Wound bed preparation and a brief history of TIME

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ABSTRACT

Management of chronic wounds has progressed from merely assessing the status of a wound to understanding the underlying molecular and cellular abnormalities that prevent the wound from healing. The concept of wound bed preparation has simultaneously evolved to provide a systematic approach to removing these barriers to natural healing and enhancing the effects of advanced therapies. This brief review of wound bed preparation traces the development of these concepts and explains how to apply systematic wound management using the TIME acronym – tissue (non viable or deficient), infection/inflammation, moisture (imbalance) and edge (non advancing or undermined).

Key words: Debridement ● Growth factors ● Infection ● Inflammation ● Moisture balance ● Proteases ● Wound bed preparation ● Wound edge

THE WORLD BEFORE WOUND BED PREPARATION

Until the 1960s, the aims of wound management were simply to cover and conceal. Materials used for wound management were adaptations of materials in use for other purposes, such as oakum (shredded rope), jewellers' cotton and gauze. These materials were passive products that did little to encourage the healing process, and no attention was paid either to their functional performance or to the healing environment required for different types of wounds. If a wound healed without problems, it was as likely to be due to chance, as to design.

Developments in wound products could only have come about through greater knowledge of the biology of chronic wounds, and it was clear that the whole management of wounds needed to be based on the same understanding. The move from an almost entirely empirical approach, to one based on an analysis of, and response to, the wound microenvironment is the underlying concept of wound bed preparation.

Key Points

- advancement in wound care products came through a better understanding of the biology of chronic wounds
- wound assessment is a prerequisite of wound management

WOUND ASSESSMENT AND WOUND MANAGEMENT

Wound management starts with wound assessment. Wound assessment methods were an important part of the development of active wound management. Standardised methods were developed that allowed wound care clinicians to monitor the status of the wound and – by implication – the effect of an intervention. Wound assessment methods, including scales, were developed for pressure ulcers, venous ulcers and diabetic foot ulcers, and much work has gone into assessing their validity and reliability.

A number of different classification systems have been developed to assess pressure

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Key Points

- a number of wound assessment tools exist allowing determination of wound progress

ulcers, using stages, grades or wound characteristics and colours to determine treatment. The most widely used tool for assessing a pressure ulcer on diagnosis [the NPUAP/AHCPR system (1)] is also used to assess healing, although, by its very nature, it is not suited to this purpose. For years, reverse staging has been required by health-care agencies to describe a healing wound. As healing progresses by granulation, contraction, re-epithelialisation, re-modelling and maturation of the scar, a system developed for the assessment of wounding is clearly not suitable. Other tools that have been developed to assess the healing of wounds include the Pressure Sore Status Tool (PSST), the National Pressure Ulcer Advisory Panel Pressure Ulcer Scale for Healing (PUSH) (2), the Wound Healing Scale (WHS) and the Sussman Wound Healing Tool (SWHT) (3) (Table 1).

The aim of all of these tools was to provide the clinician with information that would show whether treatment had been effective and whether the wound was progressing in a positive manner. The development of assessment tools was a useful step in developing a systematic approach to the management of chronic wounds. However, they did not link observations with recommended interventions, nor did they provide any understanding of the underlying abnormalities that would enable the clinician to understand the reasons for why a wound was not healing. If one intervention did not work, another one would be tried in a random fashion, rather than on an understanding of why the first had failed to work. At the same time, advances were being made in understanding the nature of chronic wounds and in developing sophisticated products to deal with them.

Chronic wound management had been hampered by a reliance on models of healing which are largely derived from the acute wound. In acute wounds, there is a linear progression through the four well-known phases of healing: haemostasis, inflammation, proliferation and remodelling (or maturation). In chronic wounds, it seems that there is a

