Extending the TIME concept: what have we learned in the past 10 years?*

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ABSTRACT

The TIME acronym (tissue, infection/inflammation, moisture balance and edge of wound) was first developed more than 10 years ago, by an international group of wound healing experts, to provide a framework for a structured approach to wound bed preparation; a basis for optimising the management of open chronic wounds healing by secondary intention. However, it should be recognised that the TIME principles are only a part of the systematic and holistic evaluation of each patient at every wound assessment. This review, prepared by the International Wound Infection Institute, examines how new data and evidence generated in the intervening decade affects the original concepts of TIME, and how it is translated into current best practice. Four developments stand out: recognition of the importance of biofilms (and the need for a simple diagnostic), use of negative pressure wound therapy (NPWT), evolution of topical antiseptic therapy as dressings and for wound lavage (notably, silver and polyhexamethylene biguanide) and expanded insight of the role of molecular biological processes in chronic wounds (with emerging diagnostics and theranostics). *Tissue:* a major advance has been the recognition of the value of repetitive and maintenance debridement and wound cleansing, both in time-honoured and novel methods (notably using NPWT and hydrosurgery). *Infection/inflammation:* clinical recognition of infection (and non infective causes of persisting inflammation) is critical. The concept of a bacterial continuum through contamination, colonisation and infection is now widely accepted, together with the understanding of biofilm presence. There has been a return to topical antiseptics to control bioburden in wounds, emphasised by the awareness of increasing antibiotic resistance. *Moisture:* the relevance of excessive or insufficient wound exudate and its molecular components has led to the development and use of a wide range of dressings to regulate moisture balance, and to protect peri-wound skin, and optimise healing. *Edge of wound:* several treatment modalities are being investigated and introduced to improve epithelial advancement, which can be regarded as the clearest sign of wound healing. The TIME principle remains relevant 10 years on, with continuing important developments that incorporate new evidence for wound care.

Key words: Chronic wounds • Debridement • Infection • Inflammation • Moisture balance • TIME • Wound bed preparation

INTRODUCTION

The TIME acronym was first developed more than 10 years ago, by an international group of wound healing experts, to provide a framework for a structured approach to wound bed preparation (1). This concept was adopted from a principle used in plastic surgery to ensure optimal preparation of a recipient

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wound bed before split thickness skin grafting, and which was deemed to be a relevant framework for optimising the management of open chronic wounds healing by secondary intention. The framework was therefore termed 'wound bed preparation' and was subsequently published in 2003 by Schultz *et al*. (1). Since then the TIME acronym has been widely used as a practical guide for the assessment and management of chronic wounds. The clinical observations and interventions relating to wound bed preparation are grouped into four areas, all of which need to be addressed at each wound assessment:

- *Tissue:* assessment and debridement of non viable or foreign material (including host necrotic tissue, adherent dressing material, multiple organism-related biofilm or slough, exudate and debris) on the surface of the wound.
- *Infection/inflammation:* assessment of the aetiology of each wound, need for topical antiseptic and/or systemic antibiotic use to control infection and management of inappropriate inflammation unrelated to infection.
- *Moisture imbalance:* assessment of the aetiology and management of wound exudate.
- *Edge of wound:* assessment of non advancing or undermined wound edges (and state of the surrounding skin).

The TIME acronym was first presented at the 2003 annual meeting of the European Wound Management Association and has since been cited frequently in wound management papers, guidelines, protocols and consensus documents, in addition to being included in several other formats such as practical teaching aids and product formulary tools. Although certain aspects of the TIME acronym have been considered by some to be problematic (which are discussed later), it has generally been found to be a useful tool. Nevertheless, the TIME principles should always be considered as part of a systematic and holistic evaluation of the patient and their healing environment (Figure 1).

Since the TIME acronym was developed, there have been several developments in wound healing science, notably in the fields of molecular and biological research, and in the development, introduction and use of new wound management therapies. Four developments stand out:

- Recognition of the presence of biofilms in chronic wounds has increased exponentially. Although still the source of much debate and discussion, biofilms are now known to have a significant negative influence in chronic wounds, and the management and eradication of biofilms is an integral part of wound healing.
- Increasing use of negative pressure wound therapy (NPWT), which has had an expanding influence in the treatment of several wound types, including acute surgical wounds as well as chronic wounds.
- Evolution of a number of topical antimicrobial treatments (particularly silver and other antiseptic dressings).
- Expanded insight into the molecular biology of wounds and the role of proteases and pro-inflammatory markers in chronic wounds, which has led to the continuing emergence of a range of diagnostic and theranostic devices.

In response to these developments and a decade of new evidence found in the literature, the International Wound Infection Institute has re-examined the TIME acronym and the principles of wound bed preparation to determine its validity for current best practice. The original table from the 2003 publication (1) has been evaluated in the context of these new developments, and a new version has been produced, detailing important developments that affect the principles of TIME.

