Autolysis: mechanisms of action in the removal of devitalised tissue in wounds

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Abstract: Chronic wounds affect millions of people worldwide. In the UK alone, the cost of their treatment is estimated to be between £4.5bn and £5.1bn. The implementation of wound bed preparation strategies remove the barriers to healing and wound debridement is a key component in preparing the wound bed for wound progression. This article aims to review one of the several debridement methods available to clinicians, autolytic debridement. Autolysis (i.e., autolytic debridement) uses the body's own enzymatic mechanisms – used in normal biological processes including acute wound healing – enables removal of devitalised tissue in order to remove the barriers to healing . This review is aimed to provide clinicians working in wound care a better understanding of the mechanisms and implications of autolytic debridement.

Key words: autolysis, necrotic tissue, slough, eschar, debridement, wound bed preparation

Key phrases:

- Devitalised tissue such as slough, eschar and necrotic tissue impedes wound healing
- Removal of devitalised tissue and wound bed preparation is imperative for wound healing to proceed
- Autolytic debridement is nature's way of harmlessly and painlessly removing devitalised tissue and allowing healing
- Hydro-Responsive Wound Dressings enable autolytic debridement in chronic and acute wounds

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Introduction

Chronic wounds affect millions of people worldwide and it is predicted that the prevalence and incidence of these wounds will expand due to an aging population with increasing comorbidities (Sen et al, 2009; Vowden and Vowden, 2016). A study in 2009 estimated that the cost of managing chronic wounds to the NHS was between £2.5bn and £3.1bn per annum (3-4% of the healthcare budget) (Posnet et al, 2009). A more recent analysis of wound care costs in the NHS (2012/2013) estimated that the cost of wound care and the associated comorbidities for both acute and chronic wounds was between £4.5bn and £5.1bn (Guest et al, 2015). In the United States, there is estimated

to be an excess of $25bn spent annually on the treatment of chronic wounds (Sen et al, 2009). In order to help address the growing problem, much work has been done to help better understand and improve the clinical management of these wounds. Wound bed preparation has been identified as a key to maximising the opportunity for the treatment of chronic wounds, with wound debridement being an important aspect in wound bed preparation (Leaper et al, 2012; Sibbald et al, 2011).

With the development of the concept of wound bed preparation in order to determine the overall status of the wound and to identify ways in which to optimise both the endogenous healing process and the effectiveness of therapies, the TIME framework (**T**issue, **I**nflammation/infection, **M**oisture balance and **E**dge of wound) for wound bed preparation was developed and continually built upon to deliver effective chronic wound management (Leaper et al, 2012; Sibbald et al, 2011).

What is debridement and what is it for?

There are many definitions of debridement, including "the process in which all materials incompatible with healing are removed from a wound" (Cornell et al., 2010, p31S). A more detailed definition highlights the importance of wound debridement for preparing the wound bed for healing: "the act of removing necrotic material, eschar, devitalised tissue, serocrusts, infected tissue, hyperkeratosis, slough, pus, haematomas, foreign bodies, debris, bone fragments or any other type of bioburden from a wound with the objective to promote wound healing" (Strohal et al., 2013).

Debridement is an essential component of wound bed preparation and plays an important role in all four of the main stages of the TIME framework (McCallon et al, 2015). Traditionally, the term debridement has been used to describe the removal of devitalised tissue from a wound, or more generally, the removal of damaged and infected tissue (Vowden and Vowden, 2011). Falanga has proposed that the term 'debridement' can be divided into two separate parts reflecting ~~to~~ two distinct treatment approaches: the *initial debridement* following the initial wound assessment and *maintenance debridement* for the ongoing requirement to intervene in order to remove non-viable tissue and maintain an optimal wound bed (Falanga et al, 2008).

