Wound healing and TIME; new concepts and scientific applications

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Wound bed preparation is a comprehensive approach to wound management that focuses on optimizing conditions at the wound bed to encourage normal endogenous processes of healing. It is based on an understanding of the underlying molecular processes of the wound and is in a continuous state of evolution as it incorporates and responds to new information about and understanding of cellular mechanisms.

This article reviews recent thinking about the relevance of wound bed preparation to diabetic wounds and burns, presents adjustments to the tissue, infection/inflammation, moisture imbalance, epidermis/edge (TIME) paradigm of wound management to reflect greater understanding concerning migration of the epidermal edge, and provides an extension of the concept to include wound assessment. Finally, it asks whether TIME should now be put to the test. The field of wound management is lacking in robust data, but now that a more systematic approach to wound care exists, perhaps a more systematic approach to gathering the evidence should also be attempted.

NEW THINKING ABOUT TIME AND CHRONIC WOUND CARE

The TIME acronym, developed in June 2002 by a group of wound care experts, was first published in 2003.[1] It is a practical guide to wound management that relates clinical observations and interventions to the underlying wound pathology in each of four areas:

- T for tissue: nonviable or deficient
- I for infection/inflammation
- M for moisture imbalance
- E for epidermis, nonmigrating (later modified, see below).

However, the word "epidermis" implies that nonmigration is a problem of the epidermis. In fact, failure of the epidermis to migrate could also be due to a problem with the extracellular matrix (ECM) or cells at the wound edge, so this component was subsequently revised[2] to read:

- E for edge of wound, nonadvancing or undermined.

This is more than just semantics; successful wound healing is most likely to be achieved if the underlying cause of failure to heal is identified and treated (Table 1).

The traditional explanation for failure to migrate is that cells at the wound margin are unresponsive; some fibroblasts in chronic wounds display phenotypic dysregulation and are therefore unresponsive to certain growth factors and other signals,[3,4] possibly due to senescence.[5–8] In vitro studies on fibroblasts from venous ulcers[5–7] and diabetic wounds[9,10] also show that there is a decreased proliferative potential and that there are other markers of senescence, such as beta-galactosidase and increased expression of fibronectin. One explanation for the senescence is that, during repeated attempts at wound repair, these cells undergo numerous cycles of replication and exhaust their replicative potential. It may also be that senescent cells are not responsive to the normal apoptosis mechanisms and cannot be easily eliminated.

However, senescence of fibroblasts does not fit all the observations. Some chronic wounds display

ECM	Extracellular matrix
MMP	Matrix metalloproteinase
TIMP	Tissue inhibitor of metalloproteinase
RCT	Randomized clinical trials

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Table 1. Wound bed preparation according to TIME

Clinical Observations	Proposed Pathophysiology	WBP Clinical Actions	Effect of WBP Actions	Clinical Outcomes
Tissue: nonviable or deficient	Defective matrix and cell debris impair healing	Debridement (episodic or continuous) Autolytic, sharp surgical, enzymatic-mechanical or biological, biological agents	Restoration of wound base and functional ECM proteins	Viable wound base
Infection or inflammation	High bacterial counts or prolonged inflammation↑ inflammatory cytokines↑ protease activity ↓growth factor activity	Remove infected foci-topical/systemic antimicrobials antiinflammatories protease inhibition	Low bacterial counts or controlled inflammation:↓ inflammatory cytokines↓ protease activity ↑growth factor activity	Bacterial balance and reduced inflammation
Moisture imbalance	Desiccation slows epithelial cell migration. Excessive fluid causes maceration of wound margin	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: nonadvancing or undermined	Nonmigrating keratinocytes. Nonresponsive wound cells and abnormalities in ECM or abnormal protease activity	Reassess cause or consider corrective therapies-debridement, skin grafts, biological agents, adjunctive therapies	Migrating keratinocytes and responsive wound cells-Restoration of appropriate protease profile	Advancing edge of wound

hyperproliferation of cells at the margins, due possibly to inhibition of differentiation and apoptosis within the keratinocyte and fibroblast cell populations.[11] In one study, biopsies taken from the edge of chronic venous ulcers revealed that epidermal cells were in a heightened proliferative state with delayed keratinization, but the epidermal basement membrane lacked type IV basement membrane collagen, which is necessary for epithelial cell attachment and migration.[12]

Proteases and wound healing

Excessive degradation of newly formed ECM can also cause failure to migrate.[2]

At the edge of the wound, keratinocytes sense the ECM, proliferate, and begin to migrate from the basal membrane onto a newly formed provisional matrix. Collagenase (matrix metalloproteinase-1 [MMP-1]) is released from migrating keratinocytes to dissociate the cell from the dermal matrix and to allow locomotion over the provisional matrix.[13] Keratinocytes also synthesize and secrete MMP-2 and -9, particularly when migrating[14,15] and as part of the remodeling process.[16]

Proteolytic degradation of ECM is an essential part of wound repair and remodeling, but excessive levels of MMPs may degrade ECM, preventing cellular migration and attachment; Trengove et al.[17] and Ulrich et al.[18] showed that the activity of proteases decreases consistently in venous ulcers as they heal. Conversely, levels of tissue inhibitor of metalloproteinase (TIMP)-1 rise more than 10-fold as healing progresses.[19]

Evidence suggests that the temporal and spatial distribution of MMPs, serine proteases, and TIMPs is disrupted in nonhealing wounds.[13,20,21] Other studies show that levels of MMP-2 and MMP-9 are higher in chronic wound fluid than in surgical wound fluids or fluids from donor graft sites.[17,19,22–25] This suggests that regulating protease activity would restore an environment more conducive to normal healing.[26] This is the rationale behind the control of inflammation (I) as described in the TIME paradigm. Cytokines stimulate the production of MMPs and inhibit synthesis of TIMPs in fibroblasts and endothelial cells, increasing the ratio of proteases to inhibitors. Thorough debridement, topical antimicrobials, and dressings that reduce levels of MMPs at the wound bed are well-known interventions, but it is also possible that adjustment of wound pH may help to control protease activity.