TIME – TISSUE

Over the past decade, there have been considerable developments in wound care technology; in particular, the devices or therapies used for wound debridement, such as low-frequency ultrasound, hydrosurgery devices, larvae and enzymatic agents. Furthermore, there is increased understanding of the role that debridement plays in the treatment of wound bioburden and infection, biofilm management, and subsequent maintenance of moisture balance.

Debridement

Necrotic, non viable tissue and excessively colonised, multiple organism-related biofilm

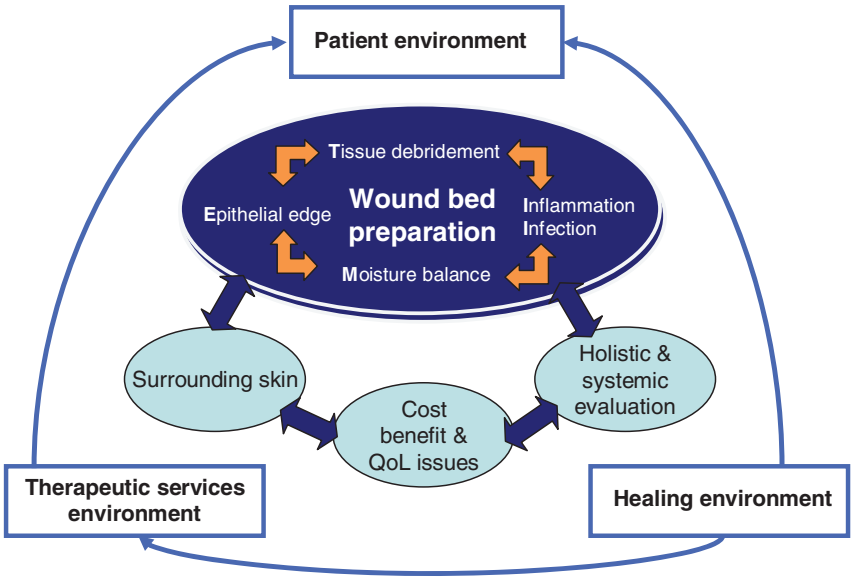

Figure 1. The TIME concept as part of the overall patient evaluation (created by David Leaper & Dianne Smith, with thanks to Caroline Dowsett for the original concept of the Care Cycle).

or slough, exudate and debris are common in chronic non healing wounds and are known to delay healing, provide a focus for infection, exacerbate the inflammatory response and impede optimal progression of wound granulation, contraction and epithelialisation. The removal of this material is therefore considered to be beneficial in stimulating healthy tissue to heal (2–4). The methods of debridement are summarised in Table 1 (5–11).

A number of guidelines and recommendations on wound bed preparation have been published following publication of the first concept of TIME. The Debridement Performance Index was published in 2002 and was shown to be an independent predictor of successful wound closure. It assesses callus removal, undermining of the wound edges and wound bed necrotic tissue (12). A wound bed score (WBS) system has been developed (13), which provides a more general assessment of the wound and wound bed preparation. It scores the following clinical parameters (from 0 to 2): healing edges (wound edge effect), presence of eschar, greatest wound depth/granulation tissue, amount of exudate, oedema, peri-wound skin inflammation, peri-wound callus and/or fibrosis, and presence of a pink/red wound bed. A total score of 16 can be achieved, and a significantly higher WBS can be expected in wounds that go on to achieve full closure, than in those that fail to heal.

Recommendations by another expert panel (14) propose the use of maintenance-debridement for removal of tissue in the wound bed when it is colonised with an excessive bacterial burden. The aim is to help maintain the wound in a healing mode, and it is recommended that maintenance-debridement should be performed if the wound is not showing evidence of closure – even if the wound bed appears clinically 'healthy'.

A list of top tips for wound debridement (5) recommends that specified procedures and principles be adhered to when undertaking commonly used methods of debridement (Box 1). Before beginning any debridement procedure, the clinical practitioner is encouraged to ensure that the patient understands the procedure, and the patient's consent should be obtained.

Wound Cleansing

Two recent Cochrane reviews have summarised methods that are used for wound cleansing. The first reviewed wound cleansing for pressure ulcers, and concluded that there is limited evidence to support the use of a saline spray containing aloe vera, silver chloride and decyl glucoside in these wounds, but could find no strong evidence to support the use of any particular solution or technique for cleansing pressure ulcers (15). The second review concluded that there is no evidence that using tap