For clinicians, debridement can be achieved in a number of ways depending upon what is most appropriate for a given patient (Vowden and Vowden, 2011; Leak, 2012; Gray et al, 2011). This article will focus on autolytic debridement, other types of debridement include sharp, surgical, biologic, mechanical and enzymatic debridement (Table 1). The choice of the optimal debridement method will depend on a number of factors including wound characteristics, patient comorbidities and clinical history, pain threshold, the availability of clinical resources, and the skills of the wound care givers (Vowden and Vowden, 2011; Gray et al, 2011). Also, some procedures are not used or are unavailable in the UK (e.g., wet-to-dry dressings, enzymatic) and are highlighted where appropriate.

TABLE 1: METHODS OF DEBRIDEMENT*

METHOD	DESCRIPTION	ADVANTAGES	DISADVANTAGES
Surgical	Removal of non-viable tissue with instruments in operating theatre	• Usually removes necrosis at one time • Fast method • Pain-free • Selective removal of tissue	• Takes time to organise • Expensive • Limited availability and level of skill • Risks associated with surgery • If incorrectly performed viable tissue can be damaged
Sharp	Removal of non-viable tissue with instruments	• Selective removal of tissue • Relatively fast method	• If incorrectly performed viable tissue can be

			damaged • Repeated procedures may be needed if not all necrosis removed • Not suitable for some patients (e.g., on anticoagulants).
Biological	Use of maggots applied directly to wound	• Specifically removes only devitalised tissue, i.e., selective • Has anti-microbial action • Relatively fast method	• Some patients and clinicians reluctant to use ("Yuck" factor)
Mechanical	Use of dressings to remove necrotic tissue during dressing removal (e.g., wet-to-dry dressings (not UK), monofilament fibre pad	• Removes soft eschar • Should be pain free	• Non-selective; removal of dressing removes viable/healing as well as devitalised tissue (wet-to-dry dressing) • Risk of spread of debris/bacteria (e.g., aerosolisation, splashback of tissues/fluids) • Relatively slow method • Can be painful
Ultrasound	Use of sound waves to physically disrupt devitalised tissue	• Fast method • Removes devitalised tissue • Suited for most types of devitalised tissue	• Risk of spread of debris/bacteria (e.g., aerosolisation, splashback) • Specialised equipment required • Cost
Hydrosurgery	Use of high energy fluid stream (saline) to remove devitalised tissue	• Fast method • Removed devitalised tissue • Suited for most types of devitalised tissue	• Risk of spread of debris/bacteria (e.g., aerosolisation, splashback) • Specialised equipment required • Cost
Enzymatic	Use of enzymes that degrade components of tissue (e.g., extracellular matrix) (not available in UK)	• Can be applied directly to wound • Easy method to use • Should be pain free	• Can cause peri-wound tissue damage (i.e., non-selective) • Possible hypersensitivity to some enzymes in some patients • Relatively slow method
Autolysis	Promotion of a balanced hydration environment at wound site	• Can be applied directly to wound • Easy method to use • Does not harm viable tissue, i.e., selective • Should be pain free	• May cause reversible hyper-hydration • May cause maceration if not appropriately applied • Relatively slow method

**Modified from Davies (2004), McCallon et al (2015) and Gray et al (2011)*

Generally, the various methods of debridement can be placed into two broad categories: non-selective and selective debridement. With non-selective debridement methods (e.g., mechanical (i.e., wet-to-dry dressings), aggressive surgical or sharp debridement), surrounding viable tissue may be removed along with the removal of devitalised tissue particularly if the devitalised tissue is tightly associated with the underlying viable tissue (e.g., wet-to-dry dressing mechanical debridement). Viable or healing tissue adjacent to a region of devitalised tissue may be damaged (leading to bleeding) as a result of the uncertainty in assessing the boundary between devitalised and viable tissue in cases of aggressive surgical or sharp debridement (Albaugh and Loehne, 2010; Gray et al, 2011). The insensate and avascular nature of devitalised tissue means that the removal of this tissue should be painless and without bleeding. However, the sensation of pain and bleeding results when

