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ORIGINAL ARTICLE

Wound bed preparation: TIME for an update

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Abstract

While the overwhelming majority of wounds heal rapidly, a significant proportion fail to progress through the wound-healing process. These resultant chronic wounds cause considerable morbidity and are costly to treat. Wound bed preparation, summarised by the TIME (Tissue, Inflammation/infection, Moisture imbalance, Epithelial edge advancement) concept, is a systematic approach for assessing chronic wounds. Each of these components needs to be addressed and optimised to improve the chances of successful wound closure. We present an up-to-date literature review of the most important recent aspects of wound bed preparation. While there are many novel therapies that are available to the treating clinician, often, there are limited data on which to assess their clinical value, and a lack of appreciation for adequate wound bed preparation needed before expensive therapy is used to heal a wound.

Introduction

The vast majority of wounds progress through the normal process of wound healing (haemostasis, inflammation, proliferation, maturation) uninhibited. However, a significant minority fail to progress through these steps, resulting in a chronic wound with associated morbidity and cost. Wound bed preparation is defined as the management of a wound in order to promote natural healing or to facilitate alternative methods to achieve healing, such as skin grafting, dermal matrices or other skin coverage products. It is of particular value in systematically assessing chronic wounds to promote the chance of healing.

Schultz *et al.* (1) first published the concept of wound bed preparation in 2003, which is a structured framework for use in the management of wounds. The TIME (Tissue, Inflammation/infection, Moisture imbalance, Epithelial edge advancement) acronym, published the following year (2), describes four aspects of wound bed preparation that need to be systematically addressed in order for wound healing to take place. This acronym has since been widely accepted in clinical practice in both the assessment and management of chronic wounds. The value of timely and meaningful intervention of a chronic wound is being increasingly recognised as the chance of achieving successful wound closure decreases the longer the wound has been present (3).

Key Messages

- wound bed preparation is the management of a wound to promote healing or to facilitate alternative methods to achieve healing; the TIME concept (Tissue, Inflammation/infection, Moisture imbalance, Epithelial edge advancement) describes various wound bed aspects to be systematically addressed to promote wound healing
- wound bed debridement removes necrotic tissue, allows inspection of underlying tissue, eliminates dead space, drains pus and optimises topical preparations to stimulate healing; selection of the debridement technique should include consideration of patient factors, wound appearance, environmental factors and practitioner competence; many chronic wounds fail to progress in healing because of imbalances of inflammatory cells, cytokines, growth factors and/or proteases, such as matrix metalloproteinases, or because of the presence of biofilm
- chronic wound exudate levels and composition are important; excessive exudate can cause maceration and promote biofilm formation; low levels may promote eschar formation and inhibit cellular activities; chronic wound fluid has also been shown to inhibit the growth of fibroblasts and has increased levels of pro-inflammatory cytokines, free oxygen radicals and proteases

- wound edge assessment can give an indication of the progress of wound contraction and epithelialisation and confirm if current wound treatment is effective; consideration should be given for corrective therapies to achieve advancement of epidermal margins

The TIME concept (Figure 1) consists of:

- Tissue

This involves assessing for the presence of non-viable or necrotic tissue; callus, foreign bodies; and exudate, biofilm or slough. Intervention consists of debridement, for which there is a wide range of techniques available; wound cleansing; and negative pressure wound therapy (NPWT).

- Infection/inflammation

This involves assessing the aetiology of the wound and treating infection or inflammation unrelated to infection. Intervention includes topical antimicrobials and systemic antibiotics.

- Moisture imbalance

This involves the assessment and management of wound fluid/exudate.

- Epithelial edge advancement

This involves the assessment and management of non-advancing or undermining wound edges and the condition of the surrounding skin.

It is imperative that the TIME concept be considered part of a comprehensive approach to each patient. This includes assessment of underlying pathology, patient comorbidities and the health care delivery setting.