Table 1 Methods of debridement

Type of debridement	Methods used
Autolytic debridement ● Moistens necrotic tissue, allowing degradation by host enzymes (2,5)	Occlusive or semi-occlusive dressings (i.e. hydrocolloids) or hydrogels (2,5,6) Hypertonic saline and honey, dressings promote autolytic debridement by osmosis (7) Polyacrylate, activated by Ringer's solution (8) Some antiseptics (silver, honey and iodine-based products) can also be used as autolytic debriding agents
Enzymatic debridement ● Frequent dressing changes needed ● Slow but specific ● May be used with other debridement strategies	*Collagenase/papain:* not available worldwide (papain has been discontinued, as have streptokinase/streptodornase & fibrinolysin desoxyribonuclease) (9,10)
Mechanical debridement (5) ● Non specific but gives fast results ● Can be painful & harm viable tissue	Hydrosurgery or wound cleansing debridement – wound cleansing 4–14 psi Hydrosurgical 15 000 psi (11) Whirlpool debridement Recently developed debriding pads with monofilaments which allegedly retain dead tissue and bacteria Ultrasound debridement (5): Two types: contact and non contact Ultrasound probe – agitates the wound bed directly; works by cavitation and acoustic streaming Atomised saline – gas-filled bubbles explode at the wound bed lifting necrotic tissue and bacterial cells
Larval (maggot) therapy (5) ● Selective microdebridement	*Lucilia sericata*, *Phaenicia sericata* and *Lucilia cuprina* used
Sharp debridement (5) ● Not selective ● Risks of bleeding & tissue damage	For removal of necrotic/septic tissue using scalpel & scissors
Surgical debridement (5) ● Surgeon or advanced practitioner ● Not selective ● Risks of bleeding & tissue damage	For large-scale removal of necrotic/septic tissue using scalpel & scissors – by a skilled practitioner only
Chemical debridement	Antiseptics (octenidine, silver, povidone iodine and chlorhexidine, PHMB) Older debridement agents can be painful & have toxic effects on healthy tissue, but can also be effective when used for limited periods of time

water to clean a wound increases the risk of wound infection, and that there is no strong evidence to suggest that wound cleansing decreases infection or promotes healing (16). This review was updated in 2012 (17), but no new studies were identified as eligible for inclusion. However, in this update, the authors concluded that there is some evidence that using potable tap water to clean a wound may reduce infection, and that it is likely to be as safe as sterile water or saline. Nonetheless, caution should be exercised in the use of tap water in immune-compromised patients, particularly if the water might be non potable (18). The use of non cytotoxic antiseptic irrigants for wound cleansing is widely practiced but the evidence base for their use is weak and requires further research.

Negative pressure wound therapy

The use of NPWT, or vacuum-assisted wound therapy, has become increasingly prominent in wound management. Negative pressure, when applied to the wound via a sealed foam or gauze dressing, facilitates wound drainage, and reduces oedema and the bioburden of microorganisms, while increasing wound perfusion. Recent developments have revealed

Box 1

TOP TIPS FOR DEBRIDEMENT (5)

- Environment
  - Ensure that the room chosen for treatment is suitable, with adequate disposal facilities
  - The room should include privacy, adequate lighting and positioning capacity
  - Close doors and windows to prevent cross-contamination
- Basic equipment should be provided, for example, scalpel, forceps, curette, sharp scissors
- Wound inspection
  - Carry out a thorough inspection of the wound bed
  - Focus on the material in the wound bed that is to be removed
  - Ensure that no structures such as ligaments or blood vessels are involved with the tissue to be removed
  - Consider patient and wound condition plus goal of treatment
  - Ensure that the appropriate debridement method is selected for the volume of tissue to be removed
- Competency
  - Ensure that the debridement method selected falls within the clinician's training and competency

that NPWT may loosen slough and necrosis, and facilitate sharp debridement (19), although caution is recommended when tissue is more than 20% devitalised. The combination of NPWT with several other debridement methods has been demonstrated to support TIME principles, as it expedites removal of exudate and infective material and promotes granulation tissue formation, contraction and epithelialisation (20).

TIME – Tissue. What has changed? The original TIME table indicated that non viable tissue, multiple organism-related biofilm or slough, exudate and debris signifies a defective wound bed that needs debridement to restore successful wound healing. This principle has not changed, although some of the practices used to facilitate this have changed over the intervening years. Advances in debridement technology such as low-frequency ultrasound, hydrosurgery and add-on use of NPWT devices with existing technology have led to more efficacious outcomes, as have advances in traditional non surgical debridement methods such as larval and enzymatic debridement. The practice of repetitive or maintenance-debridement for the management of static chronic wounds has also improved outcomes.