The mechanism of action of proteases is pH-dependent; therefore pH is also likely to affect protease activity.[27] Every protease shows peak enzyme activity at a certain pH at which protein is broken down more rapidly than at other pH values. Recently, the pH-dependent activity profiles of four proteases important in wound healing were assessed using a standardized method.[28] It was found that maximum protease activity occurs in precisely the region of pH found in chronic

wounds.[29] Adjusting the pH from 8 to 4 reduced protease activity approximately 80 percent, suggesting that an additional approach to nonhealing wounds may be to reduce the environmental pH (Figure 1).

Increased understanding of the cellular factors that may delay healing confirm that it was correct to shift the emphasis in the TIME paradigm away from abnormalities in the epidermal edge. The revised TIME table now acknowledges that failure to migrate may equally well be due to corruption of the wound matrix or activity of proteases. As research into the microenvironment of wounds continues, further such modifications to the TIME table can be expected.

Cellular dysfunction in the diabetic patient

Diabetic patients often have coexisting peripheral vascular disease and polyneuropathy that impair wound healing, but there is increasing evidence to suggest that cellular abnormalities may also play a role.

The fibroblast is a crucial component in the processes of deposition of ECM and remodeling. It deposits a collagen-rich matrix and secretes growth factors during the repair process. Any impairment to fibroblast function will therefore obstruct normal wound healing. Hehenberger et al.[9] and Loots et al.[10] observed that the proliferation of fibroblasts from chronic diabetic wounds was inhibited or disturbed. Earlier, Spanheimer had observed reduced collagen production in fibroblasts from diabetic animals.[30] It has also been seen, in vitro, that diabetic fibroblasts are 75 percent less able to migrate than normal fibroblasts and that they produce 15% as much vascular endothelial growth factor (VEGF).[31]

As is the case with chronic wounds such as venous ulcers and pressure ulcers, levels of proteases are disrupted in diabetic ulcers. Lobmann et al. measured the concentrations of various MMPs and tissue inhibitors of matrix metalloproteinases in biopsy samples taken from diabetic foot ulcers and trauma wounds in nondiabetic patients.[32] The concentrations of MMPs were significantly higher in diabetic wounds than in traumatic wounds in nondiabetics: MMP-1 ($\times$ 65), MMP-2_{pro} ($\times$ 3), MMP-2_{active} ($\times$ 6), MMP-8 ($\times$ 2), and MMP-9 ($\times$ 14). At the same time, the expression of TIMP-2 in diabetic wounds was half that seen in nondiabetic lesions.

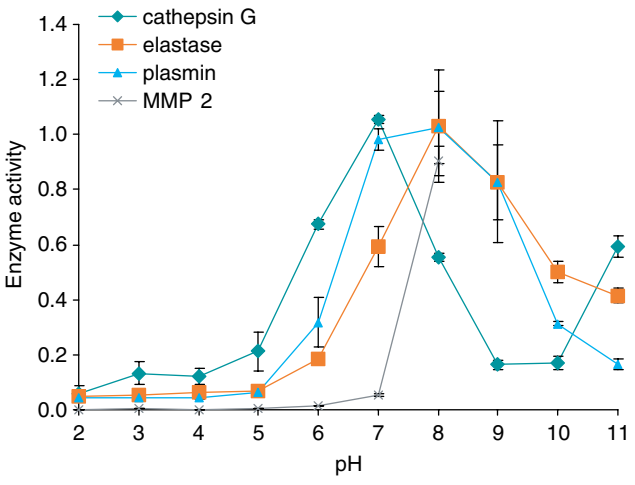

FIGURE 1. pH dependent enzyme activity levels of proteases found in wounds.

Loots et al. found differences in the pattern of deposition of ECM molecules and the cellular infiltrate in diabetic wounds from that in chronic venous ulcers and acute wounds.[33] ECM molecules, including fibronectin, chondroitin sulfate, and tenascin are expressed early in normal dermal wounds and reach a peak at 3 months before returning to prewounding levels; a prolonged presence of these molecules was noted in chronic wounds. The chronic wounds also had a higher level of cellular infiltrates such as macrophages, B cells, and plasma cells.

The standard therapy for diabetic wounds is meticulous wound care and revascularization, but in light of recent research, it may be reasonable to consider alternative strategies such as the use of protease inhibitors, adjustment of pH to reduce protease activity, and anti-inflammatory dressings or drugs.

Infection? Or inflammation?

It has often been assumed that excess proteolytic activity, characterized as inflammation, is secondary to an increased microbial burden in the wound, but the evidence from studies such as those described above and others suggests that elevated MMP levels can also occur in the absence of infection.[17,34]

In 2002, Wright et al. used a porcine model of wound healing to examine the effect of nanocrystalline silver–coated dressings on wound healing.[35] (Nanocrystalline silver is a patented technology of NUCRYST Pharmaceuticals.) Nanocrystalline silver–coated dressings promoted rapid wound healing during the first few days after injury, with the development of well-vascularized granulation tissue that was able to support tissue grafting after 4 days. This was in contrast to wounds dressed with control dressings. Of particular interest is the observation that the proteolytic environment of wounds dressed with nanocrystalline silver had lower levels of MMPs and a higher frequency of cellular apoptosis. When cells die by apoptosis, the integrity of the plasma membrane is maintained and the cells are recognized and phagocytosed by macrophages, minimizing local inflammation and tissue injury.[36] When cells, such as neutrophils, die by necrosis, they burst and release cytotoxic compounds that prolong the inflammatory process.

The wounds in the Wright study were not chronic, but a pilot study on 10 venous ulcer patients comparing nanocrystalline silver dressing with standard

polyethylene dressing in the chronic wound environment has been reported.[37] This randomized controlled trial assessed levels of MMP-2, MMP-9, interleukin-1, and TNF-a under the two dressings. Over a 20-day period, protease levels, in particular those of MMP-9, were substantially lower than those in the wounds covered with the nonsilver dressing (Figure 2).

Antimicrobial therapies, topical or systemic or in the form of dressings, have established roles in the management of infected wounds, but in many cases, a reduction in inflammatory activity may be all that is required to stimulate healing.

