TECHNOLOGY UPDATE:
Wound bed preparation revisited

The concepts of wound bed preparation and TIME were created in 2003 to help clinicians identify the key barriers to healing in individual patient's wounds and to design treatment strategies to correct them. Studies showed that educating wound care providers on the principles of wound bed preparation and implementing TIME-based treatments as the standard for wound care significantly improved the knowledge levels of wound care providers and resulted in improved healing. Since 2003, the science of wound bed preparation has advanced in several important areas and new technologies have been developed, which are improving the effectiveness of TIME-based treatments.


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INTRODUCTION

Normal healing of skin wounds proceeds through four sequential phases (haemostasis, inflammation, repair, and remodelling) and results in a scar that repairs the damaged tissue structures adequately enough to enable the skin to maintain its major functions[1].

Unfortunately, some acute wounds fail to progress through all four phases of healing and become stalled at some point in the sequence, resulting in acute wounds becoming chronic. Most wound care providers are eventually confronted by a wound that fails to heal despite their best efforts to identify the factors impairing healing and design a treatment regimen that creates an optimal healing environment for that patient's wound.

WOUND BED PREPARATION

In the 1990s, the knowledge base around the molecular and cellular regulation of normal wound healing was rapidly expanding[2]. In addition, major discoveries were being made about abnormal parameters of molecular, cellular, and microbial environments of chronic wounds[2].

In 2003 a group of 10 physicians, nurses, and basic scientists met to generate a simple framework of key clinical assessments and treatment options that would identify and remove/correct the barriers to healing in most chronic wounds[3-6]. The result was the integrated concept of wound bed preparation and the acronym TIME, which provided a structured approach to wound management[6].

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ORIGINAL SCIENCE OF WOUND BED PREPARATION AND NEW ADVANCES

T — tissue

Debridement or removal of devitalised or non-functional tissue (fibrous scar or callous), which was not optimal repair tissue was generally recognised as beneficial for healing.

However, frequent debridement was not fully recognised as a major factor in enhancing healing of chronic wounds until a retrospective analysis of patients in a randomised controlled trial of growth factor therapy (platelet-derived growth factor [PDGF]) showed an enormous improvement in healing for diabetic foot ulcers that had received both standard care and growth factor therapy[7].

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This led to the first important component of wound bed preparation — TISSUE — which formed the 'T' of the TIME acronym. More recent retrospective analysis of large randomised pivotal clinical trials of topical wound treatments found centres where patients were debrided more frequently and which were associated with higher rates of wound closure for both chronic venous leg ulcers and diabetic foot ulcers[8].

Biofilms

As described in more detail in the next section, recent data has revealed that wound debridement plays a very important role in reducing the levels of bacterial biofilms, which are tightly attached to components of the extracellular matrix of chronic wound beds, to the surfaces of bones (osteomyelitis), or to the surfaces of orthopaedic implants[9]. Thus, debridement (mechanical or surgical) of devitalised tissues and bacterial biofilms has become a 'must-do' component of wound bed preparation, which is essential for effective management of chronic wounds. Recent advances have also further emphasised that wound debridement is a vital component of wound bed preparation[10]. This led some groups to propose the acronym of DIME to emphasise the benefit of frequent wound debridement.

Infection/inflammation — I

It had been recognised for centuries that infection and excessive inflammation could impair healing and, prior to the 1990s, some general knowledge existed about how this took place. For example, it was known that many bacteria synthesise exotoxin and endotoxin molecules that were toxic to wound cells.

However, in the 1990s more thorough biochemical analyses of acute and chronic wound fluids began to discover major differences in key molecular regulators of wound healing, especially the elevated levels of proteases (matrix metalloproteinases [MMPs]) and neutrophil elastase[11,12]. The persistently elevated levels of proteolytic activity in chronic wound fluids were linked to the destruction of essential growth factors, their receptors and extracellular matrix proteins[13]. Furthermore, healing of chronic wounds was found to be depressed in wounds that had high levels of MMP activity[14]. Clearly, reduction of infection and inflammation was a major concept that needed to be incorporated into wound bed preparation[15].