TIME – INFECTION/INFLAMMATION

Inflammation is a physiological response to wounding and is required for wound healing to progress. However, excessive or inappropriate inflammation, often in the presence of infection, may have serious consequences for the patient. Chronicity or the stalling of healing in wounds may be due to persistent inflammation (2,18). Wounds that do not progress beyond an inflammatory phase often demonstrate an increased activity of proteases such as matrix metalloproteinases (MMPs) and elastase, as well as the persistence of inflammatory cells. Prolonged degradation of the extracellular matrix and suppression of growth factors may also hinder wound healing. The presence of wound biofilm may further inhibit downregulation of the immune response, causing systemic debilitation, unless adequately disrupted and treated (21). Elimination or reduction of prolonged inflammation revitalises tissue healing, reduces exudate and is usually associated with a reduction in bioburden. It is important that the clinician can confidently distinguish signs and symptoms of inflammation related to normal physiological healing from those related to excessive inflammation caused by underlying adverse aetiologies and infection. The clinician should, however, be aware that inflammation may also be the result of a number of non infective, autoimmune diseases, such as systemic lupus erythematosus, rheumatoid arthritis, vasculitis or scleroderma, or due to an inflammatory condition such as inflammatory bowel disease where pyoderma gangrenosum may result. Their recognition and management is beyond the scope of this article.

The signs and symptoms of infection may be subtle or non specific (Box 2) – so care should be taken to ensure that they are recognised (22). All wounds are potentially subject to exogenous and endogenous microbial contamination. The microbial bioburden in a wound can range from contamination, colonisation or critical colonisation and ultimately to local and systemic infection if not appropriately controlled (Table 2). It has been suggested that this progression is also influenced by the presence of maturing bacterial biofilm in the wound (23).

The clinician needs to be aware of the signs and symptoms of localised, spreading (such as cellulitis and lymphangitis) and systemic infection. The classic signs of infection are usually obvious in acute or surgical wounds in otherwise healthy patients. When patients are immunosuppressed or malnourished, however, or have comorbidities such as diabetes mellitus, anaemia, renal or hepatic impairment, malignancy, rheumatoid arthritis, morbid obesity or arterial, cardiac and respiratory disease, these signs of infection may be more subtle. An increase in pain and wound size in chronic wounds are probably the two most useful predictors (24). The decision to use systemic or topical antibiotics should be carefully considered in light of the risk of antimicrobial resistance, but topical antiseptic dressings might prove to be valuable prophylactic measures in patients where infection is suspected – particularly as more recent evidence suggests that they may prevent attachment, as well as maturation, of biofilm (25).

Box 2

MADE-EASY GUIDELINE FOR SIGNS OF INFECTION IN CHRONIC WOUNDS (22)

General signs

- Malaise
- Appetite loss

Local wound signs

- Increased discharge
- Delayed healing
- Wound breakdown
- Pocketing at the base of the wound
- Epithelial bridging
- Unexpected pain or tenderness
- Friable granulation tissue
- Discolouration of the wound bed
- Abscess formation
- Malodour

Biofilms

A biofilm is a complex microbial community, consisting of bacteria embedded in a protective matrix of sugars and proteins (glycocalyx). Biofilms are known to form on the surface of medical devices and are also found in wounds (21,23,26). Biofilms provide a protective effect for the microorganisms embedded within them, improving their tolerance to the host's immune system, antimicrobials and environmental stresses. Biofilm communities interact with host tissue resulting in stable attachment, sustainable nutrition and a parasitic relationship (21,23,26,27). The bacteria in biofilms have considerable phenotypic and genotypic diversity (21).

Biofilms first form a reversible attachment to the wound surface, which may then become permanent with bacterial differentiation and further accumulation of the protective glycocalyx. Biofilm structures have been recognised in biopsies, using scanning electron and confocal microscopy, in 60% of chronic wounds and 6% of acute wounds (28). Biofilms are a major contributing factor to persistent, chronic inflammatory changes in the wound bed, and it is likely that almost all chronic wounds contain biofilm communities on at least part of the wound bed (21,23,26). They are a problem in wounds because of the chronic inflammatory response that they stimulate, which benefits the organisms in the biofilm. Mature biofilms also shed biofilm fragments, planktonic bacteria and microcolonies, which can disperse to form new biofilm colonies, with the risk of local or distant invasive infection.

The recommended treatment for managing biofilms is a combination strategy to reduce the biofilm burden and prevent it reconstituting itself. Once the biofilm has been disrupted, it reconstitutes itself via a metabolically active, growth phase of the microorganisms present and is more vulnerable to treatment agents during this stage. It is important to understand the genetics of the biofilm using molecular diagnostic methods, thereby allowing therapy to be more specifically targeted. The

Table 2 Overview of the wound infection continuum

Contamination	Bacteria do not multiply or cause clinical problems
Colonisation	Bacteria multiply but wound tissues are not damaged
Critical colonisation/localised infection	Bacteria multiply to the extent that healing is impaired & wound tissues damaged May also mean that biofilm communities are present in the wound bed
Spreading infection	Bacteria spread from wound, causing problems in nearby healthy tissue (cellulitis and erythema)
Systemic infection	Bacteria spread from wound, causing infection throughout the body (systemic inflammatory response, sepsis and organ dysfunction)

use of frequent aggressive debridement, long-duration high-dose systemic antibiotics, selective biocides and combinations of antibacterial biofilm agents are major strategies in biofilm-based wound care (Box 3) (21,23,26). There is evidence that silver-containing dressings can be useful in preventing biofilm reformation. However, their efficacy has been found to be variable, with silver-impregnated charcoal and alginate-carboxymethylcellulose-nylon dressings not being able to prevent biofilm formation (29).