WOUND BED PREPARATION AND BURN CARE

Similar developments in the management of thermal injuries preceded many of the recent developments in chronic wound management. The TIME paradigm for management of chronic wounds parallels the standard elements of organized burn care (Table 2). Although robust data to support the basic principles of wound bed preparation for chronic wounds are hard to come by, there is a substantial body of data that supports the efficacy of similar interventions in the management of burns. Managed burn care improved survival of patients by adopting many of the practices that have subsequently been incorporated into chronic wound management.

Early excision of burn wounds

Dedicated burns centers emerged in the late 1940s and significantly improved patient care through better understanding of the effects of smoke inhalation and the role of nutrition and total patient care, but while management of the patient improved, management of the wound itself was unsystematic. Up to the 1970s, aggressive excision was practiced on deep burns, but partial thickness injuries were treated with antiseptic creams, and the burn eschar was kept moist through regular bathing until it sloughed off. As well as being extremely uncomfortable and painful to patients, this conservative approach increased infection and reduced the chances of graft-take and survival.

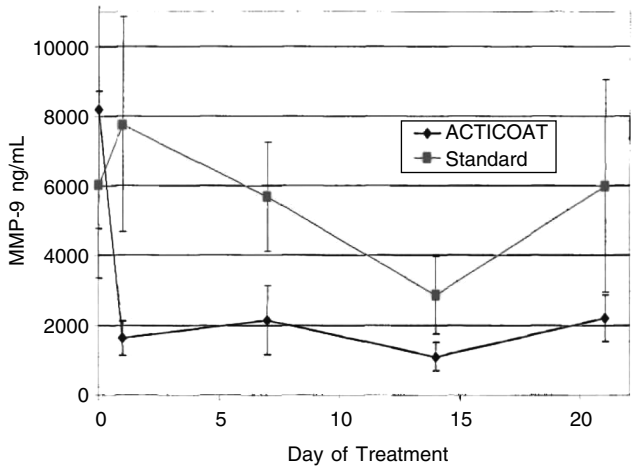

FIGURE 2. Levels of MMP-9 in wound fluids from patients with chronic venous leg ulcers treated with silver release dressing or standard care.

Table 2. Managed burn wound care and the TIME paradigm for chronic wound management

Burn wounds	TIME for chronic wounds
Early excision of nonviable tissue	T – tissue, nonviable
Microbial control	I – infection and inflammation
Control exudate/avoid desiccation	M – moisture balance
Advanced wound healing techniques	E – edge of wound

By the 1970s, although early excision of deep burns was widespread overall, no significant increases in survival were noted. In 1970, Janžekovic proposed that early excision should be performed on all burns, including partial thickness injuries, to remove nonviable tissue that would otherwise act as a focus for infection and impede reepithelialization of the burn wound.[38] She found that early excision of all wounds, within the first 3 to 5 days of injury, followed by grafting, reduced infection rates and improved survival better than conservative management using topical antimicrobials plus excision in the second or third week.

This study had a profound effect on burn care. Other clinicians went on to confirm the benefits of early excision,[39–42] although there is some doubt about the benefits of this approach in the very elderly.[43] Caldwell et al. suggested that early harvesting of donor sites might be a more important factor in survival of patients with large burns; they question the value of massive early burn wound excision if there is insufficient autograft available to close the wounds.[44]

Of perhaps more importance for the hospital administrators was that early excision and grafting also appeared to decrease the duration of hospitalization[40,41] and the cost of burn treatment.[45]

Although there have been few prospective studies into the relative merits of early excision versus conservative management of burns, thousands of patients have been reviewed in retrospective studies, which has clearly shown the benefits of this approach. It is interesting to question why there are so few similar studies comparing debridement with no debridement in the management of chronic wounds.

Management of infection

Burn wounds and donor sites are highly susceptible to opportunistic colonization by endogenous and exogenous organisms. Early excision of wounds, along with improvements in fluid resuscitation and general medical care, significantly reduced the incidence of infections after thermal injury.[40,46] The pattern of infection also changed,

with alteration in the organisms that are mainly responsible for infection and an increase in the interval between injury and infection.[47] Barret and Herndon carried out quantitative bacteriological assessments of excised wound and biopsy samples taken from wounds that were managed with excision 24 hours after burning and those that received topical treatment and delayed excision.[48] Patients who received early excision had fewer than 10^5 bacteria per gram of tissue in biopsy samples, compared with more than 10^5 in the other group of patients. Patients in the first group suffered no infection or graft loss, compared with three in those receiving delayed excision. The pattern of colonization differed between the two groups, with the conservatively managed group displaying a greater concentration of Gram-negative species. Overall, greater bacterial colonization and higher rates of infection were correlated with topical treatment and late excision.

Infections by *Pseudomonas aeruginosa* have been the leading cause of morbidity and mortality in burn patients for many years and the most serious cause of burn wound sepsis.[49] These organisms rapidly develop resistance to many antimicrobial agents, limiting the utility of these therapies. Burn physicians readily embraced silver nitrate and silver sulfadiazine preparations to help control burn wound infections and found them to be effective broad spectrum agents, but not without their drawbacks. Lloyd and Hight questioned whether silver sulfadiazine—a commonly used antimicrobial in burn care—could penetrate burn eschar sufficiently to prevent infection and suggested that it could only be effective when preceded by extensive laminar excision.[50] Enterobacter resistance has been reported with this agent, as has cytotoxicity. It also forms a pseudo-eschar, which has to be removed before reapplication, which may damage new epithelial growth.[51] Silver nitrate solution is messy to apply, can irritate tissues, and, like silver sulfadiazine, requires frequent application.

In recent years, a number of silver dressings have been developed that are intended to provide silver more consistently, be easier for the burn care physician, and become more acceptable to the patient. Six silver-containing dressings with varying degrees of absorbency are currently available:

- ACTICOAT (Smith & Nephew) consists of a rayon/polyester nonwoven core laminated between an upper and lower layer of silver-coated high-density polyethylene (HDPE) mesh. The silver-coated HDPE layers are designed to be barriers against microbial infection of a wound.
- ActisorbSilver 220 (Johnson & Johnson) consists of an outer sleeve of nonwoven nylon and an inner layer of activated charcoal–containing silver particles which adsorb bacteria.
- Aquacel Hydrofiber Dressing (Convatec) contains ionic silver within a carboxymethylcellulose fiber matrix that gels on contact with wound fluid.
- Arglaes (Maersk) is a semipermeable film dressing that incorporates a complex of calcium and sodium phosphates.
- Avance (SSL International) is an absorbent hydropolymer foam dressing with silver zirconium phosphate bonded into it.
- Contreet-H (Coloplast) is a hydrocolloid containing ionic silver.

