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ChloraSolv®
By RLS GLOBAL

# ChloraSolv® Wound Debridement Gel White Paper



RLS GLOBAL
Gentle Methods

# 1:

# Therapeutic context - the healthcare and economic significance of hard-to-heal wounds

## Definition and aetiology overview

Hard-to-heal wounds (previously referred to as chronic wounds) are defined as wounds that 'do not heal properly during an amount of time that normally should be sufficient for healing'[1] or 'fail to progress through a normal, orderly and timely sequence of repair, or in which the repair process fails to restore anatomic and functional integrity after 3 months'[2]. Hard-to-heal wounds are symptomatic of a system that is out of control and in need of treating. A key step in the management of these wounds is debridement; regular and effective debridement results in significantly faster healing and increased healing rates[3].

In the UK, a report commissioned by NHS England stated that 'the burden of chronic lower limb wound care is large and growing, with significant and unwarranted variation in the use of evidence-based care'[4]. Data on the global prevalence of hard-to-heal wounds are surprisingly limited; however, they affect approximately 1-2% of people at some point in their lives[5,6], with this figure expected to rise in the future[7].

There are a number of factors that contribute to delayed wound healing, including[8]:

- Underlying pathology and comorbidities (i.e. diabetes and venous insufficiency)
- Wound-related factors, such as ulcer size, duration and location
- Wound infection
- Clinical competency factors, such as the knowledge and skill of the clinician treating the wound

Hard-to-heal wounds are classified by their aetiology into four broad categories: diabetic, arterial and venous ulcers and pressure injuries, each of which has its own typical location, appearance and physical characteristics[2]. Of the four, venous leg ulcers (VLUs) and diabetic foot ulcers (DFUs) are the two most commonly encountered[5].

## Venous leg ulcers

VLUs are caused by chronic venous insufficiency and are responsible for about 70% of hard-to-heal ulcers of the lower limbs[9]. Major risk factors include family history, obesity, deep vein thrombosis and increasing age[9]. It has been estimated that VLUs affect up to 3% of the adult population worldwide, increasing to 4% in the population aged >65 years[9]. The majority of VLUs occur in women, with female to male ratios estimated at between 1.5 and 10:1[9].

In the UK, a report commissioned by NHS England estimated that in 2019 there were 739,000 leg ulcers in England, with associated healthcare costs of approximately £3.1 billion[4]:

- There was wide variation in the quality of care provided: many people with leg ulcers did not receive effective evidence-based care to increase healing rates and reduce recurrence.
- On this basis, the report concluded that 'unless action is taken to improve care, the prevalence could grow by 4% per annum'.
- Given the increasing prevalence of the risk factors of obesity and an ageing population, it seems likely that the prevalence of VLUs will only increase in the UK.

## Diabetic foot ulcers

A DFU is an open wound that occurs in patients with diabetes, usually located on the bottom of the foot[4]. Estimates suggest that there may be as many as 4.9 million people in the UK with diabetes, of whom 90% will have type 2 diabetes, with a total of 13.6 million at risk of diabetes[10]. DFUs are relatively common, with at least 10% of patients with diabetes estimated to develop a DFU at some point in their lives[9]. Global prevalence of DFUs is approximately 6%, with DFUs occurring more frequently in men than women, and being more frequently associated with type 2 diabetes than with type 1[9]. Furthermore, patients who develop a DFU tend to be older, with a lower body mass index and longer duration of diabetes, and also have a greater incidence of hypertension, retinopathy and smoking history than those who do not develop a DFU[9].

DFUs have significant clinical impact, with 6% of patients aged ≤65 years who had a DFU being hospitalised due to complications[11]. More significantly, DFUs precede more than 80% of amputations in people with diabetes, and about 50% of patients who develop a DFU die within 5 years[9]. As with leg ulcers, prevalence of DFUs is expected to increase in line with the increased prevalence of diabetes[12], due to earlier onset of disease and increasing population age[1,4].

## Economic and social impact of hard-to-heal wounds

Olsson et al[1] state that hard-to-heal wounds 'have significant humanistic and economic burdens, both at an individual (e.g. quality of life [QoL]) and a societal level (e.g. healthcare costs)' and that these are likely to become more significant because of increasing population age and the earlier onset of conditions that predispose individuals to the development of hard-to-heal wounds. However, they also pointed out that these burdens on the individual and healthcare system are often underappreciated[1].

## Impact on patients

Hard-to-heal wounds may require several years, possibly decades, to heal completely and until they do heal, patients can suffer from severe pain, emotional and physical distress, reduced mobility and social isolation[13].

A metanalysis of published data in 30 articles undertaken by Olsson et al[1] assessed the physical and psychological QoL in patients with hard-to-heal wounds. Studies assessing adults ≥18 years of age having hard-to-heal wounds specified by wound duration of ≥3 weeks, or labelled as chronic, complex, hard-to-heal or having led to an amputation were included. Overall, when compared with controls, it was found that reductions in health-related QoL (HRQoL) were driven by the presence of physical pathologies associated with hard-to-heal wounds and were worse for those that had experienced amputations (such as those with DFUs). There was less clarity about psychological parameters of QoL, with studies either finding a neutral or native effect. However, there was evidence that long wound duration and/or large wound size correlated with worse HRQoL scores and that this was worse in those patients with hard-to-heal wounds who also experienced wound-related pain[1].

Hard-to-heal wounds do not just impact the patient's QoL, they also detrimentally affect their finances[13]. Finally, there is also evidence that hard-to-heal wounds can also cause severe emotional trauma to patients and their families[13].

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# 2:

# Hard-to-heal wounds

## Review of the normal wound healing process

The normal process of wound healing is made up of four stages (Figure 1)[1]:

- **Haemostasis** - an immediate response to injury that comprises blood vessel contraction and clot formation. Platelets are key to this process, secreting growth factors and driving recruitment of immune cells to the site of injury as well as themselves acting directly to reduce the risk of microbial colonisation.
- **Inflammation** - a vital part of the immune response to injury, triggered by injury-induced signals released by damaged tissues and microbial components. These lead to the activation and amplification of a battery of immune cells, including neutrophils and T cells early in the response and then macrophages as key effectors of the clearance of necrotic tissues and microbial pathogens, as well as stimulating wound repair through the release of cytokines.
- **Proliferation** - characterised by activation of a range of cell types, including keratinocytes, fibroblasts, macrophages and endothelial cells, that are responsible for wound closure, matrix deposition, angiogenesis and nerve fibre regrowth. Angiogenesis is required so that there are sufficient blood vessels to support newly repaired tissue and, again, macrophages play a significant role in this by coordinating microvascular endothelial cells involved in vessel growth. Nerve fibre regeneration remains understudied, despite the significant role played by skin denervation in wound pathogenesis in diabetes.
- **Remodelling** - takes place throughout the entire response to injury, beginning with the initial deposition of a fibrin clot and ending years later with the formation of a collagen-rich scar. Much of the matrix remodelling process is mediated by fibroblasts.

