REVIEW ARTICLE

Optimizing Wound Bed Preparation With Collagenase Enzymatic Debridement

Stanley K. McCallon, DPT, CWS^a, Dorothy Weir, RN, CWOCN, CWS^b,
John C. Lantis II, MD, FACS^{c,*}

^aDepartment of Physical Therapy, Louisiana State University Health Sciences Center, School of Allied Health Professions, Shreveport, LA, USA

^bOsceola Regional Medical Center, Kissimmee, FL, USA; and

^cDivision Vascular/Endovascular Surgery, Division of Clinical Surgical Research, Mt Sinai St. Luke's and Roosevelt Hospital Center, New York, NY, USA

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Abstract Difficult-to-heal and chronic wounds affect tens of millions of people worldwide. In the U.S. alone, the direct cost for their treatment exceeds \$25 billion. Yet despite advances in wound research and treatment that have markedly improved patient care, wound healing is often delayed for weeks or months. For venous and diabetic ulcers, complete wound closure is achieved in as few as 25%–50% of chronic or hard-to-heal wounds. Wound bed preparation and the consistent application of appropriate and effective debridement techniques are recommended for the optimized treatment of chronic wounds. The TIME paradigm (Tissue, Inflammation/infection, Moisture balance and Edge of wound) provides a model to remove barriers to healing and optimize the healing process. While we often think of debridement as an episodic event that occurs in specific care giver/patient interface. There is the possibility of a maintenance debridement in which the chronic application of a medication can assist in both the macroscopic and microscopic debridement of a wound. We review the various debridement therapies available to clinicians in the United States, and explore the characteristics and capabilities of clostridial collagenase ointment (CCO), a type of enzymatic debridement, that potentially allows for epithelialization while debriding. It appears that in the case of CCO it may exert this influences by removal of the necrotic plug while promoting granulation and sustaining epithelialization. It is also easily combined with other methods of debridement, is selective to necrotic tissue, and has been safely used in various populations. We review the body of evidence has indicated that this concept of maintenance debridement, especially when combined episodic debridement may add a cost an efficacious, safe and cost-effective choice for debridement of cutaneous ulcers and burn wounds and it will likely play an expanding role in all phases of wound bed preparation.

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* Corresponding author. Division Vascular/Endovascular Surgery, Division of Clinical Surgical Research, Mt Sinai St. Luke's and Roosevelt Hospital Center, 1090 Amsterdam Ave, Suite 7A, New York, NY 10025, USA. Tel.: +1 2125234797.

E-mail address: jlantis@chnpnet.org

Introduction

Wound healing is an intricate biological process of repair, which typically progresses through four overlapping phases: hemostasis, inflammation, proliferation, and remodeling.¹ This complex and fragile process is usually quite efficient, but is susceptible to interruption or failure that can result in non-healing chronic wounds. Unlike acute wounds, chronic wounds do not follow the natural biological healing process and are instead regarded as stuck in the inflammatory or proliferative phases of wound healing.² However, recent data have indicated that the addition of a pro-inflammatory agent such as plasminogen to a non-healing wound can stimulate the wound to heal, indicating the complexity of the healing process.³ As the healing process is dynamic and complex, wounds can progress to a proliferative stage yet return to an inflammatory one due to insufficiencies in the chronic wound.^{2,4,5} The most common factors that impede normal healing processes include uncontrolled diabetes, venous disease, arterial disease, advanced age, peripheral neuropathy, inappropriate bacterial balance and malnutrition.⁴⁻⁷

Unlike wounds that typically heal within a reasonable timeframe, chronic or hard-to-heal wounds often contain a number of microbial, biochemical and cellular abnormalities that prevent or slow progression to healing. While such delays are common even for wounds with seemingly adequate wound beds, the difficulty of chronic wounds to heal go beyond the temporal aspect of healing. The most salient feature of chronic wounds is the fact that they are difficult to heal. Recent estimates suggest that, after 20 weeks of treatment, complete wound closure is achieved in as few as 25%–50% of chronic or hard-to-heal wounds, especially venous and diabetic ulcers.⁸⁻¹⁶ Other pathologies such as arterial insufficiency and peripheral neuropathy without diabetes are understudied.¹⁷