One of the main advantages of these dressings is that they overcome the need for regular reapplication by providing a reservoir of silver within the dressing. Other proteins in the wound bind the silver in silver nitrate and silver sulfadiazine, which may only be active for a few minutes. The various silver dressings available have different levels of absorbency and are therefore suitable for different types of wounds.

One of the main perceived advantages of using antiseptics rather than antibiotics is that they were thought to be less likely to result in the emergence of resistant species. Silver exerts its antimicrobial effect through many mechanisms, making it difficult for organisms to develop resistance. It interferes with the respiratory chain at the cytochromes and with components of the microbial electron transport system.[52] It binds DNA and inhibits DNA replication.[53–55] However, resistance by bacteria to silver—although rare—is not unknown. There were reports throughout the 1970s and 1980s about resistant strains of Pseudomonas and Enterobacter emerging on treatment with silver nitrate and silver sulfadiazine.[56–59]

Microbes can bind silver in the form of an intracellular complex and can excrete silver using an active efflux mechanism.[60] Resistance remains an important problem, even with some of the newer silver dressings.

The ACTICOAT dressings are the only dressings to use nanocrystalline silver. This readily dissolves in water, unlike crystalline silver, and exists in solution in two forms: Ag^+ and Ag°. The Ag° form of silver is far less rapidly deactivated by chloride or organic matter than the ionic form and can therefore be effective at much lower concentrations. In 1999, Wright et al. assessed the kill kinetics in vitro of mafenide acetate, silver nitrate, silver sulfadiazine, and nanocrystalline silver dressing against common burn wound fungal pathogens.[49] The nanocrystalline silver–based dressing had the fastest and broadest-spectrum fungicidal activity.

Silver binds in a nonspecific fashion to proteins, so it can potentially be toxic to all cells, whatever the method of delivery. If bacterial numbers are low, silver may affect other cells, and healing may be delayed,[61] suggesting that silver should be used with caution in wounds with a low bio-burden.[62]

Moisture control

Occlusive dressings have long been used in the management of burns and donor sites to create optimal conditions for reepithelialization and to act as barriers to limit

infection. Several studies have shown that a moist environment encourages epithelialization of partial-thickness wounds and that this can be achieved with semiocclusive[63] or fully occlusive, impermeable dressings.[64,65] Fear of bacterial proliferation under occlusive dressings was initially a reason for caution in burns units, as it sometimes still is in chronic wound management, but clinical infection has rarely been noted.

A large body of evidence has been gathered in the field of burn care regarding the use of occlusive dressings compared with traditional gauze. Most of the studies investigated different dressing types on donor sites rather than on actual burns, allowing comparative studies to be made on mirror-image donor sites of the same depth in the same person. In addition to reducing pain and providing a barrier to bacterial invasion, occlusive dressings have been found to improve wound epithelialization through maintaining the wound at an optimal moisture level (see for example Madden et al.[66]).

TIME AND WOUND ASSESSMENT

Routine wound assessment is a critical part of reaching a diagnosis and monitoring the effect of treatment, and in some cases it can be used to predict the outcome of treatment. The initial wound assessment provides baseline data against which future observations can be measured, but meaningful comparisons can only be made if a standardized assessment system is used.

Wound assessment provides more than just a retrospective view of the effect of a particular intervention; in some cases, the rate of healing in the early stages provides an indication of the likelihood of total healing. This has been found to be the case for diabetic foot ulcers[67] and venous ulcers,[68] for which the rate of healing in the first 4 weeks was strongly correlated with healing at 12 or 24 weeks. Routine wound assessment in these patients in the first 4 weeks will allow early identification of individuals who are unlikely to respond to the therapy being applied. However, this has traditionally been a difficult area in wound management because terminology is not standardized and consensus has not even been reached on the most appropriate wound healing parameters to monitor.[69] Numerous tools are available for the evaluation of pressure ulcers, and it is hard to see how these can be accommodated into one universal system.[2,69,70]

Although rigorous assessment is common in the clinical trial setting, the challenge is to find an assessment tool that can easily be used at the bedside and that does not require expensive or complicated equipment. What are the parameters that give useful information about a wound, and is it possible to identify a core set of observations that can be used to monitor the overall progress of a wound? The following assessments are the ones that are most commonly used, in existing assessment protocols or in clinical trials. Many excellent papers have been published on the methods available for making these assessments, so this information will not be duplicated here, but the references provide further information for the reader interested in pursuing these topics.

AREA, DEPTH, AND VOLUME

As the wound heals, in-growth of granulation tissue decreases the wound depth and volume, and new epithelium decreases wound area. Measurements of wound size therefore provide direct indicators of healing, but there has usually been a trade-off of accuracy for simplicity. The simplest method is to make a rough calculation of area based on measurements of maximum length and width, but this is difficult to apply to large and irregular-shaped wounds, whose area can be overestimated by 44 percent, while the use of an elliptical formula to calculate area tends to overestimate by 13 percent (Figure 3).[71] Digital photography and computer-assisted techniques provide greater accuracy but are not widely available and can rarely be used at the bedside. A new tracing tool by Smith & Nephew may fill the gap; the VISITRAK system calculates the area captured on transparent tracing sheets, providing area calculations with approximately 94 percent accuracy (Figure 4). Probes, molds, and scanning systems can be used to estimate wound depth.