It is not possible to categorically state when a wound is biofilm-free, because there is a lack of definitive clinical signs and available laboratory tests. The most likely clinical indicator is progression of healing, with reduction in exudate and slough. Standard clinical microbiology tests are not optimised to adequately measure biofilm bacteria; the most reliable method of detecting microbial biofilm is by using specialised microscopy. A simple diagnostic is eagerly awaited. The clinician's judgement is vital when deciding how to manage wounds that contain a suspected biofilm. It is important to frequently reassess the wound and also to practice a holistic approach to the patient's health to promote healing. Antibiofilm agents (such as silver, PHMB, iodine and honey dressings) are recommended for treatment of wounds containing biofilm or suspected biofilm, but wounds must be regularly assessed on a patient-by-patient basis (26).

Box 3

SUGGESTED STRATEGIES FOR REMOVAL AND PREVENTION OF BIOFILM

1. Biofilm removal
   - Physical disruption (aggressive/sharp debridement is generally agreed to be the best method of removing biofilm)
   - Regular debridement to reduce the biofilm potential for regrowth
     - Accompanied by vigorous physical cleansing (such as irrigation or ultrasound)

Some products are thought to aid physical cleansing by facilitating removal of biofilm and debris, and disturbing biofilm (for example, PHMB is thought to be effective in disrupting biofilm due to its surfactant component).

2. Prevention of biofilm reconstitution
   - Rational dressing use to prevent further wound contamination
   - Use of a topical broad-spectrum antimicrobial (silver, iodine, honey, PHMB) to kill planktonic microorganisms
     - Change to a different antimicrobial if there is a lack of progress

Are biofilms visible?

Although the existence of wound biofilms is accepted, there is still much discussion about their visibility to the naked eye (30). It has been suggested that the opaque material seen on chronic wounds may be biofilm that reforms after removal, and may indicate the presence of critical colonisation that precedes overt infection. Wound biofilm, if it is visible to the naked eye, may therefore also represent an assessment tool in managing chronic wounds (31). However, this evidence is entirely conjectural and biofilm will continue to need confocal or scanning electron microscopy or molecular technologies for definition. The appeal for a diagnostic is clear.

Managing wound colonisation with microorganisms

Prudent use of modern antiseptic-impregnated dressings or irrigants may reduce microorganisms on the wound surface and in biofilms. The concerns relating to traditional antiseptics and their toxicity to host tissue have been widely discussed (32), but the prevailing clinical view is that it is appropriate to use most contemporary antiseptic solutions and dressings, in accordance with the manufacturer's instructions or local protocols.

Antimicrobials

The term 'antimicrobial' is used broadly to describe disinfectants, antiseptics and antibiotics. The main reason for using antimicrobials in wound care is to prevent or treat infection, and thereby facilitate the wound healing process. Unlike antibiotics, disinfectants and antiseptics have broad-spectrum antimicrobial activity, and microbial resistance is rare, particularly in human pathogens. However, antibiotics have a selective antimicrobial activity, and microbial resistance to antibiotics is a serious concern (33–35). Colonisation and infection in chronic wounds are usually due to a mixed population of microorganisms. To select the most appropriate antimicrobial therapy, accurate diagnosis of the infecting organisms is vital, especially when antibiotics are being used, as microbial sensitivities can also be used to guide the best therapy choice. Diagnosis can be performed by tissue biopsy or by swab culture; in particular, high accuracy has been seen when using the Levine technique (36,37).

Microbial resistance

Microbial resistance to antibiotics is of increasing concern (34). The major difference between antibiotics and antiseptics is that antibiotics work more specifically, allowing bacteria an opportunity to mutate and form resistance, whereas antiseptics work at all levels of cell biology, so bacterial resistance is less likely to occur. The activity of topical antimicrobial agents has been tested against multi-drug resistant (MDR) bacteria isolated from burn wounds. No susceptibility of topical antimicrobial agents was found to be associated with MDR isolates; mafenide acetate was the most effective agent against Gram-negative bacteria, and silver also had moderate efficacy (38). No silver resistance has been found in a collection of bacterial strains tested from 349 clinical and 170 non clinical isolates from humans, meat and production animals (39). The use of topical antibiotics is not generally recommended as they further increase the induction of resistance and allergy.

Topical antiseptic dressings are recommended for the following (22):

- Prevention of infection in patients who are considered to be at an increased risk.
- Treatment of localised wound infection.
- Local treatment of wound infection in cases of local spreading or systemic wound infection, in conjunction with systemic antibiotics.