Table 1 Tools for wound assessment

NPUAP/AHCPR staging system	Developed by Shea in 1975, revised by the International Association of Enterostomal Therapy in 1987, further revised by the National Pressure Ulcer Advisory Panel in 1989, adopted for use in the 1992 and 1994 pressure Ulcer Guidelines by the AHCPR, revised again by NPUAP in 1998.	Four stages (1–4) describing progressive tissue destruction.
PSST (automated version: Wound Intelligence System)	Research-based tool developed in 1997 by Bates-Jensen (55) for assessment and documentation of pressure ulcers. Observations can be quantified and tracked over time.	Fifteen wound assessment indices each assigned a value and the score plotted along a Pressure Sore Status Continuum from 1 (healthy) to 65 (wound degeneration).
PUSH	Developed and revised by the NPUAP. Validated by two studies and a test conducted by HCFA.	Scores are assigned to wound area, exudate and tissue type and plotted on a wound healing record and healing graph.
WHS	Developed by Krasner in 1997 (56) to provide an alternative to back-staging and that will be applicable to other wounds.	Eight factors are assessed and used to modify the pressure ulcer stages (1–4) or depth designations for all other wound types.
SWHT	Developed in 1998 by Sussman and Swanson (3) as a tool for physical therapists. Based on the acute wound healing model.	Ten wound attributes classified as good or not good for healing. Available in short or long form.

AHCPR, Agency for Health Care Policy and Research; HCFA, Health Care Financing Administration; PSST, Pressure Sore Status Tool; PUSH, Pressure Ulcer Scale for Healing; NPUAP, National Pressure Ulcer Advisory Panel; SWHT, Sussman Wound Healing Tool; WHS, Wound Healing Scale.

failure of the normal response to injury, resulting in non healing. Abnormalities can occur in any of the phases of normal healing, but it is not always clear to the clinician where the abnormality has occurred. Chronic wounds often seem to be stuck in one of the phases where they undergo a circular process of impaired healing and continual damage. Improved understanding of the molecular pathophysiology and biology of chronic wounds was a significant step in the development of wound bed preparation.

Chronic wounds may be inflammatory, producing substantial amounts of exudate that contribute to necrotic burden (4). Furthermore, studies on chronic wound fluid revealed that the composition is very different from that of acute wound fluid and had a deleterious effect on healing. Chronic wound fluid was found to contain high levels of proteases, including matrix metalloproteinases (MMPs) and serine proteases (elastase) that break down or corrupt extracellular matrix (ECM) proteins and growth factors, and to inhibit proliferation of cells such as keratinocytes, fibroblasts and endothelial cells (5–7). Macromolecules in wound fluid also bound growth factors, making them unavailable to the healing process. Mendez *et al*. (8) showed that fluid from chronic venous ulcers induced senescence in cultures of normal neonatal foreskin fibroblasts, suggesting that factors present in chronic wound fluid adversely impact the capacity of normal fibroblasts to proliferate and heal wounds.

RELEVANCE AND HISTORY OF WOUND BED PREPARATION

In a chronic wound, the cellular processes are disrupted and abnormal functions may be due to a variety of intrinsic or extrinsic factors, acting either singly or in combination. If it is not clear to the practitioner what the underlying problem is, he/she may only react to the presenting symptoms instead of considering a more scientific approach to wound management. Wound bed preparation attempted to systematise chronic wound management, underpinned by an understanding of why the wound was behaving as it did.

As the name suggests, wound bed preparation initially emerged as a means of preparing the wound to accept advanced wound healing therapies. In the 1990s, many new and innovative technologies – such as bioengineered skin and topical growth factors – were developed for the treatment of chronic wounds. But, the performance of these products in the clinic was far below that seen in the rigorous environment of the clinical trial due, in part, to inadequate preparation of the wound bed.

It became clear that it was not possible to treat a poorly prepared wound bed with advanced therapies and to expect them to succeed. Before advanced products could be applied, the wound bed required preparation. This preparation included attention to non viable tissue, control of bacterial burden and inflammation and moisture balance and stimulation of the wound edges to bring about migration. It was recognised that, in general, a wound must have a well-vascularised wound bed, must not be infected and must be free of fibrinous material, scarring and excess exudate if it is to be suitable for grafting, gene therapy or other advanced methods. Thus, wound bed preparation was initially described as a means of improving the wound bed to accept new products (9).

It had been widely assumed that most wound care clinicians were already working to established protocols and treatment guidelines and that the wound bed would be adequately prepared to accept newly developed therapeutic agents. However, this proved not to be the case. The management of chronic wounds was still largely experimental and not rooted in an understanding of the underlying defect that was preventing the wound from healing. Some guidelines were available but were not generally followed (9).