COLOR

Color is a simple but powerful indicator of the status of a wound. Considerable variation in color definition exists, but black (necrotic tissue), yellow (slough), red

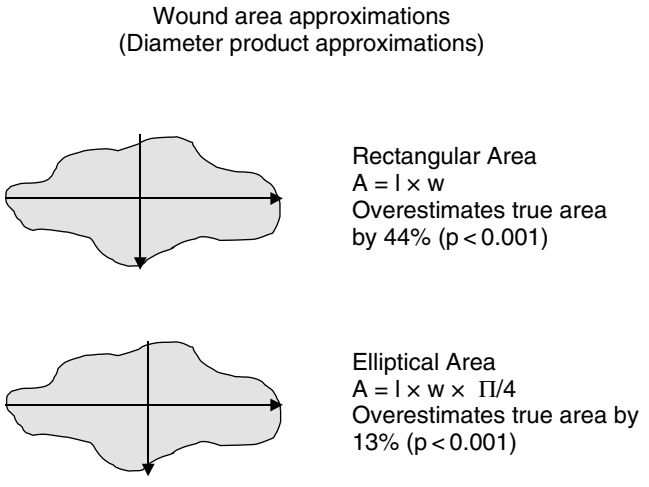

FIGURE 3. Schematic diagram showing length x width wound calculations, rectangular and elliptical.

FIGURE 4. Photograph of the VISITRAK system for wound area calculation.

(possible infection), pink, and white are the most common colors seen in the wound bed. Many wounds show a combination of colors as different parts of the wound heal at different rates, and a semiquantitative assessment should be made to improve accuracy. The color of the surrounding skin is also an important indicator of the level of hydration at the wound: overmoist, macerated skin at the wound edge will be an unnatural gray/white, and normal color will return as the skin dries out.

pH

There is now clear evidence of an association between decreasing wound surface pH and wound healing. The pH of intact skin is weakly acidic due to the keratin layer, which prevents bacterial growth and inhibits the activity of digestive enzymes. Open wounds tend to have a neutral or alkaline pH, predominantly in the range 6.5 to 8.5.[29] Tsukada et al. demonstrated that the pH of chronic ulcers reflected the stage of the ulcer; the more advanced the stage, the higher the wound pH. Although the pH of nonepithelialized wounds was similar to that of Stage III pressure ulcers (pH 7.5), the pH of newly formed epithelium at wound edges was similar to that of normal skin (around pH 5.9).[72]

Developing a wound assessment tool

TIME is now a widely used concept in wound management, providing a practical and systematic guide to bedside care. The wound care practitioner proceeds stepwise through a simple series of interventions, which form an iterative process, until healing is achieved or the lack of response indicates that other methods are required. Given that the TIME approach is becoming more widely adopted in practical wound management, it seemed sensible to develop a wound assessment system that would correspond exactly with the steps in the TIME process. Thus, as well as breaking down wound management into the four

Table 3. TIME wound assessment tool (M. Romanelli)

Clinical observations	Proposed pathophysiology	Wound bed preparation noninvasive measurement	Effect of wound bed preparation on measurements	Clinical outcome
Tissue	Defective matrix and cell debris impair healing	Debridement assessment: - color assessment - tissue perfusion TcP02, colour Doppler, angiography	- promotion of granulation tissue - improved wound bed vascularity	Viable wound tissue
Infection	High bacterial counts or prolonged inflammation: ↑Inflammatory cytokines ↑Protease activity ↓Growth factor activity	Wound bed and surrounding skin: - temperature - odor - color - pH	- controlled temperature - reduced odor - vital color - acidic pH	Bacterial balance and reduced inflammation
Moisture	Excessive fluid causes maceration of wound margin. Desiccation slows epithelial cell migration.	Leg volume Color of surrounding skin Surrounding skin transepidermal water loss (TEWL)	- reduced leg volume - natural skin tones regained - reduced TEWL	Moisture balance
Edge	Nonmigrating keratinocytes. Nonresponsive wound cells and abnormalities in extracellular matrix or abnormal protease activity.	2D evaluation: - acetate tracing - digital photography - digital tools and PC software 3D evaluation - probes, molds - scanning systems	Ability to determine healing progression, wound area is reduced Wound depth is reduced	Advancing epidermal margin Wound stage decreased

components of tissue, infection/inflammation, moisture and edge, the wound care practitioner can now also use these four categories to carry out a systematic assessment of the wound.

The TIME assessment tool proposed in Table 3 can be as simple or as complex as the setting requires. For simple bedside monitoring, color can be classified as black, yellow, red, pink or white, whereas in the research setting, colorimetry, spectrophotometry, and other sophisticated methods can be used. Area can be assessed using simple tracing methods, or sophisticated computer software can be employed for more-precise measurements.[73,74]

It is generally agreed that regular wound assessment, carried out consistently, using the same technique, is significantly better than no assessment at all, and this simple, easily applied assessment tool complements the more-systematic approach to wound management that is described in the TIME approach to wound bed preparation.

TESTING THE EVIDENCE

At all levels in the health service, there is an increased requirement for evidence of effect and for quantification of that effect. Yet how is value assigned to a therapeutic intervention in wound management when there are so few large, well-conducted trials to assist in evaluation? This absence is largely due to the difficulties in assessment and in agreeing on surrogate markers of healing, but economic evaluation techniques may be able to assist with decision-making in this environment by using modeling techniques to make the most of the available evidence.

- If there is no single study that includes all the evidence relevant to an intervention, a decision analytic model allows evidence from a variety of sources to be combined in a transparent way.
- A model can be used to extrapolate from surrogate endpoints to clinical outcomes and to extrapolate costs and benefits over time in an explicit and transparent way.
- A model allows the effect of an intervention to be estimated in different clinical and system settings so that the evidence of effect can be applied to more representative patient populations.
- A comparison of a number of alternatives can be made where these may never have been directly compared in a traditional randomized, controlled trial (RCT).
- A decision model can be used to characterize the uncertainty surrounding the estimates of effect and cost and can represent the uncertainty surrounding a decision to adopt a particular intervention.

Availability of evidence

The lack of RCTs is particularly noticeable in the field of wound management, but this does not mean that there is no evidence. There is a wealth of clinical data, epidemiological studies, and observational data. It is important to bear in mind that most patients with chronic wounds are excluded from RCTs because of their age, comorbidities, or comedications. Paradoxically, RCTs therefore provide little information about the efficacy of an intervention in the majority of patients usually seen in wound clinics. The lack of RCT data should not be used as a reason for not applying the concepts of wound bed preparation.