Difficult-to-heal wounds affect tens of millions of people worldwide. In the U.S., studies have shown that approximately 2.5 million people have venous ulcers,^{18,19} while pressure ulcers afflict an additional 1.3–3 million people,²⁰ including an estimated 10%–18% of those in acute care and up to 28% of those in extended care facilities.²¹ Approximately 15% of the 16 million U.S. adults with diabetes will develop serious foot ulcers within their lifetime.²²⁻²⁵ A foot ulcer is a risk factor for the development of additional ulcers, infection, and/or lower extremity amputation (LEA).²² Epidemiologic studies suggest that foot ulcers precede approximately 85% of non-traumatic LEAs in individuals with diabetes.²⁵ Furthermore, it is estimated that 9%–20% of diabetic amputees will undergo a new or second leg amputation within 12 months and 28%–51% will undergo a second leg amputation within five years of their first.²⁵ Perioperative mortality among diabetic amputees is estimated to be 5.8%, with some studies indicating that the five-year mortality rate may be

as high as 39%–68%.²⁵ The total direct annual costs incurred in the treatment of these wounds are estimated to exceed \$25 billion.²⁶

The prevalence and rising costs associated with chronic wounds in the U.S. will only increase due to the obesity epidemic and the fact that the population is growing older.²⁶ To address this growing problem, much attention has been given to understanding and improving the clinical management of chronic wounds. Chronic wounds require a paradigm distinct from the acute wound model. Wound bed preparation and the consistent application of appropriate and effective debridement techniques are recommended for the optimized treatment of chronic wounds.^{6,27-31} Proactive, continuous debridement often is thought to be necessary to accelerate the wound healing process.^{20,32-35}

The “TIME” Paradigm for Wound Bed Preparation

The development of the concept of wound bed preparation was brought to the clinician’s attention by Vincent Falanga, among others. They characterized the overall state of the wound and the steps necessary to optimize both the endogenous healing process and the effectiveness of advanced therapeutic agents.³⁶ It is a critical concept for chronic wounds, particularly since they cannot be managed with the same treatment strategies as acute wounds.^{29,31} Since the pathophysiology of chronic wounds differs significantly from acute wounds, it is especially important for wound bed preparation paradigms to be supported by scientific evidence. It is in this way that these models can be useful for both the evaluation and treatment of chronic wounds. Scientifically-based wound bed preparation paradigms offer several opportunities to optimize the management of chronic wounds, from basic aspects such as managing infection, necrotic tissue and exudate to more complex challenges such as managing phenotypic changes in wound cells.³⁷ Its overarching goals are to remove barriers to healing and stimulate the healing process by establishing a stable wound with healthy granulation tissue and a well-vascularized wound bed to prepare for the next stage of repair.²

The TIME framework for wound bed preparation provides a comprehensive approach to removing barriers to healing and stimulating the healing process.^{27,28,37,38} Its intent is to enable clinicians to optimize the wound bed by reducing edema and exudate, reducing the bacterial burden, and correcting the abnormalities that impair healing.³⁷ Based on the recommendations of the International Wound Bed Preparation Advisory Board, the acronym “TIME” is now commonly used to identify the following four components of wound bed preparation, which address the different pathophysiological abnormalities underlying chronic wounds.^{6,27,37-39}

TIME represents four different aspects of managing chronic wounds: Tissue, Infection/Inflammation, Moisture