Use of antiseptic dressings should be continued for 14 days (the '2-week rule') and the need for further topical antimicrobial therapy should then be reassessed (40). Use of antiseptic dressings should be considered for those patients at high risk of infection, or for the early treatment of locally infected wounds (cellulitis, lymphangitis or erythema), and discontinued if these signs of spreading or local infection resolve. However, if signs of infection persist, use of a systemic antibiotic is warranted and should be prescribed in accordance with microbiological wound swab culture or blood culture results and sensitivities. Empirical treatment with broad-spectrum antibiotics may be commenced following clinical diagnosis, but specific antibiotic regimens should be prescribed once the infecting organisms and their antibiotic sensitivities have been identified. Concurrent use of topical antiseptic dressings and debridement may reduce the local wound bioburden.

Silver dressings

Silver has a long history of use as a topical antimicrobial in wound care – from historical application directly to wounds in its solid form to the modern day application of silver salt solutions such as silver nitrate for wound cleansing and creams or ointments such as silver sulfadiazine (SSD) (40). Metallic silver (Ag^0) is relatively inert, but when exposed to moisture, highly reactive silver ions (Ag^+) are released, which avidly bind to tissue proteins and cause structural changes in bacterial cell walls and intracellular and nuclear

membranes. This antimicrobial action, enacted through the ionised Ag^+ ion, forms strong complexes with essential bacterial metabolic pathways, rendering them unworkable and leading to microbial death.

Several silver-containing dressings are available to manage wound bioburden and are available in a number of different forms:

- *Elemental:* silver metal, nanocrystalline silver.
- *Inorganic:* silver oxide, silver phosphate, silver chloride, silver sulphate, silver-calcium-sodium phosphate, silver zirconium compound, SSD.
- *Organic:* silver-zinc allantoinate, silver alginate, silver carboxymethylcellulose.

Silver is incorporated into dressings either as a coating, within the dressing itself, as part of the dressing, or as a combination of these agents. Dressings incorporating nanocrystalline technology donate a high sustained release of Ag^+ ions at the wound surface. Silver salts are associated with minimal toxicity when applied topically, and there have been no substantiated clinical reports of silver toxicity. Nanocrystalline silver dressings have been associated with improved wound healing (41,42). In a clinical study, nanocrystalline silver dressings, under four-layer compression bandages, promoted healing in patients with recalcitrant chronic venous leg ulcers (VLUs). The VLUs were not clinically infected but treatment was found to reduce bioburden and neutrophil-related inflammation (43). Nanocrystalline silver dressings have also been found to promote healing with reduced levels of MMPs, in a porcine model of wound infection (44).

Silver alginate dressings have been revealed to have broad antimicrobial activity against wound isolates grown in both the biofilm and non biofilm states (45), and to rapidly decrease bacterial viability with >90% of the bacterial and yeast cells, on the silver alginate dressing tested, being no longer viable after 16 hours (46).

However, not all research has been supportive of silver dressing use. The multicentre, prospective, randomised controlled VULCAN study examined the efficacy and cost-effectiveness of antimicrobial silver dressings in treating VLUs by comparing silver dressings with non antimicrobial, low-adherent control dressings. No statistically significant difference in healing was found between the two dressing types, and it was concluded that there was a lack of benefit from silver dressings (47). Following this, a review article expressed the opinion that the evidence base supporting silver dressing use was weak and that it was difficult to justify the amount spent by the NHS on silver dressings (48). A negative impact on the perception and use of silver dressings resulted, leading to restrictions in their availability for clinical use (40). Further reviews have asserted that the VULCAN study has a number of flaws, the main one being that the silver dressings were not used as recommended (49–51). Others have commented that antimicrobial dressings, including silver, are key components of the management of patients with wound infection and that failure to use these products in appropriate cases may put patients at risk (22,40).

Iodine dressings

Iodine-based preparations have a long history of use in surgery and wound care. Elemental iodine is toxic to tissues, but in its povidone iodine (PVP-I) and cadexomer iodine forms, which are both iodophores, it is not (52). There is evidence, including that from a recent Cochrane review, to suggest that wound healing rates are higher with cadexomer iodine than with standard care (52,53), and while its antimicrobial properties are well known, several studies have indicated that cadexomer iodine may potentially be effective against biofilms. *Staphylococcus aureus* and its related glycocalyx were not detected in the vicinity of cadexomer iodine beads in a mouse dermis wound model (54), and cadexomer iodine has been found to be effective against *Pseudomonas aeruginosa* biofilm in a porcine skin model (55). A further study has demonstrated that cadexomer iodine penetrated biofilms more effectively than either silver or polyhexamethylene biguanide (PHMB) (56).