Over the last 13 years, numerous novel wound care diagnostics, developments and therapies have been developed. This review paper will provide an up-to-date summary of the key research findings relating to wound bed preparation and the TIME approach to chronic wounds.

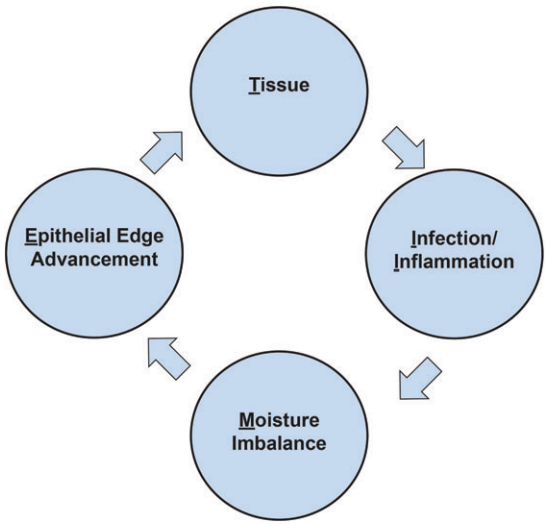

Figure 1 The TIME concept.

Tissue

Chronic wounds often result in the build up of necrotic tissues, which require treatment to facilitate healing. The purpose of wound bed debridement is the removal of necrotic tissue, reduction of pressure, inspection of underlying tissue, elimination of dead space harbouring bacteria, drainage of pus and optimisation for topical preparations in an attempt to stimulate healing. Debridement has long been recognised as necessary for the management of chronic wounds (4) and consists of a range of methods, including surgical (or sharp), autolytic, chemical, larval, mechanical, hydrosurgery and ultrasonic methods, or a combination of these (Table 1). Surgical debridement is traditionally perceived to represent the gold standard form of debridement; however, no form of debridement has been proven superior over another, and there are insufficient data from randomised controlled trials (RCTs) in surgical wounds, venous leg ulcers and diabetic foot ulcers on which to base current practice (5–7). When deciding on the appropriate debridement technique, consideration needs to be given to patient factors, wound appearance, environmental factors and practitioner competence.

Wound cleansing is defined as the removal of surface contaminants, bacteria and remnants of previous dressings from the wound surface and its surrounding skin (8). There are various wound-cleansing solutions in clinical use – potable tap water, sterile water, sterile normal saline and antiseptics solutions such as polyhexanide with betaine (PHMB), povidone-iodine and octenidine with ethylhexyl glycerine. International consensus recommends that infected chronic wounds require cleansing on each dressing change (9). Results from a single-blind RCT supported the use of propylbetaine-polihexanide solution when compared to normal saline to accelerate the healing of vascular leg ulcers and pressure ulcers (10). However, a Cochrane review found that there is no strong evidence that wound cleansing either speeds healing or decreases infection risk (11).

NPWT is a widely used technology that is predominantly utilised as an adjunct therapy to standard wound care. NPWT involves the application of a wound dressing through which a negative pressure is applied. NPWT is thought to work through numerous actions: removing wound exudate and infectious materials, reducing oedema, promoting granulation tissue formation and perfusion, and drawing the wound edges together (12–14). However, NPWT may be unacceptable to patients (because of pump noise and lack of portability) and can be associated with high costs. Despite the wide use of NPWT, there is currently limited evidence to support its use, and the efficacy and cost-effectiveness has yet to be established in a range of wounds (15–17).