Balance and Edge of wound (see Table 1). The *Tissue* aspect of TIME refers to the assessment and management of non-viable or deficient tissue.^{27,28,37-39} This aspect focuses on the need to address problems associated with a defective extracellular matrix (ECM), senescent cells and the presence of cell debris that impairs the healing process. The clinical action required is typically debridement (episodic or continuous). The *Infection* or *Inflammation* element of the TIME principle is the determination of the etiology behind the infection (including biofilms) or prolonged inflammation (e.g., increases in inflammatory cytokines or protease activity) associated with chronic wounds.^{27,28,37-40} Infected foci are removed through the use of topical or systemic antimicrobials, anti-inflammatory agents and/or protease inhibitors. Both enzymatic and mechanical debridement play a role in this pathway, with mechanical debridement especially important in the presence of biofilms.⁴¹⁻⁴³ *Moisture balance* is the assessment and management of wound exudate, of which mismanagement results in either desiccation, which slows epithelial cell migration, or excessive fluid, which causes maceration of wound margins.^{27,28,37-39} Finally, *Edge of wound* assesses the non-advancing or undermined wound edges. The etiology of these non-advancing wound edges can be non-migrating keratinocytes, other phenotypic changes in wound cells, abnormalities in ECM, or abnormal protease activity. Potential therapies include strategies aimed at creating a more responsive wound edge; these strategies are usually focused around debridement.

Since its conceptual introduction more than ten years ago, the TIME paradigm has demonstrated that it is a dynamic and highly evolving model and that the framework is not necessarily linear in process.^{27,37} Problems with its four components will not necessarily occur sequentially and treatment methods often have overlapping purposes. A single intervention often can impact more than one element of the framework. For example, debridement will not only remove necrotic tissue but will also reduce bacterial load. In addition, wound bed preparation should be viewed as one piece of a comprehensive wound assessment, which encompasses the patient's psychosocial needs, patient concordance, as well as underlying and associated etiologies. TIME is a valuable consideration when assessing the needs of patients with chronic wounds.

Types and Purposes of Debridement

Debridement is essential for successful wound management and plays an increasingly critical role in all phases of the TIME framework for managing difficult-to-heal and chronic wounds.⁴³ It has been suggested that the efficiency and frequency of debridement can potentially impact healing rates.⁴⁴⁻⁵⁰ Traditionally, the term debridement has been used to address the removal of necrotic, damaged or infected tissue.⁵¹ The intervention is repeated periodically (typically once or twice a week for chronic wounds) for

as long as these tissue problems are present. Falanga refined the terminology by dividing the actions involved in debridement into two distinct approaches.^{30,52} *Initial debridement* refers to the first debridement performed on a wound following the initial evaluation by the clinician, which may not always be the first debridement performed during the life cycle of a particular wound. *Maintenance debridement* refers to ongoing interventions intended to not only remove non-viable, damaged or infected tissue but also to maintain an optimal wound bed for the completion of the healing process.^{36,53}

Maintenance debridement is thought to be a necessary treatment but a potentially overlooked intervention because several factors that impair wound healing may not be clinically detectable.^{27,30} These include a high bacterial burden in the form of either planktonic bacteria or biofilm, or unstable tissue metalloproteinases and wound cells that have become phenotypically abnormal (the cellular burden). Regardless of the appearance of the wound bed, maintenance debridement may be clinically indicated if the wound does not show evidence of closure.

Debridement serves several purposes that synergistically help accelerate healing during all phases of the TIME paradigm.^{27,51} The removal of non-viable tissue from the wound bed shortens the inflammatory stage of healing by removing devitalized tissue that is conducive to the growth of bacteria and can impair the formation of granulation tissue.^{54,55} The removal of the cellular burden—nonviable and senescent cells—can also prevent the development of abnormal phenotypic changes that may cause cells to be less responsive to growth factors. Such non-responsiveness retards the normal proliferative and migratory behavior of cells, which is necessary for proper wound healing.⁵³

Debridement has also been shown to reduce alterations in the molecular environment and other cellular characteristics of chronic wounds that contribute to the failure of these wounds to heal.² For example, debridement may reduce the presence of inflammatory cytokines and metalloproteinases that are produced in chronic inflamed wounds.⁵⁶ In addition, debridement promotes DNA synthesis and the proliferation of keratinocytes, which are highly important for proper epithelialization.⁵⁶

Debridement Methods

Clinicians can choose from a number of debridement methods (or combination of methods) to determine which would be most appropriate for a given patient (see Table 2).^{32,51,57-59} The selection of the optimal method will depend on several factors, including wound characteristics, patient comorbidities, pain limitations, health needs, timing considerations, the skills of the clinicians or caregivers, and the setting (for example, an outpatient clinic or home).^{32,51,58-60} Although this paper will primarily focus on one of the techniques, enzymatic debridement, a brief

Table 1 TIME – Principles of Wound Bed Preparation (WBP).