Although wound bed preparation initially arose out of a need to prepare the wound bed in a specific manner to accept advanced wound healing products, it soon evolved into a method that could be used to stimulate the endogenous process of wound repair without the need for advanced therapies. It has since become established as a method for addressing chronic wounds that is independent of models of acute wound healing (9).

Wound bed preparation evolved by combining basic principles of good standard wound care and an improved understanding of the molecular and cellular abnormalities that prevent chronic wounds from healing. Applying the concepts of wound bed preparation helps to correct specific abnormalities

Key Points

- chronic wounds may have persistant inflammation present containing high levels of proteases
- advances in the understanding of chronic wounds has led to the development of wound bed preparation paradigm

Key Points

- wound bed preparation requires debridement, moisture balance and bacterial balance
- has now been redefined as the global management of the wound to accelerate endogenous healing or to facilitate the effectiveness of other therapeutic measures

such as high pro-inflammatory cytokine levels, elevated MMP levels, low growth factor activities, abnormal matrix and senescent wound cells. The four principles encompass many currently recommended clinical actions, but the key is to understand how the integrated actions alter the molecular and cellular profiles in chronic wounds to bring about healing.

DEFINITION OF WOUND BED PREPARATION

In 2000, Sibbald *et al*. (10) defined wound bed preparation as 'a changing paradigm that links treatment to the cause and focuses on three components of local wound care: debridement, wound-friendly moist interactive dressings and bacterial balance'.

Thirteen recommendations for wound management were provided that began with a comprehensive assessment of the patient's overall health status to establish the cause of the wound and to identify factors that may be impairing healing. This has remained a constant feature of wound bed preparation: local wound care must be preceded by thorough attempts to correct any underlying defect. This approach owes a debt to earlier work by Orsted and colleagues on nutritional and patient-centred concerns (11,12), and to Ovington (13) on dressings.

A definition of wound bed preparation was later put forward that included 'removing the barriers to healing' (14). This concept was subsequently modified by a panel including Harding to focus on the removal of negative factors (such as necrotic tissue, bacteria and exudate, poor nutrition or concomitant illness), which may lead to the conclusion that once these negative factors have been removed, the wound would then heal (15). Unfortunately – as every wound care practitioner knows – many wounds do not heal despite scrupulous attention being paid to systemic and local wound factors. Wound bed preparation is not just about removing barriers to healing but needs also to encompass active measures that stimulate healing such as growth factors, active dressings that reduce proteases and engineered tissue substitutes.

Wound bed preparation was eventually redefined as 'the global management of the wound to accelerate endogenous healing or to facilitate the effectiveness of other therapeutic measures' (4). Global management reflects the fact that wound management must always start not only with local interventions but with an assessment of the overall health status of the patient to identify what underlying conditions may have caused the wound in the first place or may be limiting its ability to heal. The incorporation of endogenous healing reflects the fact that even very recalcitrant wounds do not necessarily need to be treated with advanced therapies in order to heal.

This revised definition was based on an improved understanding of the abnormalities in chronic wounds and incorporated recommendations for dealing with these problems (Table 2).

INITIAL COMPONENTS OF WOUND BED PREPARATION

The classification of wounds into acute or chronic has sometimes been unhelpful. The word 'acute' is generally used to imply a wound that occurred very recently and usually as a result of a single type of tissue damage, such as an incision or a burn. Most acute wounds begin healing within a few days, and the damaged tissue is repaired within a couple of weeks. The term 'chronic' is generally used to refer to wounds that have not completed healing in 4–6 weeks. Yet, in some respects, all chronic wounds begin as acute wounds, usually with an identifiable, initial injury such as an abrasion or blister on the foot of a diabetic person or a small bruise on the ankle of a person with venous disease. However, the underlying pathology that accompanies the acute injury slows the acute phases of healing so much that other factors (infection and ischaemia) begin to alter the molecular and cellular environment of the wound and healing cannot proceed through the normal phases. The first stage in wound bed preparation therefore is always to consider the cause of a wound before carrying out local interventions at the wound level. It is not sufficient to make a diagnosis that a patient has a leg ulcer without specifying whether it is due to venous, arterial or inflammatory disease. Similarly, diabetic foot ulceration could be due to neuropathy, ischaemia or neuro-ischaemic disease.