## Why don't some wounds heal properly?

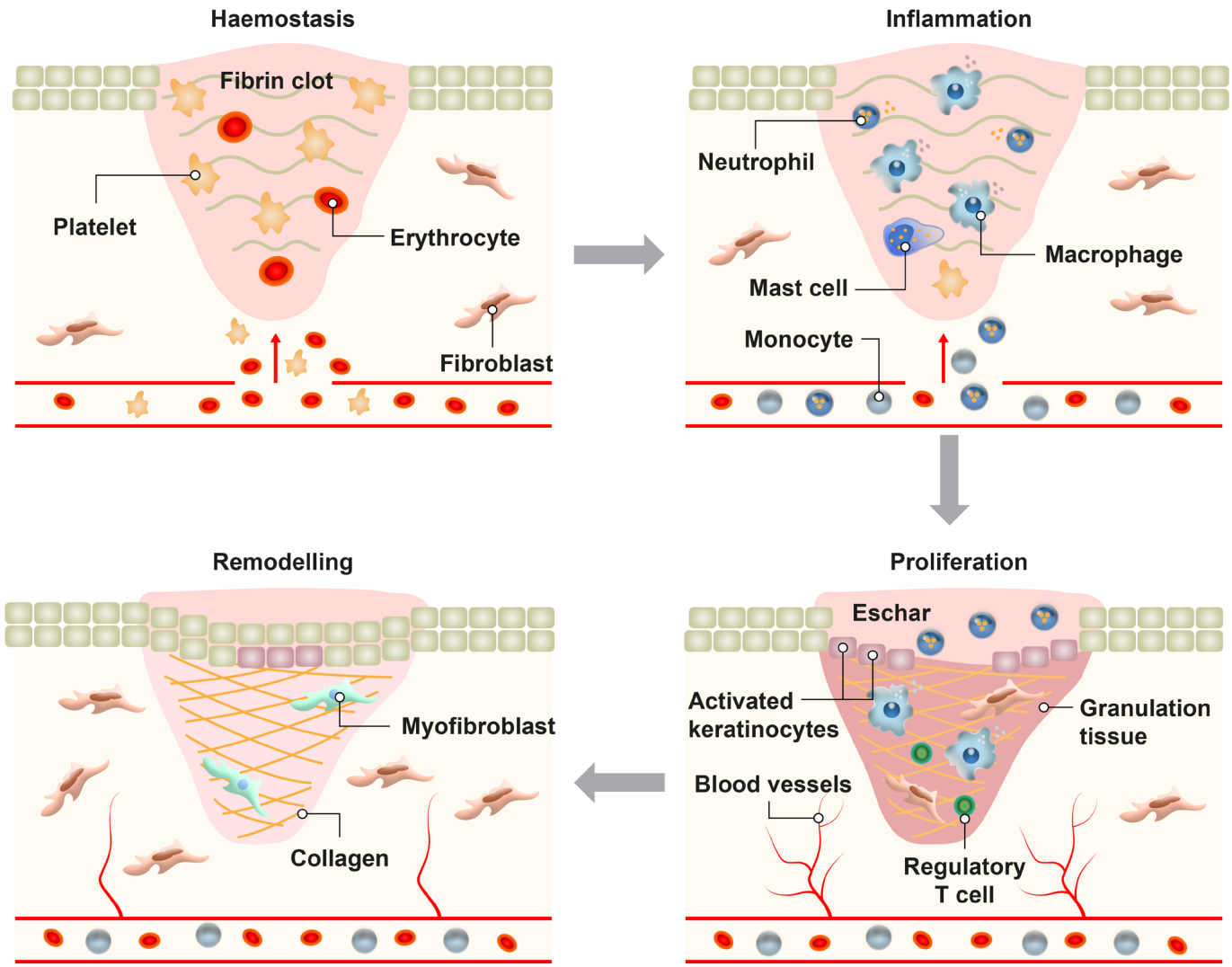
Wound repair involves a dynamic cascade of cellular signalling and behavioural events that ensure fast closure of the skin barrier[1]. The normal mechanisms of repair do not seem to fail due to small alterations to this response[1], but they are often a result of the alteration of several components together (summarised below).

## Patient age

Over the age of 60 years, patients may have delayed wound healing due to physical changes that occur with advancing age, such as:

- Alterations in the body's inflammatory response[2]

**Figure 1.** Stages of wound repair




Adapted from: Wilkinson and Hardman, 2020[1].

- A delay in the angiogenesis process[3]
- Slower epithelialisation[2]
- Decreased collagen synthesis, which can also lead to delayed wound healing[2]

One factor widely implicated in hard-to-heal wound pathology in the elderly (and patients with diabetes) is cellular senescence, which is exacerbated by high levels of inflammation and oxidative stress[4]. Senescent cells produce significantly larger quantities of pro-inflammatory cytokines and tissue-degrading proteases, driving mechanisms that inhibit wound repair[5]. Both diabetes and the ageing process lead to the gradual degradation of the dermal matrix with corresponding changes in tissue mechanics and loss of resilience, potentially leading to an increased susceptibility to pressure and friction damage[6,7].

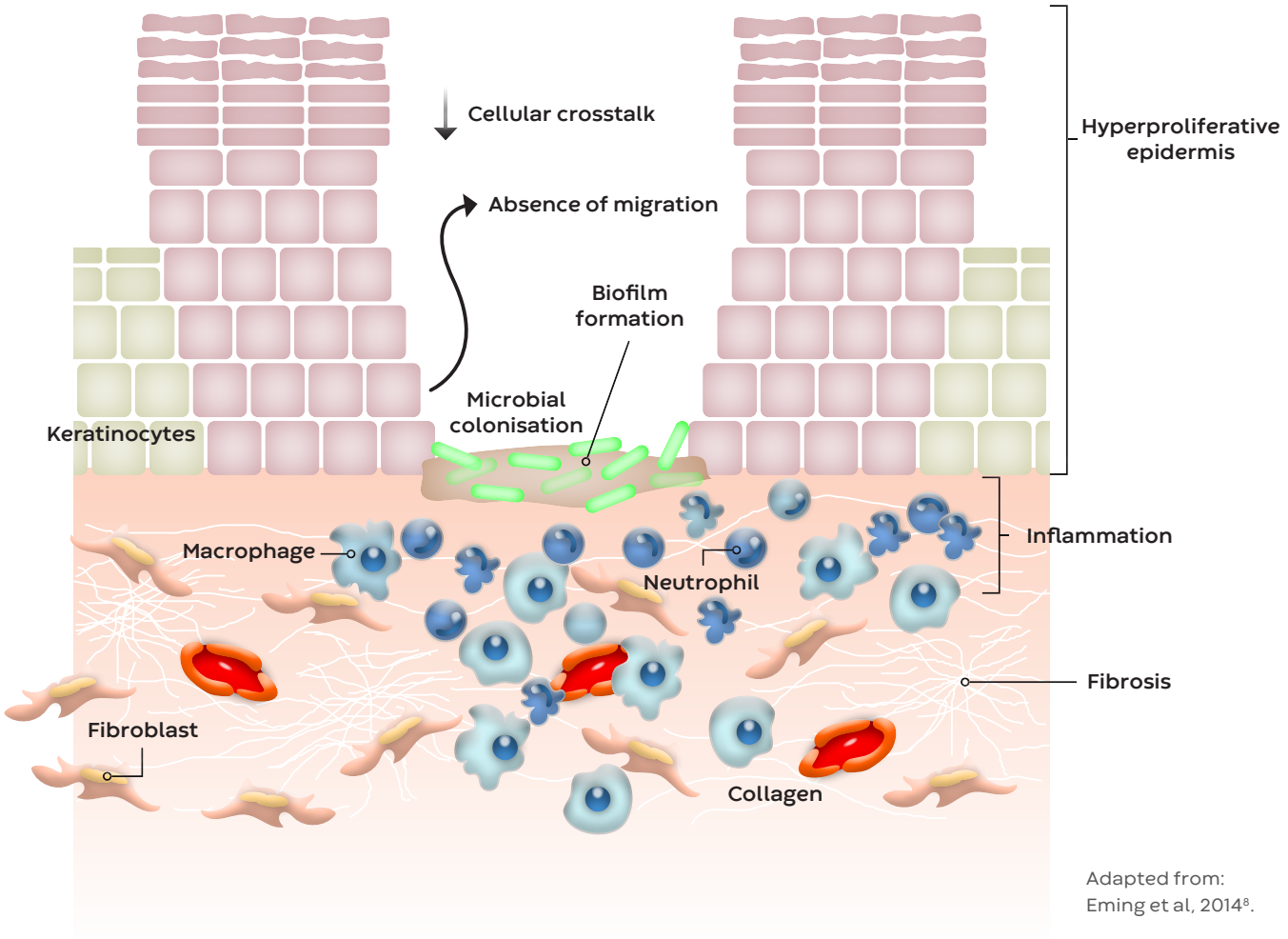
## Inflammation

Excessive inflammation is a key contributor to the failure of wounds to heal through continued destruction of wound tissue (Figure 2)[1]. Hard-to-heal wounds are characterised by the infiltration of elevated numbers of inflammatory cells and mediators, including neutrophils, pro-inflammatory macrophages and proteases, as well as changes in immune cell function that together contribute to poor healing[1]. Furthermore, aberrant immune cell function can increase the risk of microbial colonisation, which can itself lead to heightened levels of inflammation, leading to a vicious cycle of colonisation, inflammation and inadequate levels of tissue repair[1]. In patients with diabetes, it has been reported that the skin exhibits higher numbers of mast cells and macrophages primed to a pro-inflammatory state, suggesting that presence of diabetes could encourage poor wound healing through a greater propensity to inflammation[1].

## Chronic disease - diabetes

Diabetes is associated with a range of pathophysiological effects that are linked to increased susceptibility to injury and significantly reduced capacity for wound healing, leading to DFUs. DFUs have a very complex pathology based on a combination of hyperglycaemia, disruption and microbial colonisation of the skin barrier,

**Figure 2**. Anatomy of a hard-to-heal wound




Adapted from: Eming et al, 2014[8].

high oxidative stress, neuropathy, microvascular complications and an inappropriate, chronic inflammatory response[9].