Clinical Observations	Proposed Pathophysiology	WBP Clinical Actions	Effect of WBP Actions	Clinical Outcome
Tissue	Defective matrix and cell debris impair healing	Debridement (episodic or continuous): <ul style="list-style-type: none"> • Enzymatic, surgical/sharp, autolytic, biologic, or mechanical 	Restoration of wound base and functional extracellular matrix proteins	Viable wound base
Infection or inflammation	High bacterial counts or prolonged inflammation <ul style="list-style-type: none"> ↑ Inflammatory cytokine ↑ Protease activity ↑ Growth factor activity 	Remove infected foci topical/systemic: <ul style="list-style-type: none"> • Antimicrobials • Anti-inflammatories • Protease inhibition 	Low bacterial counts or controlled inflammation: <ul style="list-style-type: none"> ↓ Inflammatory cytokine ↓ Protease activity ↑ Growth factor activity 	Bacterial balance and reduced inflammation
Moisture balance	<ul style="list-style-type: none"> • Desiccation slows epithelial cell migration • Excessive fluid causes maceration of wound margin 	<ul style="list-style-type: none"> • Apply moisture-balancing dressings • Compression, negative pressure or other methods of removing fluid 	Restored epithelial cell migration, desiccation avoided, edema, excessive fluid controlled, maceration avoided	Moisture balance
Edge of wound	<ul style="list-style-type: none"> • Non-migrating keratinocytes • Non-responsive wound cells and abnormalities in extracellular matrix or abnormal protease activity 	Re-assess cause or consider corrective therapies: <ul style="list-style-type: none"> • Debridement • Skin grafts • Biological agents • Adjunctive therapies 	<ul style="list-style-type: none"> • Migrating keratinocytes and responsive wound cells • Restoration of appropriate protease profile 	Advancing edge of wound

Adapted From Dowsett C. Br J Comm Nurs. 2008;13(6):S15-16,S18,S20.³⁸

Table 2 Methods of Debridement.

Method	Description	Pros	Cons
Enzymatic	Enzymes that degrade components of the ECM	<ul style="list-style-type: none"> • Can be applied directly to wound • Easy to use 	<ul style="list-style-type: none"> • Hypersensitivities are possible to some enzymes in some patients
Surgical	Removal of non-viable tissue with instruments	<ul style="list-style-type: none"> • Simple • Immediately visualize wound edges • Removes all or large amount of necrotic tissue in one episode of debridement 	<ul style="list-style-type: none"> • Limited by availability and level of clinical skill • May make wound larger
Autolytic (hydrogels, hydrocolloids)	Creates/promotes balanced moisture environment and hydrates wound	<ul style="list-style-type: none"> • Can be applied directly to wound • Easy to use • Does not harm normal tissue 	<ul style="list-style-type: none"> • Provide a minimal level of debridement aid to wound • May macerate surrounding tissue if not properly applied
Biologic	Sterile maggots applied directly to wound site	<ul style="list-style-type: none"> • Specifically debrides necrotic tissue 	<ul style="list-style-type: none"> • Reluctance by some patients and clinicians
Mechanical (wet-to-dry, ultrasound, pulsed lavage)	Use of dressings or devices to remove necrotic tissue by force	<ul style="list-style-type: none"> • Removes soft eschar 	<ul style="list-style-type: none"> • Not specific for non-viable tissue; some healthy tissue may be removed • Can be painful

review of the other four most common debridement methods is provided.