Three main components were proposed as the mainstay of wound bed preparation (10):

Table 2 Wound bed preparation

Basic	Abnormalities and corrections		Complex
Necrotic tissue Oedema Infection Haemodynamics	Biofilms Necrotic tissue and exudate (necrotic burden)	Corrupt matrix Fibrin, trapped growth factors MMPs	Cellular burden Phenotypic changes in wound cells
↓	↓	↓	↓
Debridement Antibiotics Surgery	Slow-release antiseptics Dressings Enzymes Maintenance debridement	Matrix materials Fibrinolysis Growth factors MMP inhibitors Gene therapy	Cell chemotherapy Bioengineered skin cell therapy Stem cells

Copyright V Falanga 2001 (16). MMPs, matrix metalloproteinases.

Key Points

- the understanding of wound bed preparation has matured over time
- wound bed preparation has provided a rationale for some of the interventions that have been historically applied to chronic wounds

debridement, bacterial balance and moisture control. These were not viewed as three isolated measures, designed to deal with single aspects of the chronic wound, but were integrated interventions that can have multiple effects.

- Regular debridement removes eschar from the wound and also removes bacteria and senescent cells.
- Bacterial control reduces the likelihood of infection but can also limit the pro-inflammatory response due to bacteria in the wound.
- Moisture control ensures that wounds neither macerate nor dehydrate but, using today's advanced dressings, can also remove bacteria and eliminate necrotic burden in the form of slough and exudate.

A common misconception in the early days of wound bed preparation was to equate it with wound debridement. However, while debridement is rarely required more than once in an acute wound, it is now clear that chronic wounds continue to generate a necrotic burden which requires regular removal if the wound is to heal (4).

In acute wounds, debridement is used to remove devitalised, damaged tissue and bacteria, and once this has been accomplished, there is a clean wound bed that is likely to heal with relative ease. Chronic wounds are slowly and constantly accumulating abnormal cells that are no longer responsive to growth factors and which impede the growth of healthier cells. Frequent maintenance debridement using surgical, chemical or autolytic methods is therefore required to remove debris that may be impairing healing. In wound bed preparation, we are not concerned solely with the removal of eschar and non viable tissue but also with exudate (16).

Moisture control has long been a standard part of wound management, and direct methods of dealing with wound exudate are well known: compression bandaging, highly absorbent dressings or mechanical systems. Compression therapy for venous ulcers will decrease the amount of exudate but, more importantly, will clear macromolecules responsible for trapping growth factors (17,18).

Wound bed preparation acknowledged that excess exudate may also be caused by heavy colonisation with bacteria, maintaining a continued pro-inflammatory stimulus in the wound. Antiseptics and antimicrobials, rather than absorbent dressings, would therefore be the most appropriate intervention. The recent development of dressings that release low levels of antimicrobial silver over seven days appears to be beneficial for critically colonised wounds (19).

Wound bed preparation has provided a rationale for some of the interventions that have been historically applied to chronic wounds. Debridement and bacterial and moisture balance have always been regarded as important in the management of wounds, but improved understanding of wound pathophysiology has led to these interventions being used in a more rational and systematic

Key Points

- the importance of the edge effect has been recently recognised
- this has put the E in TIME
- WBP becomes a cyclical process of wound management where assessment was followed by intervention, which in turn was followed by further assessment

manner. The concept of wound bed preparation has led to a re-evaluation of commonly used therapeutic agents and opportunities to explore their other properties.

ADDING AN EDGE TO WOUND BED PREPARATION

These three initial components of wound bed preparation were valuable in bringing about a more systematic approach to wound management. They provided a tool for systematically assessing the wound in terms of tissue, infection/inflammation and moisture and for carrying out interventions based on an understanding of the underlying cellular disruption.