This increased understanding of the link between infection and inflammation and elevated levels of proteases in chronic wound beds led to the eventual development of dressings that contain collagen fibres. These fibres serve as 'sacrificial substrates' that are then 'chewed up' (degraded) by the elevated proteases in chronic wound fluids, which dramatically reduces the proteolytic damage to proteins that are essential for healing like growth factors, receptors and extracellular matrix proteins in the wound bed[16].

Complementing the development of dressings that reduce protease activities is the recent development of rapid, point-of-care detectors that assess the levels of active MMPs in wound fluids. Even more advanced rapid point-of-care detectors that can simultaneously measure multiple biomarkers of healing in wound fluids or serum are currently under development.

Another recent discovery that reinforced the importance of limiting infection and inflammation in wound beds was the discovery that a majority (~60%) of chronic wounds contained bacterial biofilms[17]. Bacteria in mature biofilm communities are extremely tolerant to antibodies and reactive oxygen species (ROS) generated by inflammatory cells, as well as to systemic antibiotics and topical antimicrobial agents, including silver and polyhexamethylene biguanide (PHMB, which normally kill planktonic bacteria (single cells) very effectively[18]. Thus, removing mature biofilms that are tightly attached to wound bed components by debridement is the best option to rapidly reduce biofilms in chronic wounds.

However, clinical studies show that biofilms can fully reform within 48–72 hours after effective debridement of chronic wounds if effective bacterial barrier dressings are not applied straightaway[19].

Moisture Balance — M

Establishing the optimal balance of moisture in the wound bed has dramatic effects on the healing of open wounds, yet it is one of the most challenging aspects of TIME for clinicians to physically manage. This is because the amount of exudate produced by wounds can change substantially over a few days and it has a significant impact on patients' well being and quality of life.

Clinicians using the TIME framework are more likely to understand the need to address the underlying cause of the problem[20], for example, a clinician trained in the principles of wound bed preparation and TIME is more likely to

Page Points

1. *Increased understanding of the link between infection and inflammation and elevated levels of proteases in chronic wound beds led to the eventual development of dressings that contain collagen fibres*
2. *Another recent discovery that reinforced the importance of limiting infection and inflammation in wound beds was the discovery that a majority (~60%) of chronic wounds contained bacterial biofilms*
3. *Complementing the development of dressings that reduce protease activities is the recent development of rapid, point-of-care detectors that assess the levels of active MMPs in wound fluids*

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Page Points

1. *Observing a healthy sheet of epithelial cells migrating from the edge of a chronic wound is probably the most sensitive indicator of when the three other components of TIME have been properly addressed*
2. *Epithelial cells cannot proliferate and migrate over a layer of fibrinous slough that has not been properly debrided*
3. *Moisture levels must be optimal or maceration will develop in sheets of non-keratinised epithelial cells and disrupt their migration*