Infection/inflammation

Many chronic wounds fail to progress past the 'Inflammation' stage of wound healing because of imbalances of inflammatory cells, cytokines, growth factors and/or proteases, such as matrix metalloproteinases (MMPs) (19–21). Specialised

Table 1 Descriptions of debridement techniques

Debridement method	Description
Surgical (or sharp)	An invasive method using either a curette or scalpel, which involves the removal of callus, non-viable tissue, biofilm, slough and/or foreign bodies as well as debridement of the wound edges and base down to healthy bleeding tissue. Traditionally, surgical debridement is regarded as the gold standard form of debridement; however, it requires a competent practitioner to perform it and appropriate local anaesthesia and carries a risk of bleeding or tissue damage. Caution should be exercised in patients on anticoagulants or who are immunosuppressed (60).
Autolytic	A method using moisturisation to allow degradation by phagocytic cells, softening of necrotic tissue and liquefaction of slough. It includes moist dressings such as hydrocolloid and alginate dressings, honey dressings, hydrogels and polyarylates (61–63). Wounds with high exudate output may not be suitable for this method.
Chemical	The use of antiseptics such as silver, povidone-iodine, chlorhexidine, PHMB or octenidine can achieve debridement (64). Hydrogen peroxide or sodium hydrochlorite have a limited role because of the toxic effects and pain experienced with their use.
Larval	Larval therapy is a form of atraumatic selective removal of moist slough using larvae from the green bottle fly (*Lucilia sericata or Lucilia cuprina*); they can ingest pathogenic organisms but cannot remove callus (65).
Mechanical	Traditionally, mechanical debridement used wet to dry gauze that adhered to the top layer of the wound bed on drying, with debridement taking place on removal of the dressing. Debridement or monofilament pads have become popular in clinical use, which comprise a fleece-like contact layer, which is used to remove debris, slough, exudate and necrotic tissue (66,67).
Hydrosurgery	Hydrosurgery consists of wound lavage through a pressurised hand piece (68,69) or whirlpool (70). It is relatively painless and has been shown to reduce bioburden (71).
Ultrasonic	Low-frequency, low-dose ultrasonic-assisted debridement can be undertaken with either contact (72) or non-contact (73) devices. Contact devices work by cavitation and acoustic streaming, which directly agitates the wound bed. Non-contact devices work in conjunction with atomised saline. They are relatively painless, but the equipment can be expensive and not often readily available.

microscopic techniques have shown that 60–90% of chronic wounds have wound biofilm present (22,23). A biofilm is defined as 'a structured consortium of microbial cells surrounded by a self-produced polymer matrix' (24). In addition to microorganisms, components such as fibrin, platelets or immunoglobulins may be integrated into the biofilm matrix. Biofilms are characterised by persisting and progressive pathology, primarily because of the inflammatory response surrounding the biofilm (25). Identifying the presence of a biofilm can be difficult as it is not always detected with the naked eye. A tissue biopsy may reveal a biofilm, but searching for biofilms in tissue biopsies from clinical samples can be time-consuming and may result in false negative results (25). Currently, the only definitive method of identifying a biofilm involves advanced microscopy or specialised culture techniques (26). However, certain clinical indicators should raise suspicion to the presence of a biofilm (26):

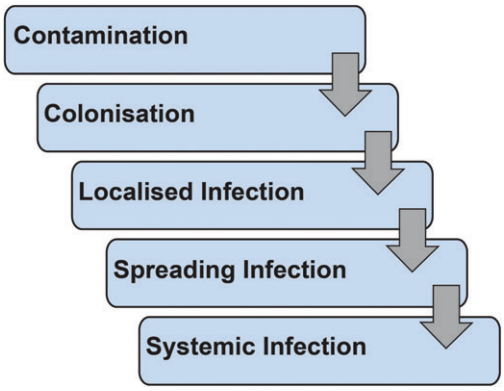

Figure 2 Wound infection spectrum.

- Antibiotic failure
- Infection of >30 days duration
- Friable granulation tissue
- A gelatinous material easily removed from wound surface that quickly rebuilds

Strategies for treating biofilm include debridement and cleansing to physically disrupt and remove the biofilm and topical antimicrobials to kill planktonic microorganisms and prevent further wound contamination.