The ultimate aim was to close the wound by stimulating epidermal migration across the wound bed. However, despite meticulous wound bed preparation, this was sometimes not achieved. Debridement of necrotic or devitalised tissue removes cellular debris that may be impairing healing and – along with other methods of infection control – also assists in removing bacteria that may be prolonging the inflammatory response. Attention to moisture balance ensures that the wound is not so desiccated as to prevent epithelial migration and removes harmful chronic wound fluid. Despite these interventions, wound cells at the wound margin may remain unresponsive or there may be abnormalities in protease activity, preventing wound closure. It became clear that a fourth component needed to be added to the observations – the wound margin or epidermal edge.

Falanga (9) observed that there was often hyperproliferation of cells at the margins of chronic wounds, due possibly to inhibition of differentiation and apoptosis within the keratinocyte and fibroblast cell populations. This hyperproliferating margin interferes with normal cellular migration. In one study, biopsies taken from the edge of chronic venous ulcers revealed that epidermal cells were in a heightened proliferative state with delayed keratinisation. The epidermal basement membrane at the wound edge was disrupted and lacked type IV basement membrane collagen, which is necessary for epithelial cell attachment and migration (20). It was assumed that failure to migrate was due to problems with synthesis of new tissue, but it has now been recognised that excessive degradation of newly formed ECM and delayed contraction are just as relevant.

Fibroblasts in chronic wounds may display phenotypic dysregulation and be unresponsive to certain growth factors and other signals (18,21–23). Fibroblasts obtained from chronic ulcers showed a decreased response to exogenous application of growth factors such as platelet derived growth factor beta (PDGF-β) and transforming growth factor-β (TGF-β) (18,23–25) which is thought to be due to these cells becoming senescent (22,26). *In vitro* studies on fibroblasts from venous (18,22,24) and diabetic (17,27) wounds reveal a decreased proliferative potential and other markers of senescence, such as beta-galactosidase and increased expression of fibronectin. The cause of this senescence is unclear, but it may be that, during repeated unsuccessful attempts at wound repair, resident cells have undergone numerous cycles of replication and have exhausted their replicative potential. However, this is only speculation at the moment, and there is no solid evidence for this. It may also be that senescent cells are not responsive to the normal apoptosis mechanisms and cannot be easily eliminated.

These cellular abnormalities need to be eliminated or corrected for wound healing to take place. The concept of wound bed preparation was therefore extended to include an understanding that the wound matrix may be corrupt and unable to sustain epidermal migration.

In practical terms, this meant that the wound care clinician would work through the first three components as needed and would then observe the edge of the wound to see if epidermal cell migration had begun. If not, this would indicate that a full reassessment of the patient and the wound should be carried out. If patient and local wound care was optimised, yet the wound still failed to heal, this may indicate that advanced wound-healing therapies are necessary to kick-start the healing process.

Thus, wound bed preparation became a cyclical process of wound management where assessment was followed by intervention, which in turn was followed by further assessment.

The addition of this fourth component – the epidermal edge – led to the TIME acronym, a

clinical tool for the management of chronic wounds that was developed in June 2002 by a group of wound care experts drawn from all disciplines involved in wound management:

- **T** for tissue: non viable or deficient
- **I** for infection/inflammation
- **M** for moisture balance
- **E** for epidermis, non migrating (later modified, see below).

These four components were first published in 2003 (15) in *Wound Repair and Regeneration* in the form of a table that related the clinical observation and intervention to the underlying pathology and the intended outcome for each of the four components.

The TIME table has since been revised (September 2003) to clarify the component relating to the epidermal edge. Initially, the incorporation of the word 'epidermal' into the acronym seemed to imply that the problem of non migration lay with the epidermis. In fact, failure of the epidermis to migrate is just as likely to be a problem with the ECM or cells at the edge of the wound. Therefore, the fourth component was revised to read: **E** for edge of wound, non advancing or undermined.

This revised table was published this year and is reproduced in Table 3 (28).

This new version of the TIME table contains, on the reverse side, a selection of photographs that provide typical examples of how each of these components may be encountered in clinical practice (Figure 1).

Since the publication of the first table in 2002, the TIME concept has been presented to many groups of wound care clinicians at educational and scientific meetings including European Wound Management Association, Pisa, May 2003; European Pressure Ulcer Association, Tampere, September 2003; and European Tissue Repair Society, Amsterdam, September 2003. Feedback has been positive, and it is becoming a valuable bedside tool for wound management.

