer, K., Meuleneire, F. Evaluation of new foam dressing for low and middle exuding wounds. Poster presented at the European Wound Management Association meeting, Geneva, Switzerland, 2010.
46. Martin, P., Nunan, R. Cellular and molecular mechanisms of repair in acute and chronic wound healing. *Br J Dermatol* 2015; 173: 2, 370-378.
47. König, M., Vanscheidt, W., Augustin, M., Kapp, H. Enzymatic versus autolytic debridement of chronic leg ulcers: a prospective randomised trial. *J Wound Care* 2005; 14: 7, 320-323.
48. Scholz, S., Rompel, R., Petres, J. A new approach to wet therapy of chronic leg ulcers. *ArztPraxis* 1999; 53: 816, 517-522.

49. Smola, H., Maier, G., Junginger, M., Kettel, M., Smola, S. Hydrated polyurethane polymers to increase growth factor bioavailability in wound healing. Presented at EORS, Nantes, France, 2014.
50. Cooper, P. TenderWet: an innovation in moist wound healing. *Br J Nurs* 1998; 7: 20, 1232-1235.
51. Malone, M., Dickson, H. A hydroactive dressing with PHMB. Analysis of clinical effectiveness using 3D wound imaging. Poster presented at the Australian Wound Management Association meeting, Gold Coast, Queensland, Australia, 2014.
52. Meuleneire, F. Prise en charge efficace de escarres de decubitus profonds: resultats de la synergie du soulagement de la pression, du debridement mecanique et du choix d'un pansement adequate. Poster presented at Conférence Nationale des Plaies et Cicatrisations, Paris, France, 2007.
53. Meuleneire, F. Clinical evaluation of TenderWet plus. HARTMANN document, 2011.
54. Meuleneire, F. TenderWet plus in the treatment of patients with problem wounds. Published by HARTMANN, 2013.
55. Paustian, C., Stegman, M.R. Preparing the wound for healing: the effect of activated polyacrylate dressing on debridement. *Ostomy Wound Manage* 2003; 49: 9, 34-42.
56. Scherer, R., Kägi, M., Geiges, R. et al. HydroTherapy. Application study. Published by HARTMANN, 2015.
57. Zollinger, C., Schwab, R., Locherer, E. et al. HydroTherapy. Application study. Published by HARTMANN, 2014.
58. Mwiripatayi, B.P., Angel, D., Dixon, P. et al. Clinical experiences with activated polyacrylate dressings (TenderWet 24). *Primary Intention* 2005; 13: 2, 69-74.
59. Meuleneire, F. Stage-adapted wound treatment using TenderWet, PermaFoam and HydroTac. HARTMANN Document, 2011.
60. Parker, B. Rapid healing in a dehisced abdominal surgical wound using hydro-active dressings. Australian Wound Management Association. *Connective Issue* 2014; 16: 4, 11-14.