Surgical/Sharp Debridement

Surgical debridement is an instrument-based technique in which the clinician uses instruments, such as a scalpel, curette, scissors and/or forceps but sometimes includes ultrasound or high pressure water devices, to manually remove non-viable tissue and debris.^{32,51,58,60,61} Surgical/sharp debridement should be considered whenever the goal is to quickly remove large amounts of necrotic tissue (for example, in infected wounds with systemic sepsis or necrotizing fasciitis), the patient can tolerate this intervention, and skilled practitioners are available.^{6,32,58–60} The ability to control pain and provide appropriate hemostasis is the main roadblock to this aggressive approach.⁶ It must be noted that individual skill and experience plays a large role in the effectiveness of this treatment.³²

Autolytic Debridement

Autolysis refers to the process by which the body's own immune system breaks down and digests necrotic debris.⁶² At the cellular level, autolysis is initiated through the lysosomal release of digestive enzymes.⁶³ While the term may imply that the process is active self-digestion, autolysis is actually the result of cessation of cellular activity. Autolytic debridement involves the use of moisture-donating or moisture-retentive dressings such as hydrogels, hydrocolloids or transparent films, which are placed over the wound and allow the endogenous enzymes within the wound fluid to digest and liquefy necrotic tissue.^{32,54,57,64} The dressing is easy to apply and is typically left in place for 2–3 days. After it is removed, the wound should be irrigated with normal saline to remove liquefied debris. Although this technique can be less stressful for the patient than other debridement techniques, it is slower and therefore can require multiple dressing applications and irrigations for several weeks or longer. Autolytic debridement may not be as effective in patients who are less able to mount an inflammatory response, such as older adults, as it requires a healthy immune system capable of supporting autolysis.^{5,65,66} This technique may be less effective for patients with chronic wounds as they often have compromised immune systems due to medications or disease states, which has been demonstrated in clinical studies.^{67,68} Autolytic debridement is also not appropriate for infected wounds or very deep cavity wounds that require packing and may not be effective in healing chronic wounds such as burns and ulcers.³²

Biologic Debridement

This debridement technique uses sterile maggots to remove necrotic tissue.^{32,40,69} Increasingly popular in Europe, this type of larval debridement therapy is quite effective and relatively rapid in removing eschar and producing good granulation tissue.³⁰ Biologic debridement usually

uses the larvae of the fly *Lucilia sericata* and other similar species, which feed only on necrotic tissue while avoiding healthy and granulating tissue. However, proper biological debridement requires considerable experience for application, precise preparation to the wound and peri-wound area, attention to proper disposal of dressings removed from the wound (full of larvae), and careful avoidance of larvae-induced damage to the surrounding skin. Additionally, patient preference, or the lack thereof, is an important consideration. In some cases, such as diabetic foot ulcers, evidence of its effectiveness is limited and inconclusive.⁷⁰

Mechanical Debridement

Mechanical debridement is a debridement method that uses force or physical energy to remove necrotic tissue.^{32,59} While wet-to-dry dressings are the most commonly used form of mechanical debridement, therapeutic irrigation (delivered by pulsed lavage or the agitation of water during whirlpool therapy) and ultrasound therapy can also be considered forms of mechanical debridement.^{59,71} However, all these techniques are nonselective because both viable and non-viable tissues may be removed during the process. All methods of mechanical debridement have the potential for causing episodic pain and premedication of the patient is usually indicated. Wet-to-dry dressings are time consuming (they are typically changed three times a day) and can cause maceration to the surrounding wound skin. Despite these drawbacks, wet-to-dry dressings are one of the most frequently prescribed (and possibly overused) methods of debridement in acute care settings.^{21,71}

Enzymatic Debridement

Enzymatic debridement is theoretically an active and selective approach to debridement often used in conjunction with other therapies, most commonly following sharp debridement in conjunction with moisture balancing dressings.^{43,52} It is a topical treatment that uses naturally occurring proteolytic enzymes or proteinases, which are critical to the wound repair process. Proteinase activity in chronic wounds is useful not only for the purpose of debridement but also for more fundamental aspects of cell migration necessary for epithelialization.