THE TIME APPROACH TO WOUND MANAGEMENT

T for tissue: non viable or deficient

Necrotic tissue consists of dead cells and debris, while slough or fibrinous material consists of fibrin, pus and proteinaceous material. Necrotic tissue and slough provide a rich growth medium for bacteria that will promote inflammation and infection. Falanga (4) proposed the term 'necrotic burden' to describe the load of necrotic tissue, excess exudate and bacteria within dead tissue. This accumulation of necrotic burden within a chronic wound is likely to prolong the inflammatory response, mechanically obstruct wound contraction and impede re-epithelialisation.

Prolonged inflammation causes neutrophils, mast cells and macrophages to enter the wound and remain there as long as the inflammation continues. The inflammatory cells attempt to phagocytise the necrotic tissue and may release proteases, superoxide anions and pro-inflammatory cytokines that perpetuate the inflammatory phase. These products of inflammation degrade growth factors, receptors and ECM proteins.

Debridement of necrotic tissue does not therefore simply remove a physical obstruction to wound contraction but also reduces the number of microbes, toxins and other substances that reduce host immune defences (29).

I for infection/inflammation

Bacterial levels in the wound bed can be categorised as contamination, colonisation, local infection or spreading infection. Contamination is defined as the presence of non-replicating microorganisms within a wound and does not impair healing. Colonisation is defined as replicating microorganisms that adhere to the wound surface, but colonisation does not cause cellular damage to the host and, therefore, does not impair healing. Critical colonisation describes the situation in which the bacterial burden in the wound is intermediate between the categories of colonisation and infection. Critically colonised wounds do not heal (or are very slow to heal) but do not exhibit the classic signs of infection such as erythema, warmth, swelling, pain and loss of function (10). Treatment of critically colonised wounds typically includes topical antiseptic agents such as the sustained-release silver dressings or slow release iodine formulations. In contrast to critically colonised wounds, typical clinical signs and symptoms of locally infected wounds are delayed healing, pain/tenderness, increased serous exudate, change in colour of the wound bed, friable,

Key Points

- advancement has seen the development of TIME within the WBP
- recently this TIME concept has been redefined and is becoming widely accepted
- TIME is built on the WBP foundation utilising the concepts of debridement, moisture balance and bacterial balance

Table 3 TIME*‡ – the principles of wound bed preparation

Clinical observations	Proposed pathophysiology	WBP clinical actions	Effect of WBP actions	Clinical outcomes
Tissue non-viable 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 extra-cellular matrix 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 oedema, excessive fluid controlled, maceration avoided	Moisture balance
Edge of wound – non advancing or undermined	Non migrating keratinocytes. Non responsive wound cells and abnormalities in extracellular matrix or abnormal protease activity	Re-assess 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

*Courtesy of International Advisory Board on Wound Bed Preparation 2003
Adapted from table 6 – ‡Schultz GS, Sibbald RG, Falanga V et al, Wound Rep Reg (2003);11:1–28
Wound Bed Preparation and TIME are clinical concepts supported by Smith & Nephew Medical Ltd.

Figure 1. Clinical illustrations of the TIME table.

Key Points

- factors known to affect the bacterial balance in chronic wounds include the number and types of micro-organisms present, their virulence and host factors
- specialised dressing can be used to achieve and maintain bacterial balance

Key Points

- a moist environment is required for optimal healing
- newer moist, interactive dressing provides moisture balance within the wound environment
- while not possible to see senescent or abnormal cells with the naked eye, the signs of a non advancing epidermal margin are obvious after a little experience

absent or abnormal granulation tissue, pus and odour (30,31). As with critically colonised wounds, topical antiseptics are used to treat locally infected wounds. Spreading infections that extend beyond the wound margins (e.g. cellulitis and ascending lymphangitis) require systemic antibiotics, often in combination with topical antiseptics.