Wound infection refers to a spectrum of microbial burden ranging from simple colonisation to systemic infection (Figure 2) (27). The investigation and management required is dependent on the degree of wound infection. As a result of poor biofilm penetration, altered tissue perfusion in the base of chronic wounds and risk of antibiotic resistance, systemic antibiotic treatment is not advocated for localised infection. In most cases of local infection wound cleansing, debridement and topical antimicrobials will treat the bioburden sufficiently (Table 2). There is little evidence to suggest that one antimicrobial is superior to another; however, some may be more acceptable to patients (28–31). If there are signs of systemic infection, spreading cellulitis or lymphangitis, then these treatments should be combined with oral or intravenous antibiotic therapy. Antibiotic therapy should be prescribed according to local microbiology guidelines and should be based on any available sensitivities from wound cultures. It is important for the assessing clinician to exercise caution in immunosuppressed or comorbid patients as they may not exhibit classic signs or symptoms of local or systemic infection.

Moisture imbalance

Exudate is an essential component of wound healing, necessary in activating the complement system (a sequence of proteins

Table 2 Topical antimicrobials in clinical use for chronic wounds

Topical antimicrobial	Delivery
Potassium permanganate	Soaks
Acetic acid	Soaks
Polyhexamethylene biguanide (PHMB)	Wound cleansing, gel or dressing
Chlorhexidine	Wound cleansing
Iodine (povidone-iodine or cadexomer iodine)	Dressing or ointment
Octenidine	Wound cleansing
Medicinal grade honey	Dressing
Silver	Dressing or ointment
Dialkylcarbamoyl chloride (DACC)	Dressing

in serum and extracellular fluid that destroys pathogens) and aiding autolytic debridement (32). However, in chronic wounds with either excessive or insufficient exudate production, wound-healing processes may be inhibited. Excessive levels of exudate can cause damage to the surrounding skin (maceration) and is also thought to promote biofilm formation as a potential nutrient source (33), whereas low levels of exudate promotes eschar formation and inhibits cellular activities. However, it is not just the volume of exudate that is important as there is evidence that chronic wound fluid composition is as important as exudate amount. In comparison to acute wound fluid, chronic wound fluid has been shown to inhibit the growth of fibroblasts (required for the deposition and organisation of collagen) (34) and has increased levels of pro-inflammatory cytokines, free oxygen radicals and proteases (prolonging the inflammatory stage of wound healing) (35).

Dressing choice is important in managing exudate levels and should provide appropriate moisture balance, avoid maceration of the skin edges, prevent leakage and be easy to apply and remove. Protease-modulating dressings may be appropriate to control wound proteases found in highly exuding wounds, which subsequently denature growth factors and the extracellular matrix (36). The development of these dressings has focused on reducing levels of MMPs by absorbing wound exudate and holding proteases within the dressing structure and inactivating the excess MMPs (20). There is evidence that collagen/oxidised protease-modulating dressings may increase healing rates in diabetic foot ulcers (37). Dressing with super-absorbent properties and skin barrier creams may be necessary to avoid peri-wound maceration. NPWT has also been advocated for exudate control because of the action of physically removing fluid from the wound bed, as discussed earlier in this paper.

There may be other factors to consider in a patient with high levels of exudate, including medical comorbidities such as congestive cardiac failure, hepatic failure, renal failure and malnourishment. Where these medical comorbidities are suspected, referral should be made to an appropriate practitioner. Failure of the lymphatic system or underlying venous disease may also be a contributory factor, and treatment should be aimed at the removal of the oedema through compression therapy (38). Compression therapy should always be performed by a competent practitioner following a satisfactory vascular examination. For patients with lymphoedema, referral to a lymphoedema team for specialist compression therapies may be useful.

Epithelial edge advancement

Wound edge assessment can indicate the progress of wound contraction and epithelialisation and confirm if current wound treatment is effective. A 20–40% reduction in wound area after 2 and 4 weeks of treatment has been shown to be a reliable predictor of healing (39). It is also important to assess the condition of the surrounding skin as dry or macerated edges can hinder healing. Consideration should be given for corrective therapies, such as debridement, skin grafting, acellular dermal matrices and adjunctive therapies, to achieve advancement of epidermal margins. There have been recent developments in edge advancement therapies, which will be discussed below.