Some of the changes to the components of wound healing in diabetes are similar to those seen in ageing skin such as atrophy, altered skin barrier characteristics and reduced hydration, loss of dermal matrix, loss of resilience and an increased susceptibility to pressure and friction damage[1]. Sustained blood sugar elevation in diabetes appears to have several effects that directly contribute to defective healing. In particular, these include compromised leucocyte function, cellular senescence and non-enzymatic glycation of the extracellular matrix, leading to the release of advanced glycation end products that damage dermal structure and lead to increased inflammation and the release of reactive oxygen species. In turn, these impair revascularisation, and this can be exacerbated by the detrimental long-term effect of uncontrolled diabetes on the microvasculature, which can lead to local tissue hypoxia, arterial vasculopathy and lower limb neuropathy[1].

Skin in patients with diabetes has been shown to have greater levels of colonisation by microorganisms, including *Staphylococcus* spp., *Pseudomonas* spp. and *Enterobacteriaceae* spp., with more severely infected DFUs exhibiting increased microbial diversity[9]. Microorganisms such as *Staphylococcus* spp. and *Streptococcus* spp. have been shown to express proteolytic factors that can disrupt the skin barrier, and an increased colonisation of intact diabetic skin by *S. aureus* is believed to contribute to the high rate of DFU infections[9].

Diabetes and associated hyperglycaemia are particularly associated with the development of biofilm in hard-to-heal wounds, which can drive prolonged persistence of inflammation, microbial colonisation and limit the effect of antibiotic therapy[9].

## Biofilm and local infection

All wounds are colonised by microorganisms to some extent, and one of the major roles of the inflammatory component of wound healing is to reduce microorganisms to a level that can be tolerated and cleared by the innate immune system[8]. However, colonisation above this level is likely to contribute to both the development and the maintenance of a hard-to-heal wound[8]. This process may be driven by the presence of specific pathogenic species, such as *S. aureus* and *P. aeruginosa*[1]. These microorganisms can promote the formation of polymicrobial aggregates or biofilm: communities of microorganisms, encapsulated in a protective matrix of extracellular polymeric substances that confers tolerance to standard antiseptics and antibiotics and impedes the efficacy of normal pathogenic clearance, thus delaying the process of wound repair[1,8,10]. Furthermore, the presence of aerobic microorganisms, such as *S. aureus*, in the biofilm can create a supportive environment for the proliferation of anaerobic microorganisms, via consumption of oxygen in the local environment[10]. There is also evidence that uncontrolled biofilm formation may encourage the development of multidrug resistance[10,11].

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# 3:

# Management of hard-to-heal wounds with Wound Hygiene and the challenge of debridement

## Review of standard of care

Historically, the TIME framework (tissue, infection/inflammation, moisture balance and edge of wound) was used to provide a structured approach to wound bed preparation[1]. As a greater understanding has developed of the processes that promote or inhibit successful wound healing, this has been complemented by the concept of Wound Hygiene[2]. In particular, this has been driven by an awareness of the importance of overcoming the barriers that biofilm presents to effective healing[2]. Wound Hygiene is an antibiofilm strategy that is designed to regularly remove biofilm to facilitate wound healing[2].

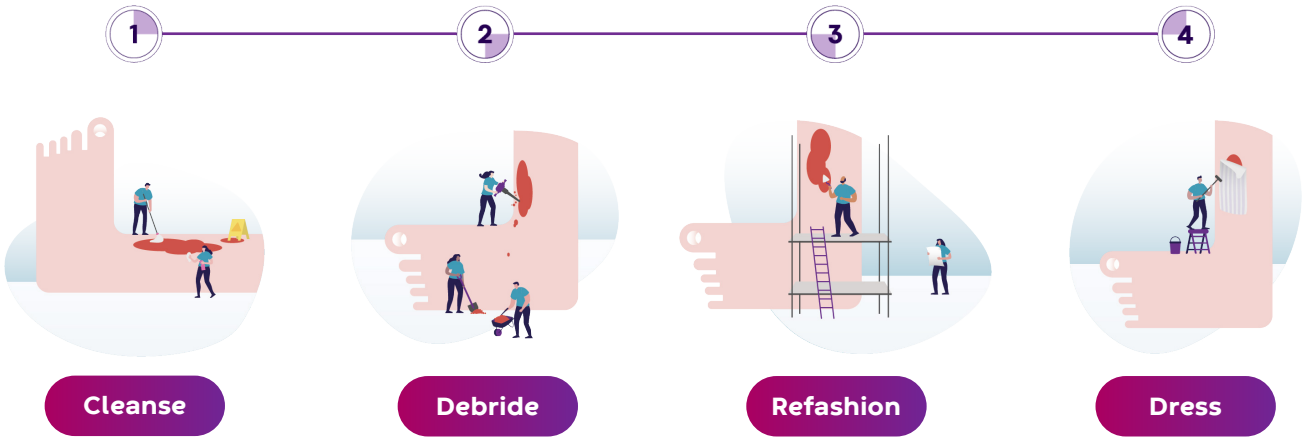
Biofilm can establish and re-form in as little as 24 hours[3] and should be assumed to be present in every wound. Any open wound can be colonised by microorganisms[4], whether tissue appears healthy or unhealthy, and biofilm is a key driver of the development of hard-to-heal wounds[2]. Given that biofilm is present in at least 78% of hard-to-heal wounds[5], is known to inhibit normal wound healing and can promote antibiotic resistance[6,7], strategies focused on its removal should be viewed as central to the treatment of all wounds, but particularly hard-to-heal wounds[2].

It is important to emphasise that the pervasive nature of colonisation of wounds and the tendency for biofilm to rapidly re-form means that some level of Wound Hygiene should be practiced with all wounds and at all healing stages, as a hard-to-heal wound remains hard-to-heal until fully healed[8].

Wound Hygiene comprises four key activities: cleansing the wound and periwound skin, debriding the wound, refashioning the wound edges and dressing the wound (Figure 3)[8]:

- **Cleanse the wound and periwound skin** - carried out at every dressing change to prevent recolonisation of the wound and the re-formation of biofilm. Cleansing the wound bed reduces devitalised tissue, debris and biofilm. Cleansing the periwound skin decontaminates it and removes dead skin, scales and callus.
- **Debride the wound** - carried out at every dressing change using a method determined by wound assessment and healthcare professional (HCP) skill level. Debridement removes devitalised/necrotic tissue, adherent exudate and senescent cells, and colonised tissues and biofilm, to optimise the wound bed for healing.
- **Refashion the wound edges** - carried out according to a method determined by wound assessment and HCP skill level. Refashioning manages areas that can harbour biofilm and ensures that skin edges are contiguous

**Figure 3.** The four activities of Wound Hygiene




Adapted from: Murphy et al, 2022[8].

with the wound bed to facilitate epithelial advancement and wound contraction.

- **Dress the wound** - application of an antimicrobial or advanced wound dressing that effectively manages residual microorganisms and biofilm, and prevents re-formation of biofilm.

It is also important to consider issues specific to the location and aetiology of the wound:

- **VLUs** - occur when venous hypertension leads to distension of the superficial veins, causing venous wall damage, exudation of fluid into the interstitial space and oedema[9]. Specific treatment, in addition to the components of Wound Hygiene, is focused in lowering venous pressure and improving venous return through exercises, elevation of lower extremities and adequate compression[9].
- **Arterial ulcers** - also referred to as ischaemic ulcers; caused by narrowing of arteries or damage to the small blood vessels in the lower extremities leading to poor perfusion and resultant oxygen starvation of overlying skin and tissue, killing these tissues and causing the area to form an open wound[10]. The first step in the management of arterial ulcers is to address the underlying causes and improve oxygen flow and perfusion to affected tissues using techniques such as vascular bypass, stents or dilation by a vascular surgeon[9].
- **DFUs** - associated with poorly controlled hyperglycaemia, their treatment begins with optimal control of blood glucose levels[9]. Most patients with DFUs also have underlying peripheral arterial disease, which requires evaluation and treatment to reduce vessel narrowing and improve arterial flow[9].

## Focus on debridement

The removal of necrotic tissue and slough occurs naturally as part of the normal wound healing process and is a pre-requisite for healing to occur spontaneously in healthy wounds. However, in hard-to-heal wounds, debridement of devitalised tissue, debris and biofilm using surgical or non-surgical procedures may need to be performed in order to support and stimulate the normal

healing process[11]. Debridement provides a number of benefits in the management of hard-to-heal wounds, including removal of barriers to healing such as necrosis, slough, debris, microorganisms and biofilm[11], all of which have an impact on exudate production, risk of infection and progression to healing[11]. When effectively performed, debridement reverts a hard-to-heal wound environment into a more acute one, supporting the restitution of the normal healing process[12].

