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REVIEW ARTICLE

Optimizing Wound Bed Preparation With Collagenase Enzymatic Debridement

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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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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