Innovations in diabetic foot care: Using a wound healing timeline for advanced therapies

Wounds International, Vol 1; Issue 2 › Practice › Innovations in diabetic foot care: Using a wound healing timeline for advanced therapies

Diabetic foot ulcers and associated wound care methodologies have been the subject of rigorous research during the last decade. It is important for clinicians to educate themselves on the latest therapies and incorporate them into wound care protocols appropriately. This report reviews innovations in diabetic foot care from a US perspective and provides a guide to the effective use of advanced therapies, including debridement, promotion of granulation tissue and wound closure, to help clinicians achieve optimum wound healing.

INNOVATIONS IN DIABETIC FOOT CARE

Key innovations in the US include:

1. Development of a wound healing timeline to guide clinicians on the optimum use of advanced wound care therapies.
2. The use of biguanides as an alternative hydrotherapy whirlpool additive or in streaming NPWT techniques to reduce infection/contamination in wounds.
3. Instillation of a chemotherapeutic agent (eg Dakin’s solution) in conjunction with NPWT to help reduce bacterial colonisation.
4. New treatment strategies for healing chronic diabetic foot ulcers could be directed towards reducing the concentration of MMPs and increasing levels of TIMPs.
5. An electrically active wound dressing approved for use in light to moderately exuding, partial- and full-thickness wounds.
6. A novel micrografting procedure that is currently being clinically tested in patients with diabetic foot ulcers.
7. The use of bioengineered alternative tissues (BATs) to increase the clinician's ability to provide soft tissue closure of lower extremity ulcers.
8. The development of a re-ulceration prevention programme in which patients are educated about self-monitoring and provided with a hand-held digital thermometer.

INTRODUCTION

Diabetic foot disease is a progressive condition that is associated with a number of major risk factors. These include neuropathy, peripheral vascular disease and infection, which can lead to poor healing
and subsequent amputation. Each risk factor along the disease pathway represents a target for intervention. This approach, coupled with a well-equipped limb salvage team, to identify, treat and manage these targets for intervention, is essential for good quality patient care.

The University of Arizona's Southern Arizona Limb Salvage Alliance (SALSA) has set up a model of interdisciplinary care. This includes a clinical team involving podiatric surgeons and vascular surgeons. However, the comprehensive care model also includes expertise from various hospital departments including: Internal Medicine, Diabetology, Infectious Disease, Physical Therapy, Plastic Surgery, Nursing, Emergency Medicine and Prosthetics.

SALSA has significantly contributed to clinical and translational research efforts in wound healing, infectious diseases, biomechanics (offloading), bioengineering, and surgery [1,2]. This has led to the development of several innovative modalities/tools that have been clinically targeted to address the disease pathology.

Wounds International, Vol 1; Issue 2 › Practice › Innovations in diabetic foot care: Using a wound healing timeline for advanced therapies

DEVELOPING A WOUND HEALING TIMELINE

Continuing advances in the management of diabetic foot ulcers mean that clinicians need to be sure that they are providing the correct evidence-based practice at the right time to ensure optimum healing. In a recent paper in the Journal of Diabetic Foot Complications, the authors proposed a wound healing timeline that details when each advanced therapy should be introduced in order to move a wound along the continuum of wound healing (Fig 1) [3]. The authors were inspired to develop a wound healing timeline to address the confusion that existed among clinicians regarding various types of wound healing technologies. The three phases within the wound healing timeline are [3]:

- Wound bed preparation (debridement)
- Promotion of granulation tissue
- Wound closure.
The wound healing timeline [3] provides guidance for clinicians on the most effective time to use advanced wound care therapies. It is important for clinicians to focus on the goal of wound healing rather than merely providing wound treatment.

A detailed knowledge of all the treatment modalities mentioned in this report will help clinicians involved in diabetic foot care to provide optimum treatment for their patients. Fitzgerald et al, provide a more comprehensive paper on the use of advanced technologies using this wound healing timeline [3]. This report will focus specifically on the recent advances that have been incorporated into the wound healing timeline following its introduction.

**PHASE 1: WOUND BED PREPARATION (DEBRIDEMENT)**

Studies have found that areas where debridement is used frequently are associated with improved wound healing outcomes and there is a significant correlation between serial debridement and higher rates of healing [4].

There are two types of debridement, non-selective and selective:

- Non-selective debridement includes mechanical debridement (wet-to-dry dressings, hydrotherapy, and some enzymatic debridement agents, eg papain-urea)
- Selective debridement includes autolytic debridement, enzymatic debridement, biosurgical debridement (maggot therapy), sharp debridement and surgical debridement (hydrosurgery: Versajet, Smith & Nephew, and ultrasound).