Some of the available evidence is for aggregated interventions, and the modeling process can be used to extract evidence for management of one particular type of wound from a number of aggregated studies. Expert judgment is also important to fill gaps in the evidence, because there may be evidence about a particular treatment but not in exactly the area wanted. Unlike systematic reviews, evidence will not be rejected if it has not been collected within the context of an RCT, but the uncertainty due to the amount and quality of the evidence available can be assessed and represented in the evaluation.

Finally, as was noted above, wound bed preparation, although under a different name, has been practiced in the management of burn wounds for decades, and a substantial body of evidence has accumulated in this area. Although few studies have assessed the effect of debridement on chronic wounds, many large-scale controlled studies have been conducted on thousands of burns patients to compare the effects of early excision with a watch-and-wait approach. These studies, and those in other areas of burn wound management, are relevant to the management of chronic wounds and can provide some insights into the efficacy or otherwise of various interventions.

In attempting to evaluate the success or otherwise of various wound management strategies, there are further complications. Chronic wound management is a large field. There are many wound etiologies to consider (venous leg ulcer, pressure ulcer, diabetic, etc.), and other patient factors such as the existence of systemic disease (e.g., neuropathy, vascular disease) and other comorbidities are likely to affect wound management interventions.

There are also many elements to wound management (four in the TIME paradigm), and it is not clear that these are entirely separable; the management of necrotic tissue, for example, may also reduce the potential for infection. However, the TIME table itself is a demonstration that an apparently complex process for managing a whole array of wounds can be encapsulated in a simple set of guidelines, and an economic evaluation could perhaps follow the same route.

Intellectually, the recommendations for wound management set out in the TIME table can be justified, because they are based on sound research of the underlying abnormalities affecting the wound healing process. However, the critical question always remains:

Does the recommended intervention make a real difference to wound healing?

A way ahead could be to:

- Identify a priority area for evaluation
- Select elements of wound bed preparation where an evaluation would have the most effect
- Focus on a particular type of wound for a group of patients
- Agree on the scope: effectiveness over what time period
- Identify key clinical events and outcomes (e.g., total healing or substantially healed)
- Identify timescale

The key question in an evaluation is: "Is the improvement in patient outcomes worth the additional resources required to fund it?" Once the various interventions have been assessed, a line can be drawn, above which an effective intervention would still be rejected if it consumed too many resources.

With a highly effective but expensive intervention, specific patients might improve, but overall patient outcome—considering the whole system—might be reduced through diversion of resources. So any model has to consider not just patients in the group under investigation, but also others who have a legitimate claim on resources elsewhere in the system.

Defining the model is currently outside the scope of this paper, but the TIME components of wound bed preparation provide an excellent opportunity to test therapies within an integrated wound management concept. Further work will be undertaken this year to gather all available evidence that will measure the economic value of wound bed preparation, initially within a specific indication.

CONCLUSION

Wound bed preparation, based on observations and studies on the cellular and biochemical environment of nonhealing wounds, has been widely adopted as an effective approach to the management of chronic wounds. The TIME paradigm was developed as a practical expression for the management of wounds, based on the principles of wound bed preparation. The paradigm is constantly evolving as new discoveries emerge about the environment of wounds. TIME appears to be applicable to the management of many types of wounds, not just chronic. Although there is a lack of substantial evidence to confirm the wound bed preparation approach within the chronic wound area, this will become the next priority for many clinicians in our field. Interestingly, there are many parallels to be found in the management of burns, for which the wound bed preparation approach (although not in name) has been used for decades, supported by many large controlled trials, and it is hoped that chronic and acute clinicians will work together to provide new possibilities within the wound bed preparation concept.

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REFERENCES

1. Schultz GS, Sibbald RG, Falanga V, Ayello EA, Dowsett C, Harding K, Romanelli M, Stacey MC, Teot L, Vanscheidt W. Wound bed preparation: a systematic approach to wound management. Wound Rep Reg 2003;11:1–28.
2. Schultz GS, Barillo DJ, Mozingo DW, Chin GA. Wound bed preparation and a brief history of TIME. Int Wound J 2004;1:19–31.
3. Cook H, Davies KJ, Harding KG, Thomas DW. Defective extracellular matrix reorganization by chronic wound fibroblasts is associated with alterations in TIMP-1, TIMP-2 and MMP-2 activity. J Invest Dermatol 2000;115:225–33.
4. Hasan A, Murata H, Falabella A, Ochoa S, Zhou L, Badavias E, Falanga V. Dermal fibroblasts from venous ulcers are unresponsive to action of transforming growth factor-beta 1. J Dermatol Sci 1997;16:59–66.
5. Agren MS, Steenfos HH, Dabelsteen S, Hansen JB, Dabelsteen E. Proliferation and mitogenic response to PDGF-BB of fibroblasts isolated from chronic leg ulcers is ulcer-dependent. J Invest Dermatol 1999;112:463–9.
6. Mendez MV, Stanley A, Park HY, Shon K, Phillips T, Menzoian JO. Fibroblasts cultured from venous ulcers display cellular characteristics of senescence. J Vasc Surg 1998;28:876–83.
7. Stanley AC, Park HY, Phillips TJ, Russakovsky V, Menzoian JO. Reduced growth of dermal fibroblasts from chronic venous ulcers can be stimulated with growth factors. J Vasc Surg 1997;26:999–1001.
8. Stanley A, Osler T. Senescence and the healing rates of venous ulcers. J Vasc Surg 2001;33:1206–11.
9. Hehenberger K, Heilborn JD, Brismar K, Hansson A. Inhibited proliferation of fibroblasts derived from chronic diabetic wounds and normal dermal fibroblasts treated with high glucose is associated with increased formation of l-lactate. Wound Rep Reg 1998;6:135–41.
10. Loots MA, Lamme EN, Mekkes JR, Bos JD, Middelkoop E. Cultured fibroblasts from chronic diabetic wounds on the lower extremity (non-insulin-dependent diabetes mellitus) show disturbed proliferation. Arch Dermatol Res 1999;291:93–9.
11. Falanga V. Classifications for wound bed preparation and stimulation of chronic wounds. Wound Rep Reg 2000;8:347–52.

