Caution: when combining topical wound treatments, more is not always better

Cowan L, Phillips P, Liesenfeld B, Mikhaylova A, Moore D, Stechmiller J & Schultz G

Abstract

Most wound care providers are aware of the principles embodied in the concept of 'wound bed preparation', which is an integrated approach that seeks to enhance healing of acute and chronic wounds by optimising four key aspects of a wound bed: 1) tissue debridement; 2) inflammation/infection; 3) moisture levels; and 4) epithelial edge healing. Ideally, treatment strategies should simultaneously address each of these four aspects. This often leads to combining advanced topical and/or systemic therapies that stimulate healing or remove barriers to endogenous healing. While some laboratory data and clinical trial results suggest specific combinations of treatments may synergistically enhance healing, other combinations may destructively interact and reduce the effectiveness of the treatment components. This brief review presents some examples of constructive, destructive and neutral interactions of combinations of wound treatments and emphasises the need for clinicians to carefully consider how combinations of wound treatments may interact in the wound bed.

Keywords: combined therapies, dressings, debriding enzymes, silver

Linda Cowan PhD, ARNP
Veterans Health System, Gainesville, FL, USA

Priscilla Phillips PhD
Dept Oral Biology, University of Florida, Gainesville, FL, USA

Bernd Liesenfeld PhD
QuickMed Technologies Inc, Gainesville, FL, USA

Albina Mikhaylova PhD
QuickMed Technologies Inc, Gainesville, FL, USA

David Moore BS
QuickMed Technologies Inc, Gainesville, FL, USA

Joyce Stechmiller PhD ACN P-BC, FAAN
College of Nursing, University of Florida, Gainesville, FL, USA

Gregory Schultz * PhD
Institute for Wound Research, College of Medicine, University of Florida, 1600 SW Archer Road, Gainesville, FL 32610-0294, USA
Email schultzg@ufl.edu

* Corresponding author

Introduction

Wound bed preparation is a comprehensive approach to wound management which focuses on optimising conditions in the wound bed to encourage normal endogenous processes of healing[1]. It is based on an understanding of cellular and molecular processes that underlie and regulate normal wound healing, and it has been applied to both chronic wounds and acute wounds, such as thermal burns[2-4]. The TIME acronym (or DIME) is a practical guide to wound bed preparation, which relates clinical observations and interventions to the underlying wound pathology in each of four key concepts (Figure 1):

1. **T** for TISSUE – debridement of non-viable or deficient tissue.
2. **I** for INFECTION and INFLAMMATION – reduce excessive bioburden, proteases and reactive oxygen species that degrade proteins that are essential for healing.
3. **M** for MOISTURE – balance moist wound healing without maceration of tissue.
4. **E** for EDGE – stimulate proliferation and migration of epidermal cells at wound edge.

In many chronic wounds, a combination of actions or therapies would appear to be necessary to remove multiple barriers to healing that are created by several problems in the wound bed. The following hypothetical cases present examples where multiple problems are present in each chronic wound and combination therapies are considered.