PHMB dressings

The antiseptic PHMB has been in general use for more than 50 years, but has now been introduced for management of bioburden in wounds as PHMB-impregnated dressings or gels and solutions for wound irrigation. The active compound is effective in

both decreasing bacterial load and preventing bacterial penetration of the dressing, which reduces infection and prevents further infection. PHMB also appears to have low toxicity to human tissue and does not promote bacterial resistance (50,57,58). Treatment with a polyhexanide-containing biocellulose dressing has been revealed to remove bacterial burden significantly faster than silver dressings (59).

Honey

Medical-grade honey dressings are non toxic, 'natural' and easy to use; they are available as hydrocolloid, alginate, synthetic tulle or gel-based dressings and promote autolytic debridement by osmosis, while maintaining a moist wound environment (8). Patients with VLUs have been revealed to have increased healing, lower infection and more effective desloughing when treated with honey dressings compared with controls (60). Application of honey also reduces or removes wound malodour (8,61). Honey is hygroscopic, can dehydrate bacteria, and its high sugar content causes inhibition of bacterial growth with improvement of wound healing through anti-inflammatory effects and reduction in oedema and wound exudate (62). There is also experimental evidence that honey may disrupt or prevent biofilm formation (8,63,64).

Surfactants

Surfactants lower the surface tension of a liquid, allowing it to spread more easily; they also lower the interfacial tension between two liquids. Surfactant action in wounds facilitates the separation of loose, non viable material on the wound surface and has potential for preventing and managing biofilm. Several combinations of surfactant and products with antimicrobial activity have been developed (PHMB and undecylenamidopropyl betaine; octenidine dihydrochloride and phenoxyethanol; octenidine and ethylhexylglycerin) and are used clinically for skin disinfection (65,66).

TIME – Infection and inflammation. What has changed? The original TIME table recommended that the removal of infected foci in the wound bed lowers inflammatory cytokines and protease activity and helps create bacterial balance and control of inflammation. This remains the case 10 years on, but it is now the type and behaviour of microorganisms in the wound, and the options for their control that is of particular interest. When biofilm microorganisms behave in a different way to their planktonic phenotype, the action of certain topical antimicrobial agents such as PHMB, iodine, silver and honey needs to be better understood, so that these agents may be effectively used in conjunction with debridement to control wound biofilm.

TIME – MOISTURE

Excessive or insufficient exudate production may adversely affect healing. Excessive exudate and odour may significantly affect the patient's quality of life. Exudate characteristics are important, and any alteration such as increasing bioburden or autolysis of necrotic tissue may indicate a change in wound status. Updated recommendations for exudate management focus on the selection of appropriate dressings or devices (18,67).

There are differences in composition between acute and chronic wound fluid. Acute wound fluid is rich in leukocytes and nutrients, whereas chronic wound fluid has high levels of proteases and pro-inflammatory cytokines and elevated levels of MMPs, which decrease as healing progresses (68,69). The increased proteolytic activity of chronic wound exudate is thought to inhibit healing by damaging the wound bed, degrading the extracellular matrix and aggravating the integrity of the peri-wound skin (67), while the high levels of cytokines promote and prolong the chronic inflammatory response seen in these wounds (69).

Appropriate wound moisture is required for the action of growth factors, cytokines and cell migration – too much exudate can cause damage to the surrounding skin, too little can inhibit cellular activities and lead to eschar formation, which inhibits wound healing. Biofilm formation has also been linked to poor exudate management (31), based on the reasoning that wound exudate is a potentially important nutrient source for wound biofilm. Rapid removal of wound exudate has been revealed to facilitate wound healing, although not all patients showed a reduction in wound bacteria (70).

The volume and viscosity of exudate should be considered when choosing a dressing,

as some dressings are better for managing excessive exudate, while others are better for managing viscous exudate. The most widely used methods for managing excessive exudate are absorbent dressings and topical NPWT. Dressings should maintain an appropriate moisture balance and avoid maceration or desiccation of the wound bed. Improved healing was found in a pooled analysis of three trials following the use of hydrogel dressings compared with gauze as standard care in diabetic foot ulcers (DFUs). It is not clear, however, whether this was achieved as a result of autolytic debridement or hydration of the wound bed (71). The ideal dressing for patient comfort and convenience is one that is not bulky, not painful to change and reduces the number of dressing changes needed. It should also be effective therapeutically, and in terms of cost, should prevent leakage and maceration and be easy to apply and remove (69). It is also important to protect the peri-wound skin around chronic wounds; the increased proteolytic activity of chronic wound exudate can cause skin damage, and excess moisture may cause maceration and erosion. Dressing sensitivity or allergy is also an important consideration, and the peri-wound skin should be monitored for signs of this (67,69).

Negative pressure wound therapy

Use of NPWT is particularly valuable in optimising the 'M' element of the TIME concept, as it provides a closed moist wound healing environment in patients with highly exuding wounds. It is particularly effective in removing viscous exudate, but frequent dressing changes may be painful (67,69).