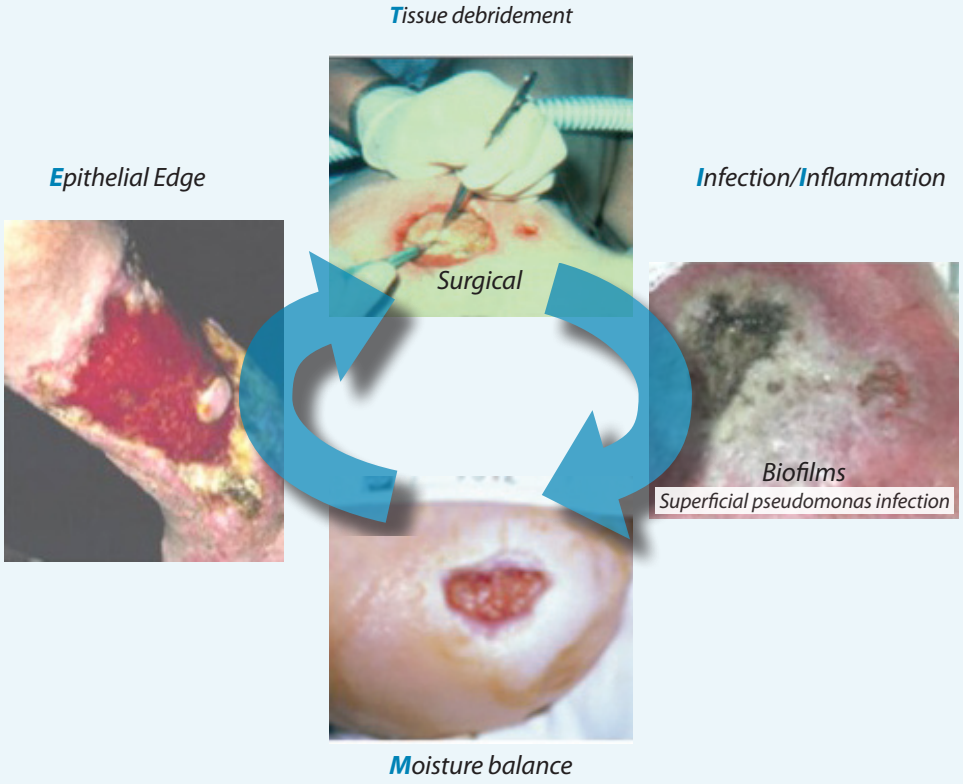

Figure 1: Wound Bed Preparation and TIME.

understand the use of compression in exuding leg ulcers with a venous component[21,22]. Additionally, he or she would be more likely to accurately assess and describe exudate levels.

Edge of the Wound/Epithelial Cell Migration — E

Observing a healthy sheet of epithelial cells migrating from the edge of a chronic wound is probably the most sensitive indicator of when the three other components of TIME have been properly addressed.

Epithelial cells cannot proliferate and migrate over a layer of fibrinous slough that has not been properly debrided[23]. Inflammation must be reduced so that protease levels can drop to low levels and not destroy the critical growth factors and extracellular matrix proteins that epithelial cells require to proliferate and migrate.

Moisture levels must be optimal or maceration will develop in sheets of non-keratinised epithelial cells and disrupt their migration. In addition, fibroblasts and epithelial cells in wounds that have remained chronic for many months or even years frequently display a 'senescent phenotype', which is evidenced by the cells' decreased proliferation and migration in response to growth factors, even when placed in ideal conditions in a laboratory culture dish[24].

The 'E' in the TIME framework is not always well understood by clinicians. This may be because the cellular environment cannot be assessed by clinical observation alone, and clinicians may have a poor understanding of the role of MMPs and the impact of cell senescence. However, an educational programme utilising the TIME framework has been shown to improve knowledge and practice in this area, ensuring patients who fail to heal in an expected time frame are referred to specialist services and have access to advanced therapies[22].

Regular wound evaluation and measurement is an essential element of implementing the 'E' element of the TIME framework so that non-healing wounds can be identified and treated in a timely manner.

WOUND BED PREPARATION AND TIME IN ACUTE WOUNDS

Although wound bed preparation and TIME was initially developed to target chronic wounds, it

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Page Points

1. *Although wound bed preparation and TIME was initially developed to target chronic wounds, it has also been used by clinicians caring for acute wounds*
2. *Many burn surgeons have been practising key principles of wound bed preparation and TIME since the 1970s*
3. *The concept of wound bed preparation and the TIME framework has gained international recognition as a framework that can provide a structured approach to wound management*

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has also been used by clinicians caring for acute wounds. Indeed, many burn surgeons have been practising key principles of wound bed preparation and TIME since the 1970s, when early excision (debridement) of full thickness and partial thickness burns was reported to reduce infection rates and improve survival better than conservative management using topical antimicrobials plus excision in the second or third week[25, 26]. However, it is reassuring that similar approaches and objectives are being used to optimise the molecular and cellular status needed for the healing of both large acute burn wounds and chronic wounds.

RECENT IMPACT ON WOUND CARE PRACTICE

The concept of wound bed preparation and the TIME framework has gained international recognition as a framework that can provide a structured approach to wound management. The concept focuses the clinician on optimising conditions at the wound bed so as to encourage normal endogenous healing[3,6]. The concept has become an established framework for the assessment and management of wounds and is commonly used as a tool for wound care education and training[22]. It offers the potential to improve the lives of people with intractable wounds and to empower clinicians to effectively manage complex wounds.

Even though the principles of wound bed preparation and TIME have evolved to incorporate new concepts revealed by basic and clinical research, the core principles have remained viable because they are based on biological processes that are fundamental and essential for wound healing. The next 10 years will see more exciting advancements in the translation of basic research into clinical treatments, however, TIME is flexible and will adapt and incorporate important new factors that influence healing of acute and chronic wounds [*Fig 1*].

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