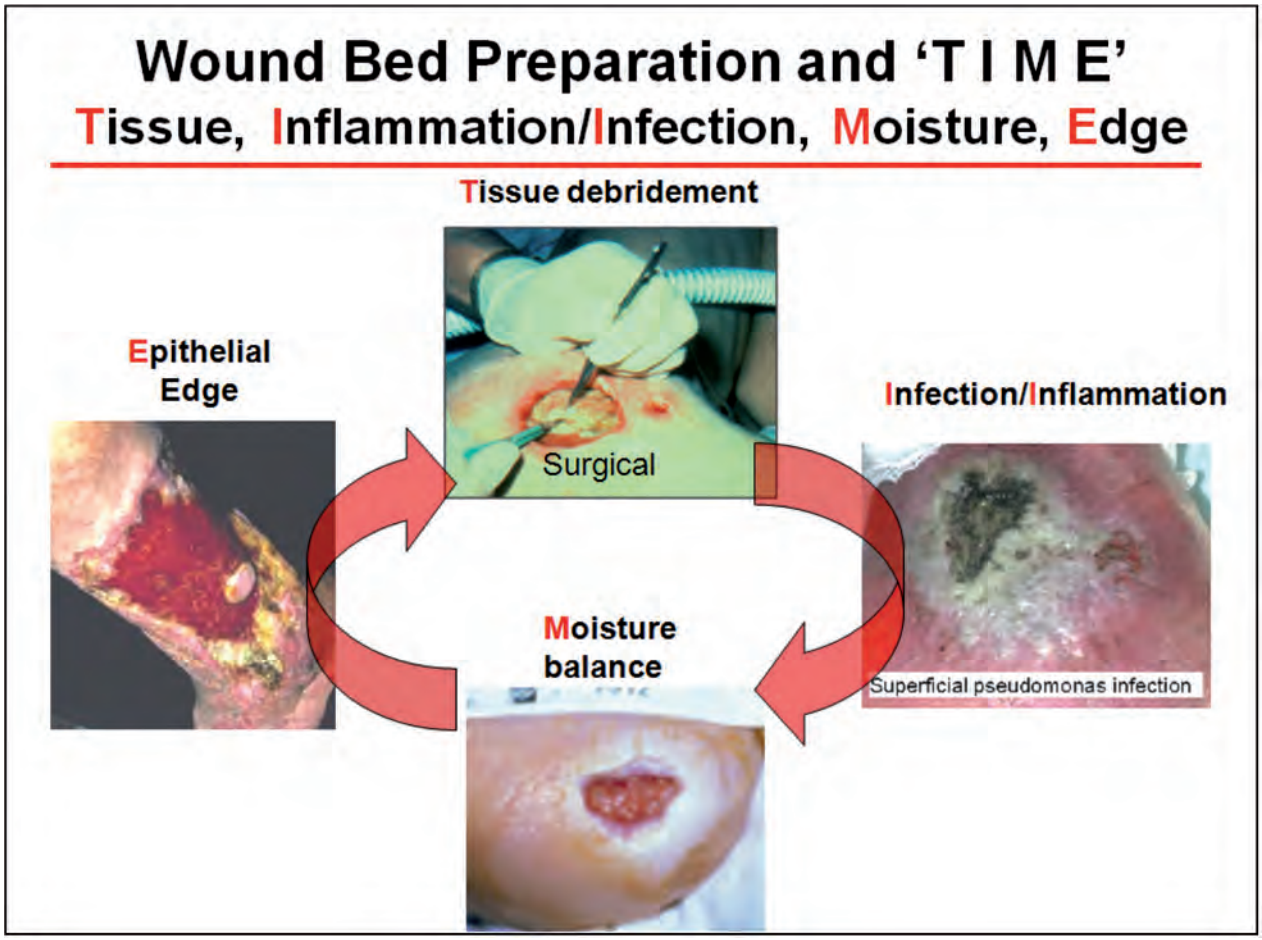

Figure 1. Wound bed preparation. Wound bed preparation is a comprehensive approach to wound management which focuses on optimising four key concepts for healing: TISSUE – debridement of non-viable or deficient tissue; INFECTION and INFLAMMATION – reduce excessive bioburden proteases, reactive oxygen species that degrade proteins that are essential for healing; MOISTURE – balance moist wound healing without maceration of tissue; EDGE – stimulate proliferation and migration of epidermal cells at wound edge.

The potential constructive and destructive interactions of the combination therapies are discussed

Hypothetical Case #1. A 60-year-old man with poorly controlled type II diabetes and a documented history of peripheral neuropathy presented to the wound clinic with a chronic ulcer of one year duration on the plantar surface of his left foot. The ulcer had been treated in the past with occasional debridement and gauze packing with an off-loading custom orthotic shoe. The patient's last Ankle Brachial Index (ABI) was 0.8, and the patient demonstrated palpable pedal and posterior tibial pulses (1–2+). The wound measured 2.0 cm length x 2.0 cm width x 0.5 cm depth. The wound edge was not macerated but there was moderate periwound callus noted and moderate yellow exudate (no foul odour detected) with thick yellow slough noted over one-third of the wound base. Bacterial swab culture of the wound bed after debridement indicated moderate growth (<1,000,000 cfu) of several typical bacteria species, but without MRSA. The client denied pain and there was no surrounding oedema but slight localised erythema noted up to 1.0 cm from the callus edges. It was judged to not be clinically infected but was considered to be moderately inflamed. Importantly, there was minimal granulation tissue over about two-thirds of the wound bed. This portion of the wound bed appeared pale pink. The wound care team decided to utilise an integrated combination of therapies to reduce the inflammation and rapidly stimulate formation of granulation tissue in the wound bed of such long duration. The patient was not on any type of anticoagulation therapy and had no known history of coagulopathy. The wound care team recommended sharp paring down of the peri-wound callus and another sharp wound debridement of the slough in the wound bed. They also recommended treatment with recombinant platelet-derived growth factor (Regranex®) to promote more rapid development of granulation tissue. They decided to replace the simple gauze dressing with a protease inhibiting dressing (Promogran®) covered by a semi-occlusive dressing. The patient was required to use a specially-fitted

off-loading orthotic at all times and return to clinic in one week for follow-up.