- Acellular dermal matrices are tissue-engineered products advocated for wound healing that are devoid of living cells and biologically inert. They can be derived from a range of products, including animal or human tissue, synthetic or a composite product. Their mode of action is by either replicating the extracellular matrix or by acting as a temporary skin substitute. Recent systematic reviews have concluded that while data are limited, there is some evidence to support their use in chronic wounds of the extremities (40,41).
- Epidermal cell harvesting has been advocated as a novel therapy as a substitute for skin grafting, which may be better tolerated in comorbid or elderly patients as it potentially has less morbidity (42,43). However, to date, there is limited evidence to support its use.
- Electromagnetic therapy provides a continuous or pulsed electromagnetic field, which is thought to induce cell proliferation; however, there is currently a lack of evidence to support its benefit in venous leg ulcers or pressure ulcers (44,45).
- Low-level gas laser therapy (helium neon or gallium arsenide) has been used to increase cellular proliferation and migration. There is limited evidence to support its use currently (46).
- Phototherapy is a relatively new, non-invasive and pain-free treatment that has received clearance from the United States Food and Drug Administration for its beneficial effects on tissue healing and has been proposed as a therapy for wound healing. However, there is no evidence to support its benefit and safety (47).
- Ultrasonic therapy delivers mechanical energy, hypothesised to stimulate cellular activity within the wound bed. There is limited evidence to support its use in venous leg ulcers; however, the authors concluded that further larger-scale trials are required (48). There was no evidence of benefit when used on pressure ulcers (49).
- Hyperbaric oxygen therapy (HBOT) is short-term, high-dose oxygen inhalation and diffusion, achieved by breathing concentrated oxygen at a pressure higher than at sea level in hyperbaric chambers (50). It has been suggested in the management of chronic wounds

in order to increase the supply of oxygen to the wound. However, HBOT has limited availability in many countries, requires frequent visits to the facility and often can not be tolerated in certain patient groups, such as the elderly. Two recent systematic reviews have concluded that it was not possible to establish the benefits of the treatment for diabetic foot ulcers, including the cost benefit (51,52).

- Topical oxygen has been hypothesised to help improve angiogenesis, reduce infection rates and increase wound-healing rates (53). An ongoing RCT is assessing its effect on healing rates for chronic diabetic foot ulcers (54).
- Growth factors are secreted by regulatory proteins, which effect cell survival, proliferation and differentiation. Recombinant human platelet-derived growth factor (Becaplermin) is the only growth factor product licensed for use in wound healing to date. Evidence from three RCTs in diabetic foot ulcers has confirmed that it is safe to use, superior to a placebo gel but inferior to an acellular dermal matrix (55–57).
- Stem cells have been theorised to help promote wound healing by migrating across the wound bed and secreting chemokines and growth factors to induce angiogenesis and extracellular matrix remodelling (58). However, further work is required to determine their use in human subjects.
- Autologous platelet-rich plasma gel consists of cytokines, growth factors and a fibrin scaffold derived from the patient's own blood. A recent systematic review showed some increase in the rate of wound healing compared to a placebo gel or standard care; however, the authors noted that the RCTs included were of low quality (59).
- NPWT has been advocated for wound edge advancement and has been described earlier in this paper.

Conclusion

Wound bed preparation is a widely utilised tool for assessing and treating chronic wounds. Its value lies in providing the treating clinician with a systematic approach to chronic wounds, which can ensure that logical treatments are given, and their responses are noted and acted upon. While there are many novel therapies that have become available over the past 13 years, to date, only a few have a significant evidence base on which practice can be based. Until such data emerges, it is likely that the vast majority of wounds are best managed with simple therapies combined with regular debridement. Well-conducted RCTs are required for both novel products and how to objectively measure adequacy/completeness of wound bed preparation.

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