Factors that are known to affect the bacterial burden in chronic wounds include the number and types of microorganisms present in the wound, their virulence and host factors (32). The number of bacteria that impede healing of open wounds is controversial, with studies showing either impaired or no impaired healing with greater than 1×10^5 organisms per gram of tissue (33,34,35). The type and pathogenicity of the organisms, rather than the simple number of microorganisms in a wound, is a better determinant of the risk of infection. For example, the isolation of any highly virulent beta haemolytic streptococci from a chronic wound should be considered highly significant, and appropriate treatment should be initiated (36). Most chronic wounds are usually colonised with at least three species of microorganisms (37,38). Some combinations of bacterial species synergistically enhance the virulence of previously non virulent organisms, resulting in damage to the host (34,39).

Another important component of infections is the presence of biofilms, which may contribute to delayed healing in chronic wounds. When some bacteria proliferate, they form microcolonies that become attached to the wound bed and secrete a glycocalyx sheath, or biofilm, that helps to protect the microorganisms from antimicrobial agents (40). Organisms may exist as clusters of individual bacterial types or as mixed bacterial colonies. The periodic release of motile bacteria from these colonies may result in infection. These bacterial colonies can undergo several changes, expressing different genes, which may then alter the antimicrobial sensitivity of the organism. Thus, biofilms might harbour bacteria that are resistant to the effects of antimicrobial agents, such as antibiotics and antiseptics, and contribute to delayed healing.

Iodine formulations are available that demonstrate antimicrobial activity and absorb wound exudate while providing sustained release of iodine in the wound bed (41). Iodine has also demonstrated efficacy *in vivo* against *Staphylococcus aureus* and methicillin-resistant *Staphylococcus aureus* (MRSA) (42).

Acticoat®, an antimicrobial barrier dressing, contains a silver-coated, high-density polyethylene mesh with an absorptive gauze core which slowly releases silver into the dressing and maintains an effective antimicrobial barrier for up to 7 days. Acticoat® has been shown to be effective against a broad spectrum of bacterial strains *in vitro*, including MRSA and vancomycin-resistant *Enterococcus*. Silver ions have been used in the past in the form of silver sulfadiazine (AgSD) cream. Bishop and colleagues (43) found a statistically significant reduction in chronic venous ulcers treated with AgSD compared to controls. A similar finding was observed by Kucan and colleagues (44) in the treatment of pressure ulcers.

M for moisture imbalance

Traditional wound dressings were mainly designed to cover wounds and to absorb excess exudate. Formerly, medical opinion was that dry wounds were essential to avoid bacterial overgrowth. In 1987, Eaglstein (45) published an important study that demonstrated that experimentally induced wounds healed 40% faster in a moist environment compared to wounds exposed to the air. Earlier studies suggested that epidermal migration appeared to be facilitated in moist conditions (46,47), and later studies confirmed the utility of occlusive dressings (48,49).

However, while a moist environment is required for optimal healing, excessive fluid can cause maceration of the wound margin and surrounding skin. Furthermore, chronic wound fluid is also known to be detrimental to wound healing.

On the other hand, excessive desiccation slows migration of epidermal cells and limits epidermal regeneration; hence, dressings must be carefully chosen to deal with various levels of exudate (Table 4).

E for edge of wound

While it is not possible to see senescent or abnormal cells with the naked eye, the signs of a non advancing epidermal margin are obvious after a little experience. A healthy advancing margin may not have a clearly

Table 4 A summary of the major classes of wound dressings

Dry wounds	Hydrogels	• high concentration of water (70-90%) contained in insoluble polymers • best choice for dry, sloughy wounds with low-to-moderate levels of exudate • need changing every 24-72 hours (not strongly anti-infective) • assist autolytic debridement.
Low exudate	Hydrocolloid	• suited to autolytic debridement for mild-to-moderately exudating wounds • occlusive • anaerobic environment which may assist in correcting hypertropic granulation • also contain adhesives which can cause allergic contact dermatitis, especially with prolonged use • fibrinolytic activity • some antibacterial properties • wear time of 2-7 days • assist autolytic debridement.
Moderate	Foam	• appropriate for sloughy or exudative wounds • foams have thermal insulation, high absorbency and a moist environment and are gas permeable • easily cut to shape, do not shed fibres • some foams have additional layers to avoid adherence to dry wounds and polyurethane backing to prevent excess fluid loss; can be worn for up to 1 week • hydrofibres are highly absorbent, have good tensile strength and can be worn for up to 1 week • crystalline sodium chloride gauze has antibacterial properties and needs to be changed daily.
High	Alginates	• form a gel upon contact, promoting moist interactive healing • after debridement, the calcium alginate fibre is converted to a sodium alginate hydrogel • ideal for exudative and infected wounds • some have high gelling property for autolytic debridement • others have good fibre integrity for packing sinuses • no crust is formed • highly absorbent.
No exudate	Thin film	• ideal at the later stages of wound healing when there is no significant exudate • permeable to water vapour and oxygen • impermeable to water and microorganisms • available in adhesive and non adhesive forms • can be left in place for long periods.