During this therapy, topical enzymes are used to remove necrotic tissue through the action of digesting and dissolving the devitalized tissue in the wound bed.³² Some enzymes are selective and recognize only devitalized tissue, while others are nonselective and do not distinguish between viable and non-viable tissue. Enzymatic treatment is not appropriate when advancing necrosis is present.³⁰

Several enzymatic debridement agents have been developed, such as trypsin, streptokinase–streptodornase combination and subtilisin.² Bromelain is an enzymatic debriding agent that is currently under investigation.^{72,73} However, the two most commonly enzymatic agents used for chronic wounds are papain-urea combinations in a cream base and

collagenase in a petrolatum base.² These preparations differ in terms of their specificity and overall effects.

Bromelain is a mixture of various endopeptidases and other enzymes, such as phosphatase, glucosidase, peroxidase, cellulase, and escharase, that are derived from the fruit or stem of pineapple.⁷⁴ Fruit and stem bromelains are prepared differently and their compositions differ. Bromelain is applied as a cream (35% bromelain in a lipid base) and typically for relatively short periods (4 h).^{72,74} While a small clinical study has shown that bromelain is a debriding agent that does not damage surrounding healthy tissue and has no significant adverse effects, the mechanism of action is still unknown.^{72,75} At present Bromelain is only available outside the United States.

Papain is a nonspecific cysteine protease derived from the fruit *Carica papaya* and capable of breaking down a variety of necrotic tissue substrates.⁷⁶ The role of urea is to facilitate the proteolytic action of papain by altering the structure of proteins.³² Papain is nonselective, targeting for degradation any protein containing cysteine residues (which are present in most proteins, including growth factors). Papain-urea preparations have been in clinical use for decades—particularly for pressure ulcers—and available literature indicates that these debriding systems are effective when used properly.⁵² Papain-urea is currently only available outside the United States.^{68,72,77,78}

Collagenase ointment is a theoretically selective enzymatic debriding agent derived from the bacterial strain *Clostridium histolyticum*.⁵⁴ It is characterized as selective because it specifically breaks down only one type of protein, collagen, an important component of the extracellular matrix whose selective degradation greatly facilitates healthy wound healing. While excessive matrix metalloproteinase (MMP) activity is a common feature of many chronic wounds, the addition of the bacterial-derived MMP actually provides a benefit to such wounds with debridement, indicating the specificity of collagenase.^{55,79} Collagenase has been demonstrated to be safe in wounds with high bacterial burdens,⁴³ although most effective in wounds with a relatively normal physiologic pH. SANTYL[®] Ointment (SANTYL, Smith-Nephew, Fort Worth, Texas) is the only collagenase-containing biologic debriding agent approved by the FDA for treatment of dermal and burn wounds.^{68,72,79} In the diabetic foot, debridement with collagenase is more efficacious after at least one episode of sharp debridement and is very effective when combined with weekly debridement.⁸⁰ This was followed by gradual granulation and epithelialization, which generally proceeded at a faster rate than expected for these types of chronic dermal lesions.

According to one systematic review of collagenase for enzymatic debridement, collagenase is an effective, selective method of removing necrotic tissue without harming granulation tissue from pressure ulcers, leg ulcers, and burns.⁵⁴ The wound bed preparatory properties of collagenase can be partially attributed to its role in expediting

the removal of the necrotic plug.^{32,52} Necrotic tissue is anchored to the wound by strands of denatured collagen. Until these anchoring fibers are severed—thereby allowing the removal of the necrotic plug—debridement cannot take place, granulation is slowed, and no supportive base is available for epithelialization.³² As described previously, some clinical evidence suggests that collagenase also enhances keratinocyte migration over granulation tissue.⁸¹ In addition Herman and colleagues have shown that matrix pretreatment with Clostridial collagenase stimulated a two-fold increase in proliferation and post-injury migration of keratinocytes.⁸² When the enzyme was added to the growth media, there was approximately five-fold enhancement of keratinocyte proliferation and migration. The findings from their *in vivo* swine model have also indicated that Clostridial collagenase promotes epithelial cell proliferation and migration when directly applied to full-thickness wounds. Herman's group attributes these phenomena to the small collagen split products that act as growth potentiators and signaling ligands.^{72,83}