adjacent viable tissue is damaged (Cornell et al, 2010) and is dependent upon the skill and extent of the debridement by these methods. Selective debridement methods offer targeted removal of devitalised tissues and minimising peri-wound tissue damage. Appropriate surgical and sharp debridement procedures can result in the removal of only devitalised tissue though this is very much dependent upon the skill of the practitioner applying surgical/sharp debridement (though devitalised tissue may remain in the wound in an effort to protect the surrounding viable tissue). Biological and autolytic debridement relies on the harnessing of tightly controlled enzymatic processes of biological systems. Larval therapy (i.e., biological debridement) the removal of necrotic and devitalised tissue via the partial liquefaction of dead tissue by enzymes secreted by the larvae. On the other hand however autolytic debridement uses the body's own enzymes that are produced as part of normal biological processes such as inflammation to digest dead tissue. The presence of a moist environment is required for the digestion of devitalised tissue to progress efficiently (Gray et al, 2011; Meaume et al, 2012).

The removal of devitalised tissue from the wound is thought to be a necessary step for wound progression to occur (Ayello and Cuddigan, 2004; James et al, 2008). Although only one of a number of potential processes that can act as a barrier to healing, the presence of necrosis and devitalised tissue in the wound is particularly important in that it forms a physical barrier to the formation of new tissue (Gray et al, 2011). Wound debridement results in the removal of these physical obstructions and allowing the processes important for healing to continue (Ayello et al, 2006; Weir et al, 2007). The removal of devitalised tissue and the establishment of a viable wound bed also allows for the optimised treatment of chronic wounds (Panuncialman and Falanga, 2009; Halim et al, 2012). In a small study in 143 patients with diabetic foot ulcers (DFUs), Saap and colleagues assessed the validity of a Debridement Performance Index (DPI), a scoring system to assess the quality of wound debridement (Saap and Falanga, 2002). They found that there was a correlation between the DPI and the incidence of DFU closure: the lower the DPI the lower the incidence of wound closure by week 12. This study suggests that effective and timely debridement of chronic wounds may support optimised healing. The authors of this study suggest that DPI may be a useful predictive tool for determining the outcome of clinical trials.

Debridement is thought to be necessary in order to help transform the chronic wound environment back to an acute wound (Panuncialman and Falanga, 2009; McCallon et al, 2015). That is, the removal of devitalised tissue with each repeated debridement helps reduce or negate the effects of chronicity by removing the local wound factors that contribute to maintaining the chronic wound (e.g., devitalised tissue, biofilm). With the removal of these factors, the wound healing process is normalised (Falanga, 2004; Ramundo and Gray, 2008) and wound progression can occur.

The removal of devitalised tissue allows clinicians to fully assess wounds (Weir et al, 2007) and to remove factors that impair wound healing and may not be clinically detectable during clinical evaluation (Leaper et al, 2012; Falanga et al, 2008). These may include a high bacterial burden (planktonic bacteria or biofilm) which may result in increased risk of infection (O'Brien et al., 2002; Kammerlander et al, 2005), and elevated tissue proteinases.

What is 'devitalised tissue'?

Although clinical observations describe several types of devitalised tissue (Table 2), there has been little research on the physical, chemical and biological characterisation of this dead tissue