12. Rogers AA, Harding KG, Chen WYJ. The epidermis at the edge of venous leg ulcers exhibits proliferative rather than differentiation markers and is associated with basement membrane disruption. Wound Rep Reg 2003;11:A13.
13. Saarialho-Kere UK, Kovacs SO, Pentland AP, Olerud JE, Welgus HG, Parks WC. Cell–matrix interactions modulate interstitial collagenase expression by human keratinocytes actively involved in wound healing. J Clin Invest 1993;92:2858–66.
14. Petersen MJ, Woodley DT, Stricklin GP, O'Keefe BJ. Constitutive production of procollagenase and collagenase inhibitor by human keratinocytes in culture. J Invest Dermatol 1989;92:156–9.
15. Sarret Y, Woodley DT, Goldberg GS, Kronberger A, Wynn KC. Constitutive synthesis of a 92-kDa keratinocytes-derived type IV collagenase is enhanced by type 1 collagen and decreased by type IV collagen matrices. J Invest Dermatol 1992;99:836–41.
16. Agren MS. Gelatinase activity during wound healing. Br J Dermatol 1994;131:634–40.
17. Trengove NJ, Stacey MC, MacAuley S, Bennett N, Gibson J, Burslem F, Murphy G, Schultz G. Analysis of the acute and chronic wound environments: the role of proteases and their inhibitors. Wound Rep Reg 1999;7:442–52.
18. Ulrich D, Unglaub F, Pallua N. Matrix metalloproteinases and their inhibitors in rapid and slow healing venous leg ulcers. Poster number P018 and oral presentation, 2nd WUWHS Congress, Paris, July 2004.
19. Bullen EC, Longaker MT, Updike DL, Benton R, Ladin D, Hou Z, Howard EW. Tissue inhibitor of metalloproteinases-1 is decreased and activated gelatinases are increased in chronic wounds. J Invest Dermatol 1995;104:236–40.
20. Vaalamo M, Weckroth M, Puolakkainen P, Kere J, Saarinen P, Lauharanta J, Saarialho-Kere UK. Patterns of matrix metalloproteinase and TIMP-1 expression in chronic and normally healing human cutaneous wounds. Br J Dermatol 1996;135:52–9.
21. Agren MS, Eaglstein WH, Ferguson MW, Harding KG, Moore K, Saarialho-Kere UK, Schultz GS. Causes and effects of the chronic inflammation in venous leg ulcers. Acta Derm Venereol 2000;210:3–17.
22. Wysocki A, Staiano-Coico L, Grinnell F. Wound fluid from chronic leg ulcers contains elevated levels of metalloproteinases MMP-2 and MMP-9. J Invest Dermatol 1993;101:64–8.
23. Tarnuzzer RW, Schultz GS. Biochemical analysis of acute and chronic wound environments. Wound Rep Reg 1996;4:321–5.
24. Yager DR, Zhang LY, Liang HX, Diegelmann RF, Cohen IK. Wound fluids from human pressure ulcers contain elevated matrix metalloproteinase levels and activity compared to surgical wound fluids. J Invest Dermatol 1996;107:743–8.
25. Nwomeh BC, Liang HX, Cohen IK, Yager DR. MMP-8 is the predominant collagenase in healing wounds and non-healing ulcers. J Surg Res 1999;81:189–95.
26. Rogers AA, Burnett S, Moore JC, Shakespeare PG, Chen WYJ. Involvement of proteolytic enzymes – plasminogen activators and matrix metalloproteinases – in the pathophysiology of pressure ulcers. Wound Rep Reg 1995;3:273–83.
27. Stryer L. Biochemistry, 3rd Ed. New York: W.H. Freeman, 1988.
28. Greener B, Hughes AA, Bannister NP. The effect of pH on proteolytic activity in chronic wound fluids and methods for determination. Poster number Z079, 2nd WUWHS Congress. Paris, July 2004.
29. Dissemond J, Witthoff M, Brauns TC, Haberer D, Goos M. pH values in chronic wounds. Evaluation during modern wound therapy. Hautarzt 2003;54:959–65.
30. Spanheimer RG. Correlation between decreased collagen production in diabetic animals and in cells exposed to diabetic serum: response to insulin. Matrix 1992;12:101–7.
31. Lerman OZ, Galiano RD, Armour M, Levine JP, Gurtner GC. Cellular dysfunction in the diabetic fibroblast. Am J Pathol 2003;162:303–12.
32. Lobmann R, Ambrosch A, Schultz G, Waldmann K, Schieweck S, Lehnert H. Expression of matrix metalloproteinases and their inhibitors in the wounds of diabetic and non-diabetic patients. Diabetologia 2002;45:1011–6.
33. Loots MA, Lamme EN, Zeegelaar J, Mekkes JR, Bos JD, Middelkoop E. Differences in cellular infiltrate and extracellular matrix of chronic diabetic and venous ulcers versus acute wounds. J Invest Dermatol 1998;111:850–7.
34. Mast BA, Schultz GS. Interactions of cytokines, growth factors, and proteases in acute and chronic wounds. Wound Rep Reg 1996;4:411–20.
35. Wright JB, Lam K, Buret AG, Olson ME, Burrell RE. Early healing events in a porcine model of contaminated wounds: effects of nanocrystalline silver on matrix metalloproteinases, cell apoptosis and healing. Wound Rep Reg 2002;10:141–51.
36. Savill J. Apoptosis in the resolution of inflammation. J Leuk Biol 1997;61:375–80.
37. Paddock HN, Schultz GS, Perrin KJU, Moldawer LL, Wright B, Burrell RE, Mozingo DW. Clinical assessment of silver-coated antimicrobial dressing on MMPs and cytokine levels in non-healing wounds. Wound Rep Reg 2002;10:A45.
38. Janžekovic Z. A new concept in the early excision and immediate grafting of burns. J Trauma 1970;10:1103–8.
39. Chamania S, Patidar GP, Dembani B, Baxi M. A retrospective analysis of early excision and skin grafting from 1993 to 1995. Burns 1998;24:177–80.
40. Deitch EA. A policy of early excision and grafting in elderly burn patients shortens the hospital stay and improves survival. Burns Incl Therm Inj 1985;12:109–14.
41. Demling RH. Improved survival after massive burns. J Trauma 1983;23:179–84.
42. Thompson P, Herndon DN, Abston S, Rutan T. Effect of early excision on patients with major thermal injury. J Trauma 1987;27:205–7.
43. Kirn DS, Luce EA. Early excision and grafting versus conservative management of burns in the elderly. Plast Reconstr Surg 1998;102:1013–7.
44. Caldwell FT, Wallace BH, Cone JB. Sequential excision and grafting of the burn injuries of 1507 patients treated between 1967 and 1986: end results and the determinants of death. J Burn Care Rehabil 1996;17:137–46.
45. Kisslaogglu E, Yuksel F, Uccar C, Karacaogglu E. Rationale for early tangential excision and grafting in burn patients. Acta Chir Plast 1997;39:9–12.
46. Merrell SW, Saffle JR, Larson CM, Sullivan JJ. The declining incidence of fatal sepsis following thermal injury. J Trauma 1989;29:1362–6.
47. Pruitt BA, McManus AT, Kim SH, Goodwin CW. Burn wound infections: current status. World J Surg 1998;22:135–45.
48. Barrett JP, Herndon DN. Effects of burn wound excision on bacterial colonization and invasion. Plast Reconstr Surg 2003;111:744–50.
49. Wright JB, Lam K, Hanson D, Burrell RE. Efficacy of topical silver against fungal burn wound pathogens. Am J Infection Cont 1999;27:344–50.
50. Lloyd JR, Hight DW. Early laminar excision. improved control of burn wound sepsis by partial dermatome debridement. J Pediatr Surg 1978;13:698–706.
51. Walter PH. Burn wound management. AACN Clin Iss 1993;4: 378–87.
52. Bragg PD, Rainnie DJ. The effect of silver ions on the respiratory chain of E coli. Can J Microbiol 1974;20:883–9.
53. Cervantes C, Silver S. Metal resistance in *Pseudomonas:* genes and mechanisms. In: Nakazawa T, Furukawa K, Haas D, Silver S, eds. Molecular biology of pseudomonas. Washington: American Society for Microbiology, 1996.