**Hydrotherapy**
Hydrotherapy includes whirlpool jet agitation therapy and pulse lavage. Whirlpool jet agitation therapy helps to loosen, soften and remove any gross contamination while providing a moist wound environment [5,6].

There are several choices of whirlpool additives that can help to decrease bacterial loads and debride the wound. The whirlpool additives currently being used include povidone-iodine (Betadine, Purdue), chlorhexidine gluconate (Hibiscrub, Mölnlycke Healthcare), acetic acid, Dakin's solution (sodium hypochlorite), chloramine-T (sodium-n-chloro-para-toluenesulfonamide), and polyhexanide (Prontosan, B. Braun). It is important for clinicians to weigh up the benefits of using antiseptic agents to prevent infection and contamination against the reported suppression of tissue repair and cytotoxic effects associated with the use of these agents [7-13].

Recently, there has been increased interest in returning biguanides to the range of products used in wound care. Biguanides have demonstrated a stronger action against gram-positive bacteria than gram-negative bacteria [14]. The biguanide polyhexanide (Prontosan, B. Braun) is currently available for use in the US in a wound gel (0.1% polyhexanide) or as an irrigation fluid. The irrigation fluid has been used in wet-to-dry dressings, foams and for instillation techniques in negative pressure wound therapy (NPWT); it can also be considered for use as an alternative whirlpool additive. At the University of Arizona, we are currently using polyhexanide regularly as an irrigation solution in our streaming NPWT regimen.

**PHASE 2: PROMOTION OF GRANULATION TISSUE**

After appropriate tissue debridement and wound bed preparation, the next step along the wound healing continuum is the effective promotion of granulation tissue [3]. Current methods include NPWT, NPWT with instillation of therapeutic fluids, PDGF and matrix metalloproteinase (MMP) inhibition using collagen-based dressings.

**Negative pressure wound therapy (NPWT)**

Numerous studies [15-18] have shown that controlled negative pressure may assist wound healing by providing a moist protected environment, reducing peripheral oedema around the wound, stimulating circulation to the wound bed, decreasing bacterial colonisation and increasing the rate of granulation tissue formation and epithelialisation [19-21]. One NPWT device (V.A.C.® Therapy, KCI) uses a sub-atmospheric pressure (100-125 mmHg) and medical-grade, open cell polyurethane ether foam dressing to convert an open wound to a controlled closed wound and to stimulate granulation tissue formation [3].

We have some concerns about increased bacterial colonisation and have followed other clinical
researchers in suggesting that NPWT could potentially be used in conjunction with an instillation of a chemotherapeutic agent (for example 0.025% Dakin’s solution) [22].

There are 15 FDA-approved NPWT devices in the US; however, only the Svedman® and Sved® wound treatment systems (Innovative Therapies) and the V.A.C.® Instill device (KCI) offer the option of fluid instillation in combination with NPWT. The V.A.C.® Instill device provides intermittent periods of instillation and continuous or intermittent suction. This involves cyclical instillation, a hold period and drainage of therapeutic fluids; however, this technique may be associated with an increased risk of wound maceration and the loss of dressing seals. The use of streaming Dakin's solution appears to resolve many of these problems [22] as this may help to reduce bacterial colonisation and prevent the pores of the open-celled foam from clogging with debris.

The Svedman® and Sved® wound treatment systems provide continuous streaming of instillation fluids. Currently normal saline is the only approved fluid for use in these systems. Unlike the V.A.C.® Therapy system, the use of a hold period is discouraged. Recent trials conducted by Giovinco et al favour modifying the V.A.C.® Therapy system to stream full-time or using the standard stream therapy incorporated into the Sved® device [22]. Clinical trials are being conducted to test the use of instillation fluids such as polyhexanide, 0.025% Dakin's solution, insulin and phenytoin (Dilantin, Pfizer). At the University of Arizona we are also using doxycyline in the Sved® continuous streaming NPWT device.

Instillation of fluids can also be completed through the use of a temporary/intermittent device in a three-hour treatment period. One of these is the Dermastream® device (Enzysurge Ltd). This is currently being tested with normal saline, but has the potential to be used with solutions such as polyhexanide, 0.025% Dakin's solution, insulin and phenytoin.

Simplified negative pressure therapy (sNPWT) (SNaP™ Wound Care System, Spiracur) is a self-contained vacuum system that is powered by a cartridge to deliver a continuous negative pressure at 75mmHg, 100mmHg and 125mmHg. This device is now being evaluated in clinical trials.

We have used all of the above NPWT modalities in our clinic and are currently awaiting results from clinical trials to confirm or refute their efficacy.