Hard-to-heal wounds are likely to require repeated debridement because devitalised tissue tends to reappear due to continuing underlying causes, and biofilm can re-form rapidly, meaning that strategies that address underlying causative mechanisms as well as constant application of an appropriate debridement technique are recommended[3,12].

Debridement can be achieved by a range of approaches that can collectively be categorised as either selective or non-selective[12]. Factors to consider when deciding on the most appropriate option include[13]:

- Wound characteristics
- Amount of devitalised tissue in the wound
- Efficiency and selectivity of the debridement method itself
- Pain management for the patient
- Procedure cost
- Exudate levels of the wound
- Presence or risk of infection
- Patient care setting
- Patient's overall medical condition

Selective methods aim to ensure that only devitalised tissue and biofilm are removed from the wound bed[12]. These include:

- **Autolytic debridement** - the process by which the body uses endogenous proteolytic enzymes to remove necrotic and devitalised tissue. This method is slower than most artificial approaches and its effectiveness depends on wound size and amount of devitalised tissue[12]. Autolytic debridement is indicated for noninfected wounds but may also be used as adjunctive therapy in infected wounds alongside other debridement techniques, such as mechanical debridement[14].
- **Larval therapy/biological debridement** - the application of sterile larvae of the green bottle fly (*Lucilia sericata*) to the surface of a wound, either directly or contained in a porous bag[12]. Larval therapy provides fast, selective debridement of devitalised tissue but attracts higher unit costs and may not be readily accepted by some patients[15]. Further, it is contraindicated if blood vessels are exposed in the wound, in wounds requiring frequent inspection or those with necrotic bone, tendon exposure or circulatory impairment[12]. Although it has been found to be effective in disrupting biofilms of various bacterial species (e.g., *S. aureus* and *P. aeruginosa*) *in vitro*[16], it appears that it may be selective in its effect, with some evidence of enhancement or promotion of biofilm formation by some pathogenic species, such as *Proteus mirabilis*[17].
- **Enzymatic debridement** - uses exogenous proteolytic enzymes, such as collagenase, to break down and soften devitalised tissue, which can be removed during wound cleansing[12]. It is relatively faster than autolytic debridement, may need to be undertaken for a shorter duration and requires fewer clinical visits compared with other debridement types, other than sharp debridement[12]. This method has been associated with adverse events[18]. In contrast, aurase, a recombinant proteolytic enzyme appears to have a favourable safety profile with adverse effects limited to transient erythema at the

site of application[19]. In a biofilm model in pigs, application of a gel containing 0.25 g/L aurase over 14 days significantly reduced methicillin-resistant *S. aureus* counts (MRSA; a surrogate for debridement efficacy) ($p<0.05$) and improved wound vascularity ($p<0.05$) compared with untreated Tegaderm-covered controls and aurase at a lower dose[19].

Non-selective methods remove both necrotic and viable living tissue and include:

- **Mechanical debridement** - physically removes debris from the wound bed using external force and does so rapidly, compared with other methods, but can be painful and is relatively non-selective[12]. Methods include wet-to-dry dressings, debridement pads and cloths, scrubbing, whirlpool and irrigation[20]. Contraindications for mechanical debridement are when wounds are epithelialising or granulating[2].
- **Sharp debridement** - the fastest method of debridement and uses scalpels, scissors, metal (as opposed to 'blunt' plastic) curettes or forceps to remove necrotic and devitalised tissue. Surgical debridement is undertaken in a sterile surgical setting by a surgeon, physician or podiatrist, whereas conservative sharp debridement is undertaken at the bedside by a trained HCP. Surgical debridement is highly effective but is a major procedure that sacrifices some viable tissue, whereas conservative sharp debridement is a minor procedure that largely removes devitalised tissue. Both types of sharp debridement require specialist knowledge and training[12,13].

Although wound debridement has seen considerable developments over recent years, the relative efficacy of the various debridement techniques is not well established in specific wound types, and further high-quality studies are required to more clearly inform choice of method[12]. Furthermore, different debridement methods require different levels of skill and training to undertake effectively (Figure 4)[11].

## Unmet needs in debridement

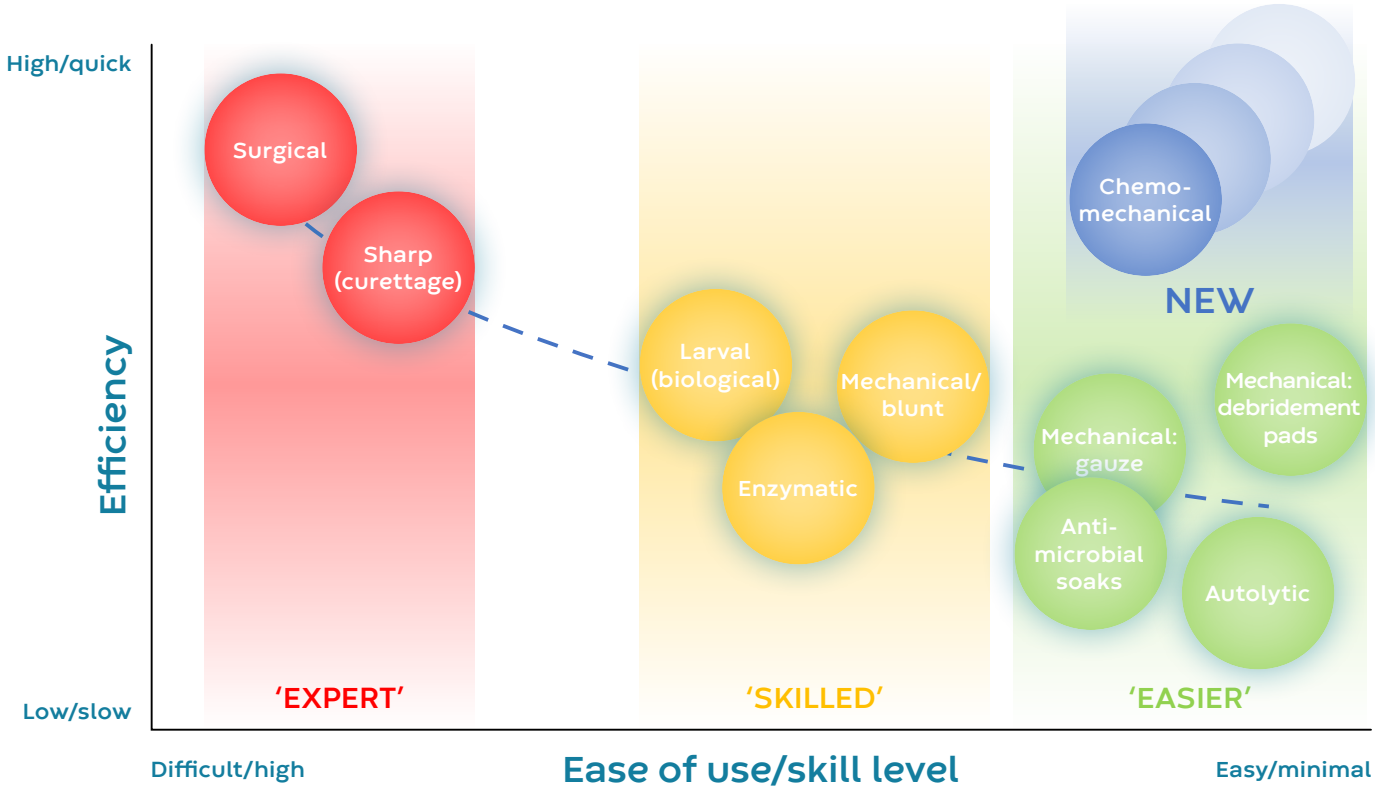
Debridement is crucial to the implementation of Wound Hygiene. For debridement to be effective, it needs to be carried out regularly, as more frequent debridement results in better healing outcomes[20,21]. However, the wide range of debridement methods available, each with its own benefits and disadvantages, can make regular debridement regimens challenging for HCPs[12].

There is a clear difference in the amount of time and expertise required for effective use of different methods of debridement. The challenge is that those that are most effective and fastest to employ are either associated with significant disadvantages or require specialist skill to perform[22]. For example, sharp debridement is invasive and has the potential to cause pain, bleeding and tissue trauma[12].

For most wound-care practitioners who do not have specialist training, the only options for wound debridement are dressings to encourage autolytic clearance of devitalised tissue or basic mechanical debridement.

A further challenge is that there is a risk of bottlenecking of procedures due to lack of appropriate staff availability or capacity. As a result, many HCPs will simply continue with autolytic debridement, even though this is of doubtful effectiveness in many wounds[23].

**Figure 4.** Comparison of efficacy and skill level required for different debridement methods




Adapted from: Strohal et al, 2013[11].