Figure 1: A diabetic foot wound showing necrosis and slough

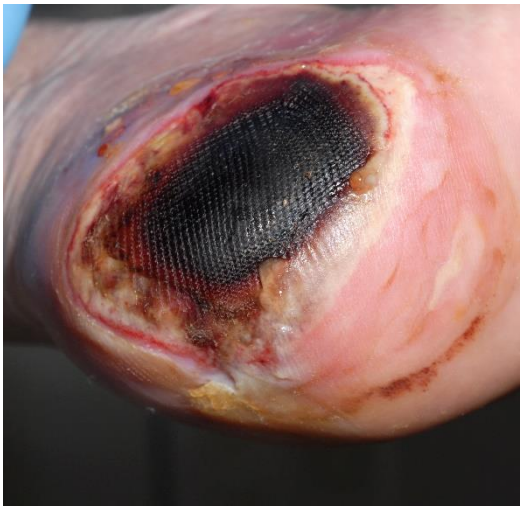

Figure 2: A heel ulcer showing eschar

(Percival and Suleman, 2015). It is clear, however, that there can be significant variability in the properties of non-viable tissues between patients (European Wound Management Association, 2004). However, despite this variability, general characteristics of necrotic tissue and slough have recently been proposed (Percival and Suleman, 2015). Necrotic tissue is a hard, dry tissue that is generally black/brown in colour and is firmly attached to the underlying viable tissue (Figure 1). Although considered to be a separate phenomenon (Grey et al, 2006), clinical experience suggests that wound eschar (Figure 2) does have a number of similar characteristics to necrotic tissue. Table 2 itemises the similarities and differences between the three main types of devitalised tissue. Dry, black and hard necrotic tissue, eschar and necrotic tissue appears to be made up of a fibrous mass of extracellular matrix components (e.g., fibronectin, collagen, elastin fibres) (Percival and Suleman, 2015; Thomas et al, 1999), dried skin and granulation tissue (Black et al, 2010).

TABLE 2: CHARACTERISTICS OF DEVITALISED TISSUE*

Characteristics	Necrotic tissue	Slough	Eschar
Black/dark brown	Generally	Not generally	Generally
Loosely attached	No	Yes – generally	No
Very firmly attached	Yes	No – not generally	Yes – generally
Dead cells	Yes	Yes	Yes
Fibrin	Yes – low level	Yes – high level	Yes – low level
Biofilm	Yes	Yes	Yes
Microorganisms	Yes	Yes	Yes
White blood cells	No	Yes	Yes
'Houses exudate'	No	Yes	No
Viscoelastic	No	Yes	No

**Modified from Percival & Suleman (2015)*

Wound slough is very different from necrotic tissue/eschar. It is generally pale yellow or yellow/brown in colour (Figure 3). It is a soft tissue and is generally more loosely attached to the

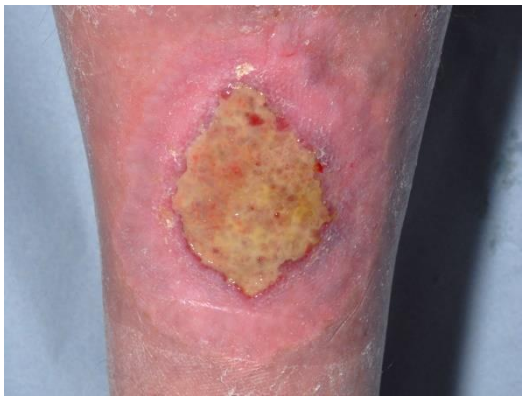

Figure 3: A leg ulcer showing slough within wound bed

underlying tissue when compared with the strength of attachment of necrotic tissue (Percival and Suleman, 2015). Slough is composed of white blood cells, bacteria and foreign material, and dead tissue. It contains a mixture of serum proteins (fibrin, albumin, immunoglobulins), denatured extracellular matrix proteins and is thought to be a by-product of the immune-related clearance of cellular components during the healing response (Brown, 2013; Percival and Suleman, 2015). Slough is thought to be the result of the heightened inflammatory state found in the chronic wound. Common to all the devitalised tissues, these dead tissues are thought to be an environment where biofilms are able to form and thrive (Percival and Suleman, 2015).

Autolytic debridement

There are a number of debridement techniques available to clinicians (Table 1). Autolytic debridement ('autolytic' derived from the Greek words meaning 'self' and 'splitting') is a process that takes place in wounds and is responsible for the breakdown of tissue damaged during wounding and the scab formed over an acute wound. In chronic wounds, autolytic debridement uses the body's own enzymes and moisture to rehydrate, soften and partially-digest devitalised tissue (Gray et al, 2011). The establishment of an optimal level of hydration is important as these enzymes require optimised moisture levels to deliver their full level of activity (Rezaei et al, 2007). The use of moist wound-management protocols and moisture-donating and/or moisture-retentive dressings (Table 3) to establish and maintain a moist wound healing environment optimises the enzymes required for autolysis (autolytic debridement). Several types of enzymes (e.g., elastases, collagenases (Matric Metallo-Proteases MMPs), myeloperoxidase, acid hydrolases and lysosomal enzymes) then begin the process of autolysis (Ramundo and Gray, 2009; Enoch and Harding, 2003; Singhal et al., 2001). Proteolysis – the breakdown of proteins by the action of enzymes (proteolytic enzymes) – is largely responsible for the breakdown of the protein components of the devitalised tissue. The initial breakdown of this devitalised tissue then allows further digestion of the tissue by specialised inflammatory cells (macrophages) (Diegelmann and Evans, 2004). The detachment of devitalised tissue is facilitated by the action of these proteolytic enzymes. It has been suggested that the breakdown and removal of cellular debris assists in maintaining the process of autolytic debridement (Hermans and Cutting, 2013).