Key Points

- different dressings provide different effects
- at present WBP and TIME have focussed solely on chronic wounds but those treating acute wounds see an evolution of the concept into their clinical arena as a distinct possibility

defined, single, uniform edge, as tendrils of epidermal growth may spread out over the wound bed. The bed itself will be healthy and pink. By contrast, an unhealthy margin may be undermined – perhaps indicating infection – or hypertrophic, while the granulation tissue will be a darker pink and may be friable and unstable to touch. Debridement, control of inflammation and moisture are essential components of wound bed preparation that may stimulate the edge of the wound to migrate, but if they fail, advanced therapies may be required.

Chronic venous stasis ulcers are usually superficial and typically have a hyperproliferating, non advancing epidermal margin. Debridement of the wound edge and compression combined with an appropriate dressing to restore moisture balance are standard treatments. If this fails, autologous split-thickness skin grafts or bioengineered skin substitutes may be effective (50,51).

In pressure ulcers with an extensive shelf of tissue and large undermined areas, several treatment strategies can be considered. In a clean wound, a vacuum-assisted dressing (VAC) can be used to reduce the ulcer volume until it can be closed surgically or treated with appropriate dressings. Critically colonised or infected wounds should not be treated with VAC until the infection has been eliminated.

In diabetic ulcers with callous and overhanging tissue, debridement of the edge to bleeding tissue and control of infection and moisture is usually effective. If the ulcer does

not respond, topical treatment with PDGF may be helpful. In four studies with a total of 922 patients with non healing lower extremity diabetic ulcers of at least 8 weeks' duration, topical PDGF treatment resulted in a 39% increase in complete healing compared with placebo gel (50% versus 36%, $P = 0{\cdot}007$) (52). Most importantly, however, the effectiveness of topical PDGF was significantly increased with the frequency of debridement, reinforcing the need to utilise the principles of wound bed preparation to achieve maximum effectiveness of an advanced therapy like PDGF treatment (54).

Another advanced therapy under evaluation for diabetic foot ulcers is the use of the metalloproteinase protease inhibitor, doxycycline, which directly inhibits MMPs and the tumour necrosis factor-α (TNF-α) converting enzyme and indirectly inhibits elastase by preventing degradation of α-1 protease inhibitor by MMPs. It also selectively reduces the synthesis of nitric oxide synthase, reducing levels of nitric oxide. In a pilot study, daily treatment with topical doxycycline improved healing of chronic diabetic foot ulcers, perhaps by altering the molecular environment of the chronic wound towards an acute healing wound (55).

THE FUTURE OF TIME

To date, wound bed preparation and the TIME clinical tool have focused solely on the management of chronic wounds; however, plastic surgeons and burns surgeons are also dealing with acute wounds that could benefit from wound bed preparation concepts. Many traumatic wounds can be considered chronic if recovery is not optimal. Burns can be considered chronic if scarring remains a problem for the patient. Surgical wounds could be chronic if they become infected.

The management of chronic wounds used to be based on models derived from knowledge of acute wounds. The concept of wound bed preparation has been largely responsible for freeing the management of chronic wounds from the traditional approach based on acute wounds. Now it seems as if the tables could be turned: many wounds that fall into the traditional classification of 'acute' could be amenable to management with the wound bed preparation concept.

It is also perhaps time to apply TIME as a clinical tool to evaluate emerging technologies in wound management and wound assessment. This is an exciting period; greater understanding of the science behind chronic and acute wounds, coupled with innovative solutions in wound care, is providing greater opportunities for us to provide a definitive evaluation of new treatments.

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