From the perspective of wound bed preparation, this treatment plan simultaneously addressed several key issues of the TIME paradigm. Firstly, the surgical debridement would remove defective tissue (peri-wound callus) and reduce the levels of planktonic (free-floating) and sessile biofilm bacteria (stationary, mature polymicrobial colony), which would reduce the level of inflammation and should reduce the level of wound exudate. The wound team suspected the level of proteases would be highly elevated in the wound bed and they understood that both endogenous and exogenous growth factors would be degraded by high levels of proteases like the matrix metalloproteinases (MMPs) and neutrophil elastase (NE)[5,6]. Therefore, they decided to combine the PDGF growth factor therapy with a dressing that contains collagen and oxidised regenerated cellulose (ORC). These two components of Promogran® act as substrate sinks for MMPs and NE and can reduce the levels of protease activities in chronic wound fluids to values that are more similar to the low levels of proteases found in acute healing wounds[7]. In addition, laboratory data show that protease-inhibiting dressings can substantially reduce the breakdown of PDGF by proteases present in chronic wound fluids[8]. Importantly, each of these topical treatments (Regranex® and Promogran®) has been shown in randomised controlled trials (RCT) to separately improve healing of chronic wounds[9-11]. Thus, it was reasonable to consider combining these two topical treatments (based on biochemical knowledge of both) with the expectation that they would enhance the effects of the other treatment and improve healing better than either treatment alone.

Hypothetical Case #2. A very frail, 70-year-old female who is a resident in an extended care nursing home presented to the wound clinic with stage III pressure ulcer on her sacrum, of reportedly five weeks' duration with no improvement. The ulcer measured 5.0 cm length x 6.0 cm width x 0.5 cm depth and had moderate serosanguinous exudate and yellow slough over two-thirds of the wound base and bacterial swab culture indicated moderate growth (<1,000,000 cfu) of several typical bacteria species, including MRSA. It was judged to not be clinically infected but was considered to be inflamed, with a high bioburden. There was minimal granulation tissue over about one-third of the wound bed, but there was substantial proteinaceous wound slough covering the wound bed. The surrounding skin showed mild erythema at immediate wound edges (up to 0.5 cm from wound edge) but no appreciable warmth, fluctuance or oedema. The wound was being treated with an alginate dressing (changed daily) as well as interventions such as pressure redistributing support surface with frequent turning but healing had not progressed in four weeks. The wound team considered using an integrated combination of therapies to first debride the wound bed with an enzymatic debriding ointment containing bacterially derived collagenase (Santyl®) while simultaneously using a silver-releasing dressing to help reduce the level of planktonic MRSA.

While this combination of treatments would appear to address two important components of wound bed preparation, specifically, debridement of necrotic or defective tissue and reduction of inflammation/infection, one of the wound team members pointed out that laboratory data included with the Santyl® product insert indicate that ionic silver and iodine both reduce the enzymatic activity of collagenase contained in the debriding ointment (Table 1). Thus, this combination of two active topical treatments would destructively interfere with the actions of the enzymatic debriding agent and this combined treatment strategy was rejected by the wound care team.

Table 1. Effect of wound dressings on Clostridium collagenase *enzyme activity.*

Dressing type	Selected product	Inhibitory effect
Nanocrystalline silver dressing	Acticoat [Smith & Nephew, Largo, FL]	>50%[13]
Carboxymethyl cellulose hydrofibre dressing with ionic silver	Aquacel Ag [ConvaTec, Skillman, NJ]	Low inhibition[14]
Alginate dressing with ionic silver	Algicell AG [Derma Sciences, Princeton, NJ]	Contraindicated+
Pigment-complexed polyvinyl alcohol dressing	Hydrofera Blue [Healthpoint Ltd, Fort Worth, TX]	None[13]
Iodine dressings	Iodoflex [Smith & Nephew, Largo, FL]	>90%[13]
PHMB gauze small cationic monomer	Kerlix AMD™ [Covidien, Mansfield, MA]	>80%*
pDADMAC gauze large cationic polymer	Bioguard™ [Derma Sciences, Princeton, NJ]	None*
Collagen dressing plus alginate	Fibracol Plus [Johnson & Johnson, Minneapolis, MN]	None[13,14]