## Challenges of biofilm

The presence of biofilm and its negative impact on wound healing presents a further challenge to debridement[1]. There is little direct evidence that many of the debridement techniques currently available are effective in the disruption and removal of biofilm[11], and the requirement for frequent debridement to keep wounds free of biofilm (which can re-form in as little as 24 hours[3]) places a significant burden on healthcare systems and personnel[2]. Consequently, there is a significant unmet need for a debridement method that can be undertaken by non-specialists, can be used frequently and both rapidly removes devitalised tissue and biofilm while minimising the risk of further microbial colonisation, to facilitate wound healing[2].

Hard-to-heal wounds commonly harbour complex polymicrobial, pathogenic biofilm that is tolerant to systemic and topical antimicrobial therapy[7]. The increased understanding of the importance of biofilms and the role that they play in hard-to-heal wounds has emphasised their importance as a therapeutic target. The use of antibiofilm/antimicrobial combinations to disrupt biofilm is one such strategy that may both increase the effectiveness of antimicrobial agents and reduce the risk of antibiotic resistance[7].
A dressing combining a broad-spectrum antimicrobial agent (ionic silver) with antibiofilm agents (metal chelator and surfactant) has been shown to facilitate healing in a variety of non-healing, biofilm-impaired wounds[25]. The ideal debridement procedure should have action against both devitalised tissue and biofilm[8].

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# 4:

# ChloraSolv® Wound Debridement Gel - a brief overview

## What is ChloraSolv?

ChloraSolv Wound Debridement Gel is an amino acid-buffered, hypochlorite-based gel that has been developed for the fast and effective debridement, and reduction of microbiological load of hard-to-heal wounds[1]. It comprises a unique combination of two components[2]:

- An amino acid-buffered carboxymethylcellulose gel of alkaline pH
- Aqueous solution of sodium hypochlorite (0.9%) of alkaline pH

The two components are mixed at the point of use in an easy-to-assemble two-barrel syringe to form a gel of 0.45% sodium hypochlorite[2].

ChloraSolv provides an alternative to traditional debridement strategies and requires little training to use, eliminating the requirement for specialist skills for effective debridement[2]. ChloraSolv may be used in hospital, clinic or home settings[2,3]. ChloraSolv is intended for use in adult patients with hard-to-heal leg ulcers and DFUs in need of debridement[4]. Chlorasolv is not indicated for the treatment of pressure injuries or burns.

## How does ChloraSolv work?

ChloraSolv provides fast and effective debridement of hard-to-heal wounds in one preparation, while preserving healthy viable tissue[4-6]. It creates a moist, alkaline environment that supports the dissolution of necrotic tissue in hard-to-heal wounds and also contains sodium hypochlorite, which lyses and softens necrotic tissue and biofilm extracellular polymers[1,7]. This makes it easy to mechanically remove softened devitalised tissue and destroyed biofilm, as well as pus and debris, by washing and wiping off the wound bed or using a blunt instrument[1,8].

Importantly, the sodium hypochlorite in ChloraSolv also provides broad-spectrum antimicrobial activity that reduces the microbiological load (Table 1)[1]. Sodium hypochlorite is known to destroy both the biofilm matrix and the bacteria cells within by denaturing proteins in the biofilm matrix and inhibiting major enzymatic functions in bacterial cells[9].

ChloraSolv is rapidly effective against *S. aureus* and *P. aeruginosa* biofilms *in vitro*, eradicating both after 2 minutes of treatment[10]. ChloraSolv has also been found to effectively debride, improve healing and reduce bacterial load in a porcine infected burn wound model*, reducing the bacterial count from an initial $5\times10^6$ colony-forming unit (CFU)/g to below the clinical infection threshold of $>10^5$ CFU/g after 10 days and to undetectable levels after 17 days[8].

Furthermore, hypochlorite has the benefit of being selective for devitalised tissue and biofilm over healthy tissue at the appropriate concentrations[4-6]. This is demonstrated in the dental applications of this high pH hypochlorite technology; for example, its use in root canal irrigation to dissolve pulp[11] and in peri-implantitis for its antibiofilm properties[12].

*ChloraSolv is not indicated for the treatment of burns.

**Table 1.** Antimicrobial effects of ChloraSolv

| Antimicrobial effects of ChloraSolv: |
|---|
| >5 $\log_{10}$ reduction of *Staphylococcus aureus* |
| ≥5 $\log_{10}$ reduction of *Pseudomonas aeruginosa* |
| >5 $\log_{10}$ reduction of *Escherichia coli* |
| >5 $\log_{10}$ reduction of *Enterococcus hirae* |
| ≥5 $\log_{10}$ reduction of *Candida albicans* |
| =4 $\log_{10}$ reduction of *Aspergillus brasiliensis* |

ChloraSolv has been tested *in vitro* to support its ancillary antimicrobial properties according to Ph Eur. 5.1.11: Determination of bactericidal, fungicidal or yeasticidal activity of antiseptic medicinal properties (PharmaControl, Uppsala, Sweden).

Adapted from: Eliasson et al, 2021[1].

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# 5:

# ChloraSolv® Wound Debridement Gel - clinical and laboratory data

Clinical evidence supports ChloraSolv Wound Debridement Gel as a valuable addition in the treatment regime of patients with hard-to-heal leg ulcers and DFUs in need of effective, easy to use and gentle assisted debridement[1-3].

## ChloraSolv improves the healing of DFUs[1]

This randomised controlled study undertaken by Bergqvist et al included 34 patients (17 in each group) and compared ChloraSolv with standard treatment for 12 weeks with 24-week follow up. Inclusion criteria were long-standing diabetes type 1 or 2, and an infected DFU for more than 4 weeks.

After 5 weeks, ChloraSolv treatment was associated with a significantly greater relative reduction in DFU area compared with standard treatment ($p=0.016$). The weekly relative reduction in DFU size was 19.4% for ChloraSolv ($p<0.0001$), compared with 11.7% ($p<0.0001$) for standard treatment (Figure 5).

Further, reduction in absolute change in DFU size occurred more rapidly with ChloraSolv (2 weeks; $p=0.026$) than with standard treatment (8 weeks; $p=0.002$), with the difference reaching statistical significance in favour of ChloraSolv after 5 weeks ($p=0.024$). After 9 weeks, healing of DFUs occurred in seven patients treated with ChloraSolv, compared with only one patient receiving standard treatment ($p=0.039$).

The study results indicated that ChloraSolv in conjunction with weekly dressing changes improved absolute and relative DFU area and time to healing of DFUs compared with standard treatment.

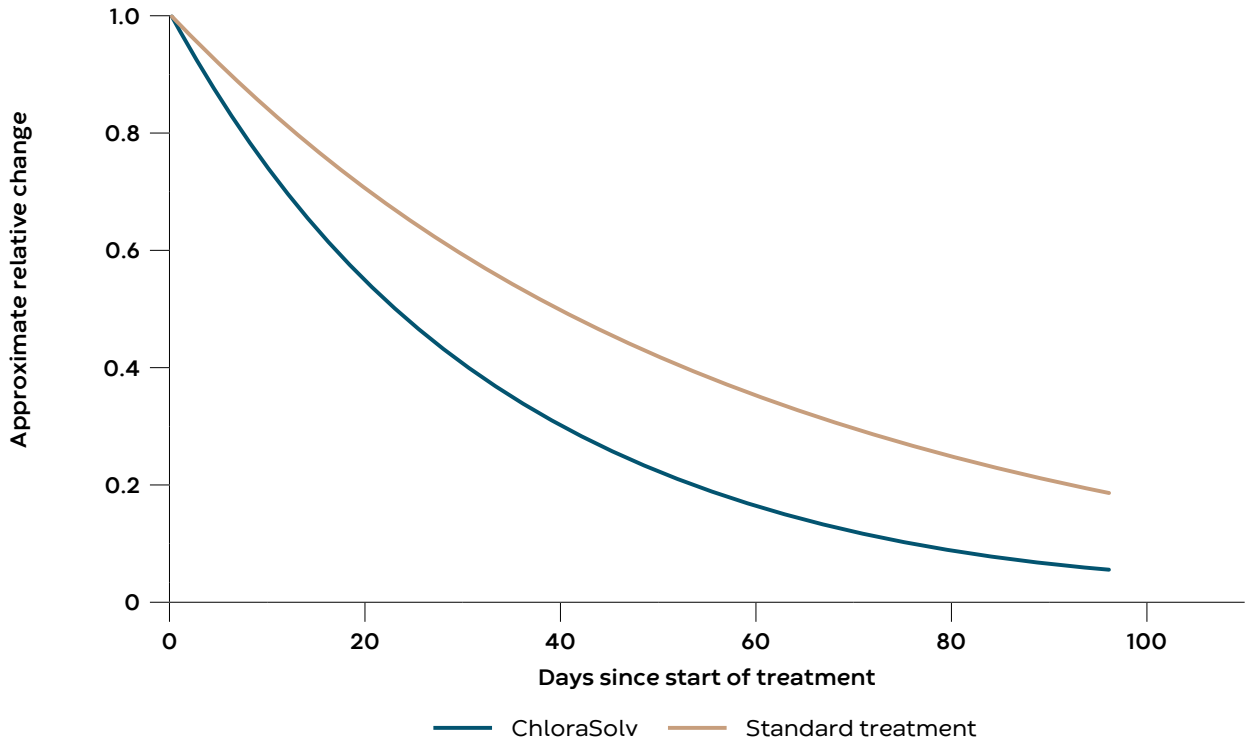
## ChloraSolv can be used to effectively soften and remove devitalised tissue in hard-to-heal leg ulcers[2]