54. Modak SM, Fox CL. Binding of silver sulfadiazine to the cellular components of *Pseudomonas aeruginosa*. Biochem Pharmacol 1973;22:2391–404.
55. Rosenkranz HS, Rosenkranz S. Silver sulfadiazine: interaction with isolated deoxyribonucleic acid. Antimicrob Agents Chemother 1972;2:373–83.
56. Bridges K, Kidson A, Lowbury EJ, Wilkins MD. Gentamicin- and silver-resistant pseudomonas in a burns unit. BMJ 1979;1:446–9.
57. Gayle WE, Mayhall CG, Lamb VA, Apollo E, Haynes BW Jr. Resistant *Enterobacter cloacae* in a burn center: the ineffectiveness of silver sulfadiazine. J Trauma 1978;18: 317–23.
58. Hendry AT, Stewart IO. Silver-resistant Enterobacteriaceae from hospital patients. Can J Microbiol 1979;25:915–21.
59. Modak SM, Fox CL Jr. Sulfadiazine silver-resistant *Pseudomonas* in burns. New topical agents. Arch Surg 1981;116:854–7.
60. Li XZ, Nikaido H, Williams KE. Silver-resistant mutants of *Escherichia coli* display active efflux of Ag^+ and are deficient in porins. J Bacteriol 1997;179:6127–32.
61. Poon VKM, Burd P. In vitro cytotoxicity of silver: implications for clinical wound care. Burns 2004;30:140–7.
62. Innes ME, Umraw N, Fish JS, Gomez M, Cartotto RC. The use of silver coated dressings on donor site wounds: a prospective, controlled matched pair study. Burns 2001;27:621–7.
63. Scales JT. Wound healing and the dressing. Br J Indust Med 1960;20:82–94.
64. Champsaur A, Amamou R, Nefzi A, Marichy J. Use of DuoDerm on skin graft donor sites: comparative study with tulle gras. Ann Chir Plast Esthet 1986;31:273–8.
65. Hermans MH, Hermans RP. DuoDerm, an alternative dressing for smaller burns. Burns 1986;12:214–9.
66. Madden MR, Nolan E, Finkelstein JL, Yurt RW, Smeland J, Goodwin CW, Hefton J, Staiano-Coico L. Comparison of an occlusive and a semi-occlusive dressing and the effect of the wound exudate upon keratinocyte proliferation. J Trauma 1989;29:924–31.
67. Sheehan P, Jones P, Caselli A, Giurini JM, Veves A. Percent change in wound area of diabetic foot ulcers over a 4-week period is a robust predictor of complete healing in a 12-week prospective trial. Diabetes Care 2003;26: 1879–82.
68. Kantor J, Margolis DJ. A multicentre study of percentage change in venous leg ulcer area as a prognostic index of healing at 24 weeks. Br J Dermatol 2000;142:960–4.
69. Keast DH, Bowering K, Evans AW, MacKean GL, Burrows C, d'Souza L. MEASURE: a proposed assessment framework for developing best practice recommendations for wound assessment. Wound Rep Reg 2004;12:S1–S17.
70. Woodbury MG, Houghton PE, Campbell KE, Keast DH. Pressure ulcer assessment instruments: a critical appraisal. Ostomy Wound Manage 1999;45:42–53.
71. Keast DH, Cranney G. Does wound surface area as measured by length and width reflect true area: analysis of a wound data base. Ninth Annual Conference, Canadian Association of Wound Care, Toronto, ON, November 6–9, 2003.
72. Tsukada K, Tokunaga K, Iwama T, Mishima Y. The pH changes of pressure ulcers related to the healing process of wounds. Wounds 1992;4:16–20.
73. Romanelli M, Gaggio G, Coluccia M, Rizzello F, Piaggesi A. Technological advances in wound bed measurements. Wounds 2002;14:58–66.
74. Romanelli M. Objective measurement of venous ulcer debridement and granulation with a skin color reflectance analyzer. Wounds 1997;9:122–6.