* QuickMed Technologies, Inc, internal data; + www.woundcareresources.net

Another treatment approach the wound team considered for this patient was to combine the enzymatic debriding agent with a bacterial barrier gauze dressing, Kerlix AMD®, that contains the microbicidal agent polyhexanide (or polyhexamethylene biguanide, PHMB). However, laboratory data (Table 1) show this bacterial barrier dressing also inactivates the bacterial collagenase, probably due to interaction with the PHMB that elutes from the dressing. In contrast, a different microbicidal bacterial barrier dressing, BioGuard®, which contains a bound microbicidal polyquat polymer (poly-diallyldimethylammonium chloride, pDADMAC) does not inhibit bacterial collagenase (Table 1). Thus, combinations of dressings with collagenase debriding agents can have very different effects on the enzyme's activity. The wound team also considered the enzymatic debriding agent requires additional moisture to activate the enzymatic activity. Since the patient was having a moderate amount of wound exudate, this would provide the adequate moisture. After cleansing the wound with saline, the enzymatic ointment was applied to the slough in the wound bed in a recommended thickness of 2 mm. It was recognised that if some of the collagenase enzymatic debriding ointment contacted the granulation tissue it would cause no harm. The microbial barrier dressing was applied over this with orders to change the entire dressing daily (using saline as a wound cleanser) and schedule a wound follow-up visit in two weeks.

Hypothetical Case #3. A 65-year-old female with chronic venous insufficiency developed an ulcer located on the lateral surface near her left ankle that was improving with standard compression therapy dressing, but after several weeks of compression therapy, the patient presented with acute, severe pain in the ulcer bed. The wound measured 3.0 cm length x 2.0 cm width x 0.3 cm depth. Macerated wound edges, erythema and warmth were noted in the surrounding skin. After examining the wound bed, the wound team noted the ulcer had developed signs of an acute infection, consistent with *Pseudomonas aeruginosa* (light-green sheen and a musty, earthy odour). The wound team decided to prescribe systemic antibiotics (gentamicin) combined with topical wound cleansing with Dakin's solution followed by gauze dressing soaked with dilute (1/4 strength) Dakin's solution (0.125% sodium hypochlorite buffered with 0.04% boric acid). The wound team initially thought about using the bacterial barrier gauze dressing, Kerlix AMD®, that contains the microbicidal agent polyhexanide, but one team member remarked that Kerlix AMD® gauze dressing inactivated sodium hypochlorite (Table 1), so the team decided to use the BioGuard® bacterial barrier gauze since it does not

inactivate the sodium hypochlorite solution. The wound team anticipates that treatment with dilute Dakin's solution will be short term (<four weeks) because they recognise that sodium hypochlorite solutions >0.01% or 0.025% are cytotoxic to fibroblasts[15-16]. However, the infection is far more detrimental to the wound bed and fibroblasts are not expected to proliferate in the presence of acute infection in a wound that is deteriorating. The wound team decided they would address the bacterial infection first. The treatment was ordered for two weeks and included continued compression stockings to bilateral lower extremities daily. A wound follow-up appointment was scheduled for two weeks. After the acute infection is resolved, a non-cytotoxic wound dressing will be ordered and wound progression toward healing is expected.

Summary

These hypothetical cases illustrate several key concepts that clinicians should consider when designing optimised treatment strategies for individual patients. Firstly, most chronic wounds first present with several aspects that need to be addressed within the concepts of wound bed preparation. This typically leads to combining several therapeutic interventions to correct the molecular and microbial problems in the wound bed. However, the clinician must recognise the potential for positive, negative or neutral interactions that can occur between the different agents and dressings. Some of these negative interactions are straightforward and rather well known. For example, certain silver dressings should be hydrated only with sterile water and not with solutions that contain substantial concentrations of anions like chloride (isotonic saline) or phosphate (phosphate buffered saline) or protein (plasma) because these solutions precipitate and inactivate silver anion (Acticoat® package insert). Another destructive combination is the use of silver dressings with Tegederm Matrix® dressing, which contains a mixture of four cations (calcium, zinc, potassium and rubidium) with chlorine counter anion (3M FAQs Wound Management). Other interactions may not be as widely recognised, such as the inactivation of debriding enzymes by reactive metal ions like silver or iodine or other microbicides like PHMB (Table 1). Another potential negative interaction may occur between collagenase debriding enzymes and systemic antibiotics of the tetracycline family (tetracycline, doxycycline, minocycline) because all the tetracycline family of antibiotics are competitive inhibitors of MMPs[12]. Of equal importance for clinicians, however, is to know when there is no known detrimental effect of combining different therapies. Examples of neutral interactions between different topical wound treatments include collagenase debriding ointment used with dressings such as saline moistened gauze, BioGuard® microbicidal gauze dressing, Hydrofera Blue® PVA dressing or Fibrocol Plus® collagen plus alginate dressing (Table 1).