This open-label, single-arm, multicentre study reported by Eliasson et al involved 57 patients with hard-to-heal lower leg ulcers. ChloraSolv was applied to each wound for 2-5 minutes in two sequential steps followed by mechanical debridement at baseline and then weekly for 5 weeks. During the study the patients maintained their initial standard basic treatment given according to international guidelines and recommendations with regard to lower extremity ulcers: diabetic leg ulcers and venous leg ulcers. Patients were followed up after 12 weeks from baseline (7 weeks after last treatment) to assess wound status.

After 5 weeks, a 72.7% decrease in devitalised tissue was seen, with 71.4% of the subjects showing a decrease in devitalised tissue of ≥50%; there was a median reduction in wound size of 30.9%. Changes in devitalised tissue from baseline at each week up to 5 weeks were all statistically significant ($p<0.0001$), and complete debridement was achieved in 23.2% of wounds at 5 weeks.

Furthermore, at 12 weeks' follow up there was an 84.4% decrease in devitalised tissue from

**Figure 5**. Relative change in DFU area as a function of time




ChloraSolv: 19.4% (95% CI: 12.2-26.0; p<0.0001) relative decrease per week; standard treatment: 11.7% (95% CI: 6.4-16.7; p<0.0001) relative decrease per week. Difference between the groups: p=0.083.

Adapted from: Bergqvist et al, 2016[1].

baseline (p<0.0001). Assessment of ChloraSolv by patients and clinical staff showed a high degree of satisfaction with treatment. In total, 89% (47/53) of patients rated ChloraSolv as 'good' or 'very good' with regard to pain, with 90% rating it 'good' or 'very good' with regard to pain during debridement. Of clinical staff involved with the study, 94% rated ChloraSolv as 'easy' or 'very easy' to apply; 70% stated that it made the debridement process easier.

The authors concluded that ChloraSolv is effective and well tolerated as a means of dissolving and removing devitalised tissue in patients with lower-leg ulcers. ChloraSolv treatment was perceived as positive and easy to handle both from the perspective of care recipients and caregivers[2].

## ChloraSolv eradicates biofilm rapidly[4]

This *in vitro* study carried out by Metcalf et al assessed the antibiofilm activities of ChloraSolv and Prontosan® Wound Irrigation Solution on biofilms of *S. aureus* and *P. aeruginosa* using an adapted version of the biofilm susceptibility method, minimum biofilm eradication concentration (MBEC) assay. Biofilms grown on plates for 48 hours were exposed to treatment with ChloraSolv or Prontosan for 0.5-, 2-, 5- and 15-minute time periods, after which the antimicrobial effects of each treatment were neutralised, the biofilms were disrupted, and biofilm cell counts (in CFU/mL) were compared.

After 2 minutes of treatment with ChloraSolv, both *S. aureus* and *P. aeruginosa* biofilms were completely eradicated (CFU reductions >8 $\log_{10}$) to below the limit of detection (p=0.011 and p=0.004, respectively) compared to Prontosan®.

This contrasts with Prontosan, where reductions in CFUs of 2.2 $\log_{10}$ and 1.4 $\log_{10}$ were observed for *S. aureus* and *P. aeruginosa* biofilms, respectively (Figure 6a and b).

**Figure 6.** Mean biofilm cell counts (CFU/mL) (±SD) following treatment with ChloraSolv and Prontosan in a) *S. aureus* and b) *P. aeruginosa*

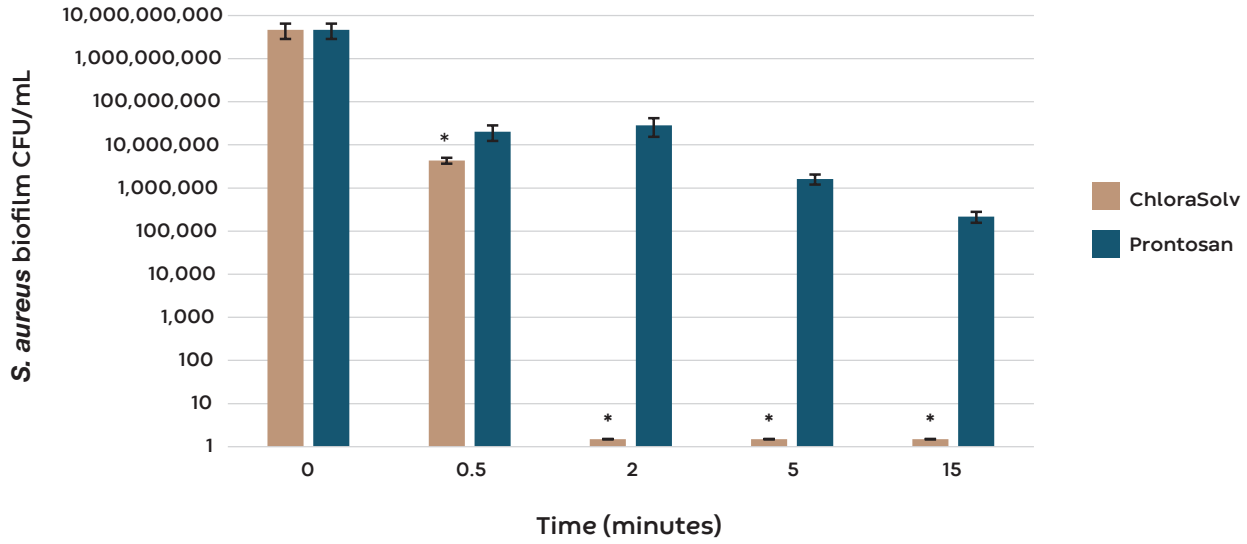



Figure 6a

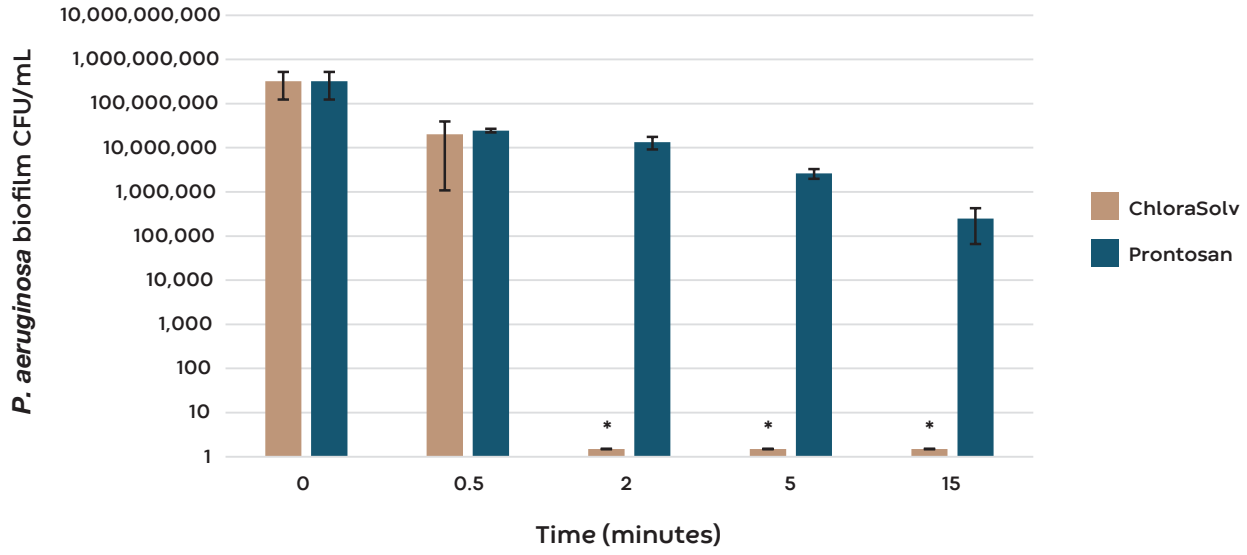



Figure 6b

*Statistically significant compared with Prontosan
Adapted from: Metcalf et al, 2023[4].