Promotion of autolytic debridement by wound dressings

Wounds dressings that promote a moist wound environment encourage autolytic debridement. There is no prescribing time limit for leaving these dressings in place, this will be determined through individual assessment of each patient and will be dependent upon manufacturer's instructions, levels of exudate, patients general condition and any underlying comorbidities. Each wound assessment should be clearly documented in the patients' notes with dates for future review. When the dressing is removed, the liquefied tissue can be removed with the dressing and the wound can be irrigated in order to wash out any remaining tissue.

Due to the selective nature of autolytic debridement (Schultz et al, 2003; Strohal et al, 2013), this method is less stressful for patients compared with other debridement methods as it causes little or no pain. It is also considered to be the safest method of debridement available because of its property of only removing devitalised tissue (Gwynne and Newton, 2006). However, debridement can take longer than other methods, requiring multiple dressing applications and can take several weeks depending upon the extent of necrosis/slough (Davies, 2004; Mosher et al, 1999; Davies et al, 2005). Because autolytic debridement requires endogenous protein-degrading enzymes – many of them from inflammatory cells – for effective removal of devitalised tissue, patients with impaired immune and inflammatory responses (due to medications or disease) may not show an effective autolytic response (McCallon et al, 2015).

As well as the promotion of autolytic debridement processes by the establishment of a moist wound environment, the dressing's ability to remove wound exudate and devitalised tissues during dressing changes probably increases the activity of autolysis. The removal of devitalised tissue – the target of the enzymes responsible for tissue digestion – allows for the limited levels of autolytic debridement enzymes present in the wound environment to digest devitalised tissues remaining at the wound site rather than digesting debris already digested.

These dressings capable of promoting autolytic debridement can generally be divided into two categories: those that donate moisture to the dry devitalised tissue and those that absorb excess moisture (wound exudate) produced by the tissues (Hofman, 2007) (Table 3). Hydrogels (gels and sheets) donate moisture to the dead tissue because of the high moisture content of the dressing. Hydrocolloids, alginates, cellulose and foam dressings are designed to absorb exudate from the wound creating a moist interface between the dressing and the wound surface and promoting a moist environment and hydration of the dry devitalised tissue. It should be noted that hydrocolloids also have absorption capacity and can generate moisture through their semi-occlusive nature and gel-forming property when in contact with exudate. This facilitates autolytic debridement (Ousey et al, 2012).

Recently, a third category of wound dressing has been developed that encourages autolytic debridement: hydro-responsive dressings. These dressings can deliver and absorb moisture 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 (Ousey et al, 2016).

TABLE 3: MECHANISM OF OPTIMAL HYDRATION FUNCTION

Dressing Class	Fluid Retention/Donation
Alginates	Retention
Foams	Retention
High-absorption dressings	Retention
Hydrofiber	Retention

Hydrocolloids	Retention
Hydrogels	Donation
Hydro-Responsive Wound Dressings (HRWDs)	Retention & donation

Low to moderate quality evidence supporting the benefits of a number of debridement methods, including autolytic debridement, in the treatment of diabetic foot ulcers (DFUs) has been reported. Two RCTs suggest autolytic debridement of DFUs is associated with a statistically significant increase in healing rates compared with standard wound debridement by gauze and conventional wound care (Elraiyah et al, 2016). A review of the impact of wound debridement in wound healing in leg ulcers noted some evidence for the benefit of autolytic debridement (Doerler et al, 2012). In a prospective, RCT in 42 patients with leg ulcers treated with either a hydro-responsive wound dressing (HRWD) or an enzymatic debridement preparation, the HRWD group showed a reduction in devitalised tissue of approximately 19% (versus 9% in the enzymatic preparation group) and an increase in granulation tissue (26% vs. 10%) during days 1-14 (König et al, 2005). Although enzymatic debridement is not routinely used in the UK and the study was not statistically significant it does identify the potential benefits of using HRWD as a debridement technique.