Wounds International, Vol 1; Issue 2 › Practice › Innovations in diabetic foot care: Using a wound healing timeline for advanced therapies

Cellular modulation

Studies have demonstrated that the use of platelet rich plasma (PRP) and PDGF, when combined with a comprehensive local wound care protocol, results in a significant increase in the limb salvage rate
amputation prevention) among high-risk diabetic patients [23,24] as well as reduced total treatment costs [25]. PDGF is a key growth factor in wound healing [26] and is the only growth factor approved by the FDA for clinical use. A phase III multicentre trial demonstrated a 10% increase in the complete healing rate of diabetic wounds [27,28]. Topical application of platelet-derived wound healing factors has also been shown to stimulate repair of chronic non-healing wounds, resulting in accelerated granulation tissue formation and epithelialisation [29,30].

While advanced wound healing modalities such as exogenous growth factors and PRP have great potential in the treatment of chronic wounds, the very nature of the chronic wound environment may impede the activity of these treatments. Therefore, inhibiting excessive protease activity [31] in these wounds may allow a prospective wound healing treatment, whether it is a single growth factor or an entire bioengineered matrix, to reach its full therapeutic potential.

It has been reported consistently that chronic wounds demonstrate an increased level of MMPs. Wound healing requires a balance between the accumulation of collagenous and non-collagenous extracellular matrix (ECM) components and their remodelling by MMPs and the tissue inhibitors of TIMPs. New treatment strategies for healing chronic diabetic foot ulcers could be directed towards reducing the concentration of MMPs and increasing levels of TIMPs [32]. Currently there are two products that are under clinical investigation for use in wounds:

- Hyroxic acid containing microspheres, which may provide localised MMP inhibition in a number of disease conditions, while avoiding systemic complications [33,34]
- Anticoagulant activated protein C, which may be useful in the treatment of non-healing wounds by preventing excessive protease activity through inhibition of inflammation and selectively increasing MMP-2 activity to enhance angiogenesis and re-epithelialisation [35].

Electrically active wound dressings

Procellera (Vomaris) with Prosit™ technology is a single layer sterile dressing that is activated by wound exudate or sterile saline to generate a sustained electrical current. Both gram-negative and gram-positive bacteria are attracted to the positive charge generated from the silver in the dressing, which also serves as an antiviral and antifungal. A phase II clinical trial comparing the efficacy of Procellera with Mepilex Border Lite (Mölnlycke Health Care) in partial-thickness wounds caused by curettage and electrodessication of skin lesions was completed in 2008 (for clinical outcomes see http://clinicaltrials.gov/ct2/show/NCT00816101). Procellera has been approved by the FDA for use in light to moderately exuding, partial and full thickness wounds.

Wounds International, Vol 1; Issue 2 › Practice › Innovations in diabetic foot care: Using a wound healing timeline for advanced therapies
PHASE III: WOUND CLOSURE

The final step in the wound healing continuum is wound closure. It is essential to provide rapid wound closure to reduce the risk of critical bacterial colonisation and to enable the patient to return to normal activities [3]. Wounds can be left to heal passively by secondary intention or through more aggressive measures, such as split-thickness skin grafts or local and free flap techniques.

Secondary intention

NPWT can be used as a bolster dressing when applied at a continuous negative pressure of 125mmHg for approximately 3-5 days post-grafting. This can reduce the risk of haematoma or seroma formation and limit the shearing forces at the graft-wound bed interface [36]. However, a non-adherent dressing must be used between the foam dressing and the graft to prevent trauma to the wound [3].

Micrografting

Micrografting is a new method of autologous skin grafting that can be used in patients with an ABPI of greater than 0.6 and full-thickness wounds that are free of necrotic tissue and not infected. This involves a novel procedure using standardised disposable instruments provided in a kit (hand-held dermatome and non-powered hand-held mincer) for a controlled harvest (up to 0.32mm thick 4cm²). The small specimen of full-thickness skin is then minced and spread on the wound. This process allows for a wider coverage than that provided by the single skin sample. The procedure can be completed in approximately 20 minutes and performed in an outpatient setting [37-39]. At the University of Arizona, we are currently testing micrografting in patients with diabetic foot ulcers.

Bioengineered alternative tissues

Bioengineered alternative tissues (BATs) have increased the clinician's ability to provide soft tissue closure of lower extremity ulcers [40,41]. Fitzgerald et al recently described new terminology for classifying bioengineered tissues, by dividing them into dermoinductive and dermoconductive BATs [42]. These products use living tissue to promote rapid wound healing by stimulating the native tissue to become more active, but do not 'engraft' in the conventional sense. However, they do provide some protection against bacterial inoculation [3].