In conclusion, the purpose of this article is to alert wound care providers to potentially detrimental interactions between certain wound products. Caution is advised when considering combining products where there may be an unknown interaction, or there exists laboratory data (such as those in Table 1) to demonstrate interactive effects. The hypothetical scenarios portrayed in this article are not meant in any way to be clinical advice for treating specific wounds, but rather an illustration of common reasoning wound providers may use in making treatment decisions. Please consult evidence-based wound treatment guidelines for specific wound treatment recommendations.

References

1. Schultz GS, Sibbald RG, Falanga V *et al*. Wound bed preparation: a systematic approach to wound management. Wound Repair Regen 2003; 11(Suppl 1):S1–S28.
2. Schultz G, Mozingo D, Romanelli M & Claxton K. Wound healing and TIME; new concepts and scientific applications. Wound Repair Regen 2005; 13(4 Suppl):S1–S11.
3. Ayello EA & Cuddigan JE. Conquer chronic wounds with wound bed preparation. Nurse Pract 2004; 29(3):8–25.
4. Sibbald RG, Orsted H, Schultz GS, Coutts P & Keast D. Preparing the wound bed 2003: focus on infection and inflammation. Ostomy Wound Manage 2003; 49(11):23–51.
5. Ladwig GP, Robson MC, Liu R, Kuhn MA, Muir DF & Schultz GS. Ratios of activated matrix metalloproteinase-9 to tissue inhibitor of matrix metalloproteinase-1 in wound fluids are inversely correlated with healing of pressure ulcers. Wound Repair Regen 2002; 10(1):26–37.
6. Yager DR, Chen SM, Ward SI, Olutoye OO, Diegelmann RF & Cohen IK. Ability of chronic wound fluids to degrade peptide growth factors is associated with increased levels of elastase activity and diminished levels of proteinase inhibitors. Wound Repair Regen 1997; 5(1):23–32.
7. Cullen B, Smith R, McCulloch E, Silcock D & Morrison L. Mechanism of action of PROMOGRAN, a protease modulating matrix, for the treatment of diabetic foot ulcers. Wound Repair Regen 2002; 10(1):16–25.
8. Cullen B, Watt PW, Lundqvist C *et al*. The role of oxidised regenerated cellulose/collagen in chronic wound repair and its potential mechanism of action. Int J Biochem Cell Biol 2002; 34(12):1544–56.
9. Veves A, Sheehan P & Pham HT. A Randomized, Controlled Trial of Promogran (a Collagen/Oxidized Regenerated Cellulose Dressing) vs Standard Treatment in the Management of Diabetic Foot Ulcers. Arch Surg 2002; 137(7):822–7.
10. Vin F, Teot L & Meaume S. The healing properties of Promogran in venous leg ulcers. J Wound Care 2002; 11(9):335–41.
11. Steed DL. Clinical evaluation of recombinant human platelet-derived growth factor for the treatment of lower extremity diabetic ulcers. Diabetic Ulcer Study Group. J Vasc Surg 1995; 21(1):71–8.
12. Chin GA, Thigpin TG, Perrin KJ, Moldawer LL & Schultz GS. Treatment of Chronic Ulcers in Diabetic Patients with a Topical Metalloproteinase Inhibitor, Doxycycline. Wounds 2003; 15(10):315–23.
13. Shi L, Ermis R, Kiedaisch B & Carson D. The effect of various wound dressings on the activity of debriding enzymes. Adv Skin Wound Care 2010; 23(10):456–62.
14. Shi L & Carson D. Collagenase Santyl ointment: a selective agent for wound debridement. J Wound Ostomy Continence Nurs 2009; 36(6 Suppl):S12–S16.
15. Heling et al. Bacteriocidal and Cytotoxic Effects of Sodium Hypochlorite and Sodium Dichloroisocyanurate Solutions *In Vitro*. J Endod 2001 Apr; 27(4).
16. Heggers JP, Sazy JA, Stenberg BD *et al*. Bactericidal and wound-healing properties of sodium hypochlorite solutions: the 1991 Lindberg Award. J Burn Care Rehabil 1991 Sep-Oct; 12(5):420–4.