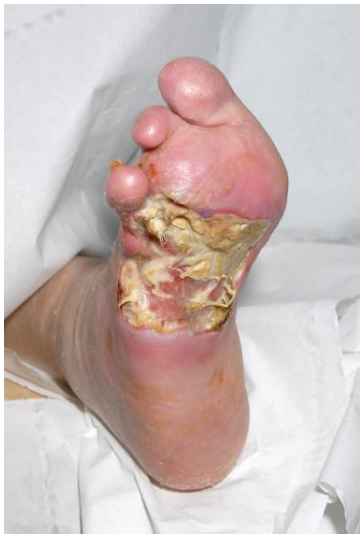

Figure 4: Autolytic debridement of necrosis and slough by HRWD dressing in a diabetic foot ulcer shown in Figure 1

Meaume (2012) used a cohesive, autolytic wound dressing featuring 'hydro-desloughing fibres' in a pilot, prospective, non-controlled open-label study evaluating desloughing in venous leg ulcers (n=35) and pressure ulcers (n=15). All patients had wounds >50% covered with sloughy material. Patients were followed over a 6-week period. All wounds were considered debrided (<40% slough) by week 3 with a median relative decrease of sloughy tissue of 75% and 89% of venous leg ulcers and pressure ulcers respectively. In a recent multicentre RCT on patients with sloughy venous or mixed aetiology leg ulcers, 159 patients were treated with one of 2 fibrous wound dressings and followed over a 6-week period with the relative level of sloughy tissue being assessed (Meaume et al, 2014). Both autolytic dressings resulted in a relative reduction of sloughy tissue and an increase in the percentage of debrided wounds at the end of the observation period. It should be noted that a total of 25 patients withdrew from the study, and that a total of 16 local adverse events considered to be potentially related to the study dressings were reported (in 15 patients).

In a recent multicentre, open, prospective, randomised and two-arm parallel study group study, Humbert et al (2014) reported on a 75-patient study to assess the autolytic debridement properties

of a hydro-responsive wound dressing on wound bed preparation in venous leg ulcers. After 14 days, there was a reduction in fibrinous and necrotic tissue of 37.6% in the HRWD group compared with a reduction of 16.8% in a comparative group treated with an amorphous gel. There was a corresponding increase in the proportion of ulcer area covered by granulation tissue. A report of a 20-patient community-set evaluation study demonstrated HRWD promoting wound bed progression and wound healing in patients with chronic wounds (Spruce et al, 2016). There was a mean reduction of 62% in the level of devitalised tissue in these wounds.

Conclusion

The increasing prevalence and negative socioeconomic effects of chronic wounds have made the need for better, more cost-effective therapies for these wounds. Wound bed preparation has been identified as being important to delivering effective wound care for these wounds with debridement being a key component as the removal of devitalised tissues displaces many of the barriers to healing. The choice of debridement method is dependent upon a number of patient- and clinician-related factors. Autolytic debridement is a selective process for removing devitalised tissue, relying on the tissue's own enzymes to soften and detach areas of necrosis and slough. The establishment of balanced hydration levels in the wound with the promotion of a moist environment with advanced wound care products maximises the autolytic potential of chronic wounds. Wound dressings that promote a moist environment through the retention of excess wound fluid (e.g., alginates) or the donation of fluid locked within the dressing (e.g., hydrogels), or innovative dressings, such as HRWDs, that are able to both retain and donate fluid offer the opportunity for autolysis to promote the selective removal of devitalised tissue.

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