While much of the Collagenase clinical trials literature is historical in nature it has to some degree shown the efficacy of collagenase in treating a wide variety of ulcers and burns.^{68,81,84–87} However more recently two more “modern” and placebo controlled trials have been carried out. A recent single-blinded, randomized study compared collagenase vs. hydrogel (SoloSite® Gel, Smith & Nephew, Largo, FL) for initial debridement in 27 institutionalized patients with pressure ulcers.⁶⁸ Ulcers were treated with daily dressing changes followed by application of either collagenase ointment or hydrogel. Investigators were blinded to randomization and evaluated wound photographs weekly for debridement progress. In the collagenase treatment arm, 11/13 patients (85%) experienced complete debridement within 42 days, whereas only 4/14 (29%) of those treated with hydrogel achieved complete debridement. The collagenase group experienced greater reduction of non-viable tissue and faster reduction in overall wound size. The other recently published trial was a randomized parallel group, open-label trial comparing collagenase as an adjunct to sharp surgical debridement vs. sharp surgical debridement with various standard of care (SC) regimens (at discretion of principal investigator). The primary objective was the percent of wound area change from baseline at the completion of the 6-week (EOS) and 12-week (EOT) trial periods. The secondary objectives were assessment of the wound status, measured using the standardized wound assessment tool, including eight sub-scale scores and the number of sharp debridements required during the trial period, measured at the same time points. The time to wound closure for each group was also assessed.⁸⁸ Wound area decreased relative to baseline for both the *clostridial collagenase* (CCO) group (–68%, –61%) and the control group (–36%, –46%) at EOT and EOS, respectively. While the inter-group differences did not reach statistical significance, wound area was significantly

decreased from baseline at both EOT and EOS for the CCO ($P < 0.001$) but not for the control group. Wound status scores (scale range 8–40) improved for both groups during treatment (CCO: –3.5, control: –3.2) and follow-up (CCO: –5.3, control: –6.4). No differences were observed in the number of sharp debridements (CCO: 3.7, control: 4.0). Median time to closure for wounds that healed was 6 weeks for CCO and 8 weeks for control.⁸⁸

Conclusion

The increasing prevalence and adverse socioeconomic effects of chronic and difficult-to-heal wounds have intensified the need for better, more cost-effective therapies. Wound bed preparation offers opportunities to improve the management of chronic wounds but the techniques involved must be optimized in order to provide the best possible outcomes for difficult-to-heal wounds. Debridement will have an increasingly important role in wound bed preparation as studies indicate that the efficiency and frequency of debridement may impact the rate of wound closure.^{44–50} The choice of a debridement method must take into account such factors as the setting and skill sets of clinicians or other caregivers. If complete debridement of non-viable tissue is immediately needed, only surgical/sharp debridement can completely debride necrotic tissue in one patient encounter.⁵⁹

However, surgical or sharp debridement may not be a viable option in long-term nursing facilities. The access to bedside sharp debridement is limited in long-term care, rehabilitation units and homecare settings.⁶⁸ Instead, it may be appropriate to treat wounds with a short course (one week) of an enzymatic debriding agent before considering surgical/sharp debridement. This approach allows the clinician to gauge the potential efficacy of this more conservative approach and to determine if the wound is progressing toward healing.³⁰ In addition, the first episode of sharp debridement is usually not the only time that a wound will need debridement. Once a wound needs two sequential episodes of sharp debridement, maintenance debridement with collagenase should be employed.^{30,32} This algorithm potentially decreases the frequency of and facilitates the ease of debridement. This can be augmented by both using autolytic debridement in the form of secondary dressings such as foams; and/or mechanical debridement strategies as well. This algorithm takes into account patient pain, hemostasis, and availability therefore allowing for better patient concordance.

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