This rapid action against biofilm is a valuable component of ChloraSolv's intended use; to facilitate debridement of hard-to-heal wounds and control wound bioburden, within minutes.

## ChloraSolv effectively debrides, improves healing and reduces bacterial load in a porcine infected burn wound model[5]*

This *in vivo* animal study carried out by Larsson et al evaluated the efficacy of ChloraSolv as a chemical enhancement for wound debridement in a porcine infected burn wound model. A total of 60 full-thickness burn wounds, 3 cm in diameter, were created using a standardised burn device and inoculated with $10^7$ CFUs of *S. aureus*. Twenty wounds were assigned to each experimental group (control group: wounds wiped with gauze; curette group: wounds treated with 0.9% saline for 5 minutes and mechanically debrided using a plastic curette; ChloraSolv group: wounds filled with ChoraSolv for 5 minutes and mechanically debrided using a plastic curette). All treatments were performed twice per week for 3 weeks. Debridement, healing and infection parameters were evaluated at 1, 2 and 3 weeks[5].

The ChloraSolv group showed a significantly higher ($p<0.05$) debrided tissue weight, a significantly lower ($p<0.05$) debridement score (i.e. lower resistance to debridement as scored by a medically experienced evaluator) and a significantly larger ($p<0.05$) vital wound area compared with the curette and control groups after 1 week. The ChloraSolv group also showed the earliest healing at 2 weeks (normalised frequency 5%, n=18) and the highest percentage of healed wounds after 3 weeks (normalised frequency 55%, n=16). Quantitative bacterial cultures obtained from wound biopsies showed that the bacterial load reduced from an initial $5\times10^6$ CFU/g to below the clinical infection threshold of $>10^5$ CFU/g in the ChloraSolv and curette groups after 10 days but was maintained at $10^6$-$10^8$ CFU/g in the control group. No CFUs were detectable in the ChloraSolv group after 17 days[5].

## Other data

Other data demonstrate that ChloraSolv kills antibiotic-resistant biofilm bacteria in a challenging, validated gauze biofilm model[6] more effectively than 15-minute antimicrobial solution soaks containing polyhexamethylene biguanide (PHMB) and betaine, octenidine hydrochloride, hypochlorous acid or hypochlorous acid with sodium hypochlorite[4]; and monofilament debridement pads, debridement wipes with poloxamer surfactant or microfibre debridement pads used with PHMB and betaine solution (Figures 7a and B)[4].

## Conclusions

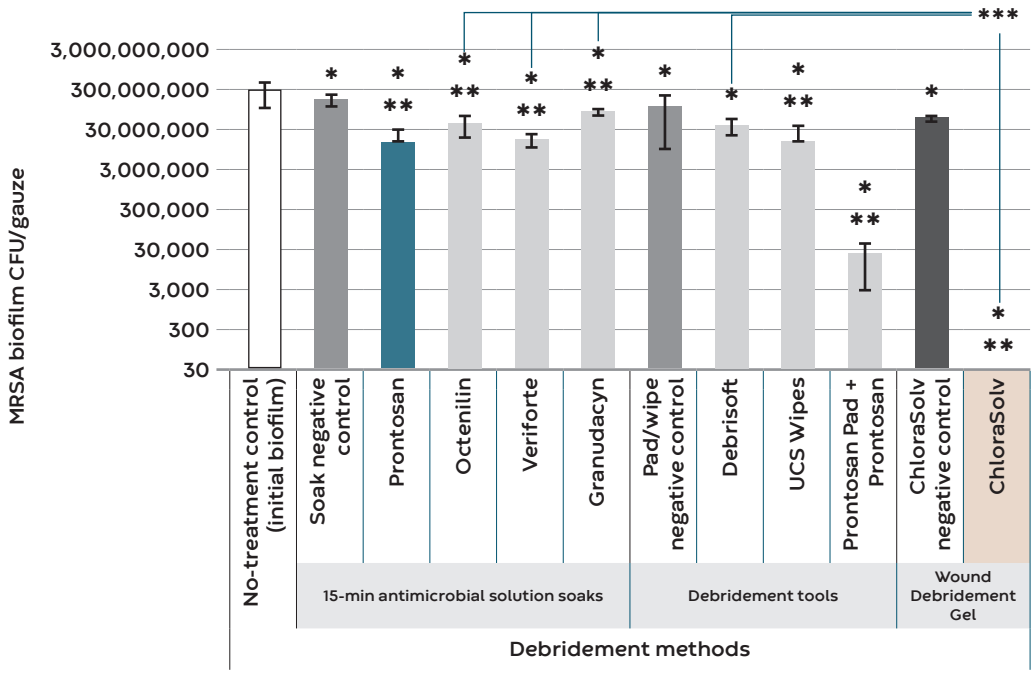
Clinical evidence supports ChloraSolv as a valuable addition to the treatment regime of patients with hard-to-heal leg ulcers and DFUs in need of effective, easy to use and gentle debridement[1-3]. ChloraSolv-assisted debridement has been demonstrated by clinical studies to be more effective than standard of care and sharp debridement in improving wound outcomes and quality of life in patients with hard-to-heal leg ulcers and DFUs[1,2].

ChloraSolv supports effective debridement of hard-to-heal leg ulcers[2] and diabetic foot ulcers[1]. Debridement of the wound with ChloraSolv is beneficial for natural wound healing[3].

*ChloraSolv is not indicated for the treatment of burns.

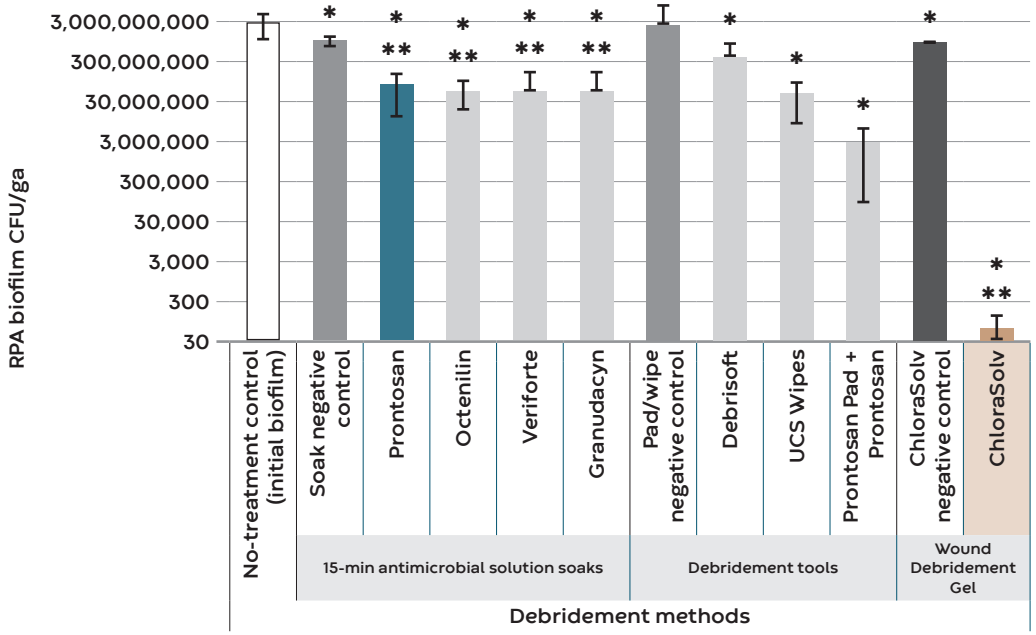
**Figure 7.** Mean biofilm cell counts (CFU/gauze) (±SD) following treatment with ChloraSolv versus antimicrobial solution soaks or debridement pads/wipes in a) Methicillin-resistant *S. aureus* (MRSA) and b) resistant *P. aeruginosa* (RPA)

## Figure 7a




*statistically significant compared with no-treatment control (initial biofilm) ($p<0.05$).
**statistically significant compared with negative control ($p<0.05$).
***statistically significant compared with other method ($p<0.05$)

## Figure 7b




*statistically significant compared with no treatment control (initial biofilm) ($p<0.05$).
**statistically significant compared with negative control ($p<0.05$)

Adapted from Metcalf et al, 2023[4].

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# 6:

# Health economic data - cost effectiveness and budget impact

## Burden on healthcare systems

Treatment costs for hard-to-heal wounds are substantial and are estimated to account for approximately 1-4% of the total healthcare expenditure in developed countries[1-3]. However, this is probably an underestimate because more recent studies report even greater proportions of healthcare expenditure committed to wound care[4].

## Cost of wound management in the UK

Wounds are common and their management creates a high burden of resource requirements and overall costs. A retrospective analysis of case records within The Health Improvement Network (THIN) database estimated that there were around 3.8 million adults with a wound in the UK in 2017/2018[5]. This represents an increase of 71% in just 5 years, from an initial estimated figure of 2.2 million wounds[5,6].

The human resource use attributable to managing these wounds was substantial, including 54.4 million district/community nurse visits, 53.6 million healthcare assistant visits and 28.1 million practice nurse visits[5]. The resulting annual cost to the National Health Service (NHS) was estimated at £8.3 billion, an increase of 48% in real terms over the preceding 5 years[5]. Despite representing only 30% of the total number of wounds, those that were unhealed at the end of the study period accounted for £5.6 billion of the total cost, compared with only £2.7 billion for the 70% of wounds that healed[5]. This indicates a significantly greater resource cost for managing unhealed wounds, with healing rate being a key driver of the cost of wound care[5]. Furthermore, hard-to-heal wounds are more likely to develop complications, such as infections, which require more costly and frequent interventions[7].

The THIN database has also been used to estimate the costs to the NHS resulting from different types of wounds, including DFUs, VLUs, pressure injuries and surgical wounds[8-11] (Table 2). Irrespective of the specific underlying type, unhealed wounds were found to cost at least twice as much per patient as healed wounds: £2,138-£6,007 vs £8,786-£14,230 per year, respectively[8-11].

## Cost of hard-to-heal wound management in the UK

An analysis of UK patients with DFUs managed in the community in the year 2015-2016 showed that only 35% of DFUs healed within 12 months and 17% of patients had at least one amputation in this time period[8]. The mean cost of wound care in the 12 month period was calculated to be about £7,800 per DFU, of which 13% was due to amputations[8]. Management costs for unhealed DFUs were four times those for healed DFUs in the assessment period (£8,800 vs £2,140, respectively)[8]. Following initial presentation, 41% received an antimicrobial dressing and 34%

were prescribed an anti-infective or antibiotic for documented or suspected infection, suggesting that infection management is a significant component of care in these patients[8]. Infected DFUs were associated with a lower healing rate and a longer time to healing[8]. Infection was also a significant contributor to increased cost of management, with uninfected DFUs costing at least 67% less to manage than those that were infected[8].

An assessment of UK patients with VLUs over a 12-month period between 2015 and 2016 found that the cost of managing an unhealed VLU was 4.5 times that of managing a healed VLU (approximately £3,000 vs £13,500, respectively), with 47% of VLUs remaining unhealed at the end of the 12-month period[9]. Up to 30% of VLUs had evidence of infection at presentation, and the presence of infection negatively impacted both healing rate and time to healing[9]. Cost of management for uninfected VLUs was at least 69% lower than for those with evidence of infection[9].

These data highlight the importance of fast and complete wound healing, not just for the associated patient benefits but also for minimising costs to the healthcare system. Appropriate debridement can play an important role. Indeed, hard-to-heal wounds were found to be around three times more likely to heal at 12 weeks when adequate debridement was performed[12]. Furthermore, repeated debridement with ChloraSolv in patients with DFUs resulted in shorter healing time, as well as improvements in wound area and the number of wounds healed, compared with standard of care[13]. Similarly, in patients with hard-to-heal lower leg ulcers, ChloraSolv led to significant reductions in wound size after 5 weeks of repeated use compared with standard therapy[14]. Shorter healing times, improvements in wound area and higher numbers of wounds healed with ChloraSolv, compared with standard of care[13], are all likely to lead to reductions in financial burden.

## Clinical setting for wound management

A further challenge for healthcare systems lies in the clinical management of hard-to-heal wounds[15]. The treatment of wounds is not a defined specialism and, as a consequence, clinicians often lack specialised training in the diagnosis and treatment of wounds. Depending on the healthcare system, a range of different specialists, including dermatologists, podiatrists, vascular surgeons and geriatricians may be involved in the care of patients with hard-to-heal wounds. It is believed that this situation has contributed to deprioritisation of wound care, leading to prolonged healing times[15].

The data in Table 2 also suggest that most of the cost of wound care is driven by management in primary care. In particular, visits by community and district nurses accounted for 52-82% of the cost of patient management[8-11]. In this context, ChloraSolv offers potential for cost mitigation. As ChloraSolv has been shown to reduce the need for sharp debridement[14], requires little training to use and eliminates the need for specialist skills, it can be deployed in patients' homes or in a clinic/hospital setting[16,17]. The lack of requirement for extensive training, specialist skills or facilities may be associated with a reduced financial burden.

Cost-effectiveness analyses specific to ChloraSolv are expected in the future. In the meantime, extrapolation from available data suggests that ChloraSolv could beneficially impact several components of the overall cost of wound management.

**Table 2**. Annual cost per patient of wound care in the UK NHS[8-11]

| | Total | Treatments* | Primary care visits† | Hospital outpatient | Hospital inpatient‡ |
|---|---|---|---|---|---|
| **Diabetic foot ulcer** | | | | | |
| Healed | 2,138 | 409 | 1,568 | 161 | 0 |
| Unhealed | 8,786 | 2,308 | 6,117 | 315 | 47 |
| Amputated | 16,941 | 1,480 | 4,444 | 708 | 10,309 |
| **Venous leg ulcer** | | | | | |
| Healed | 2,981 | 471 | 2,469 | 19 | 22 |
| Unhealed | 13,455 | 2,283 | 10,986 | 150 | 36 |
| **Pressure ulcer** | | | | | |
| Healed | 5,143 | 820 | 4,287 | 36 | - |
| Unhealed | 12,296 | 1,945 | 10,318 | 34 | - |
| **Surgical wound§** | | | | | |
| Healed | 6,007 | 960 | 3,832 | 293 | 921 |
| Unhealed | 14,230 | 2,896 | 9,523 | 527 | 1,285 |

All costs are in GBP based on 2015/16 prices.
*Includes bandages, dressings, compression, analgesics, anti-infectives, debridement, etc.
†Includes visits by or to a community/district nurse, practice nurse, general practitioner, physiotherapist, etc.
‡Includes amputation where relevant.
§From planned (rather than emergency) procedures.

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# Summary

Hard-to-heal wounds are a common problem, affecting around 1-2% of people at some stage in their life[1,2], with this figure expected to rise[3]. The most frequent aetiologies are VLUs and DFUs[1]. The effects on patients can be profound and can include severe pain, emotional and physical distress, reduced mobility, impaired quality of life[4,5] and, in the case of DFUs, amputation[6], with a potential reduction in life expectancy of up to 5 years in individuals who have had lower limb amputations[7,8].

These wounds also have significant societal impacts: a recent analysis estimated that wound care costs the NHS around £8.3 billion per year[9]. Of this sum, £5.6 billion was attributed to managing the minority of wounds that remain unhealed, suggesting that healing rate is a key driver of costs[9].

Biofilm and local infection are key treatable risk factors[10,11]. Indeed, biofilm is present in at least 78% of hard-to-heal wounds[12] and may play a significant role in inhibiting normal healing[13]. The recent Wound Hygiene consensus document highlighted four key strategies for mitigating the risk of biofilm at every dressing change: cleansing of the wound and periwound skin; debridement; refashioning of the wound edges; and use of antimicrobial dressings with antibiofilm properties[14].

Regular debridement is crucial in optimising the wound bed for healing[15,16]. However, there remains an unmet need for methods that can be undertaken by non-specialists, can be used frequently, rapidly remove both devitalised tissue and biofilm, and minimise the risk of further microbial colonisation.

ChloraSolv® is a hypochlorite-based wound debridement gel developed for use in hard-to-heal leg ulcers and DFUs[17]. It offers a number of potential advantages:

- Softening of devitalised tissue to facilitate its easy removal[17,18] while preserving healthy viable tissue[19-21];
- Broad-spectrum antimicrobial activity[17], with rapid biofilm eradication demonstrated *in vitro*[22];
- A reduced requirement for training, thus eliminating the need for specialist debridement skills[23]; and
- Flexibility for deployment in clinical, hospital and home settings[23,24].

Clinical studies have shown that ChloraSolv supports fast, effective debridement of hard-to-heal wounds[17,25]. Patients and clinical staff also show a high degree of satisfaction, with 70% of users stating that ChloraSolv makes the process easier compared with previous debridement methods[17].

Although cost-effectiveness analyses specific to ChloraSolv are not yet available, ChloraSolv has the potential to beneficially impact several components of the overall cost of wound management, by supporting fast and effective debridement and by reducing the requirement for extensive training and specialist debridement skills and facilities.

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