TIME – Moisture. What has changed? Excessive wound fluid severely affects patient well-being and wound healing. Exudate regulation has been the cornerstone of chronic wound management since the 1960s, with moisture balance as the goal. Over the past 10 years, the main focus has been in two core areas – developing ways to understand and improve the moisture management of dressings and the role of NPWT in removing and containing large amounts of exudate. Research into the components of wound exudates, and their relationship to wound healing and infection in particular, continues.

TIME – EDGE OF WOUND (ALSO KNOWN AS EPITHELIAL EDGE ADVANCEMENT)

The final component of the TIME acronym is probably the one that has led to the most debate with regard to what the 'E' represents and how it fits in with the other components of the TIME concept. If wound bed preparation is satisfactory, the closure of chronic wounds can be expedited by the use of split thickness skin grafts or biological skin replacements. Assessment of wound edges can indicate whether wound contraction and epithelialisation is progressing, and confirm either the effectiveness of the wound treatment being used or the need for re-evaluation. An increasing range of treatment modalities are proposed to improve wound healing and thus influence the 'edge' effect. These therapies include electromagnetic therapy (EMT), laser therapy, ultrasound therapy, systemic oxygen therapy and NPWT.

The clinician should also consider the condition of the peri-wound skin in assessing wound contraction, as dry or macerated wound edges may affect the ability of the wound to contract.

Developments in managing 'edge of wound'

Electromagnetic therapy

EMT delivers a continuous or pulsed electromagnetic field, which allegedly induces tissue healing and cell proliferation, although the exact mechanism is unclear. Pulsed EMT consists of short-duration pulses, which has the advantage of protecting tissues from damage by the heat generated by continuous fields. EMT has been used to treat VLUs, but a Cochrane review concluded that there is no high-quality evidence to support the hypothesis that EMT speeds healing in VLUs. However, the same review suggested that further studies are needed to explore the effects of EMT as an adjunct to compression therapy or in patients who cannot undergo compression therapy (72).

Laser therapy

Low-level laser therapy, such as such as helium neon (HeNe) or gallium arsenide (GaAs) gas lasers, has been used to treat wounds, based on the hypothesis that this may enhance cellular proliferation or migration. A Cochrane review of laser therapy for VLUs concluded that there

is no evidence of either benefit or no benefit from using laser therapy on VLUs (73).

Ultrasound therapy

Ultrasound therapy, generated in the megaHertz or kiloHertz range, provides mechanical energy that is thought to alter cellular activity. Until recently, megaHertz therapy was used to treat sclerotic peri-wound skin. There has been a recent shift towards use of low-frequency ultrasound in the kiloHertz range for healing in bone and tissue, which is considered to promote vascular vasodilation and debridement (74). Several types of commercial low-frequency ultrasound therapy devices are available, with differing mechanisms of action.

Systemic oxygen therapy and wound healing

Oxygen is considered to have a vitally important role in wound healing, particularly in the inflammatory and proliferative phases. A 2011 review on the role of oxygen in wound healing concludes that supplementing treatment with oxygen (either breathed by mask or hyperbaric therapy) may improve angiogenesis, reduce infection rates and facilitate improved healing (75). Further evaluation, however, is required before it can be recommended for clinical use in wound healing.

NPWT

The use of NPWT has been revealed to stimulate granulation tissue formation and wound closure (76–78). One study has demonstrated that tissue changes varied at three layers within the wound – each responding differently under NPWT. The most superficial layer developed granulation tissue, while the two deeper layers demonstrated a decreased proliferation rate and clearance of chronic inflammatory markers and oedema, with tissue stabilisation (76). NPWT has been found to lead to significantly reduced tissue infiltration of CD68+ macrophages and reduced IL-1β and TNFα expression in skin-grafted free muscle flaps. There was also a reduction in interstitial oedema formation, which improved the microcirculation and reduced tissue damage (79). A number of studies have also demonstrated effective use of NPWT in wounds that have bacterial colonisation or reveal active signs of infection (80–84). Increased evidence supports the value of NPWT in treating hard-to-heal wounds (2); when compared with advanced moist wound therapy in DFUs, a greater proportion of wounds achieved closure with NPWT (85). Amputations, secondary to DFUs, also revealed faster postoperative healing when treated with NPWT, compared with controls (86). However, a systematic review and meta-analysis of 21 studies found no clear evidence that wounds heal either better or worse with NPWT compared with conventional treatment (87), although the authors conceded that NPWT may have a positive effect on wound healing. Overall, study evidence supports improved wound closure with NPWT (78,85).

TIME – Edge of wound. What has changed? Epithelial edge advancement and an improved state of the surrounding skin (which was not discussed in the original TIME document) is the clearest sign of healing, and a 20–40% reduction in wound area after 2 and 4 weeks of treatment is seen as a reliable predictive indicator of healing (69). Various wound modalities for stimulating wound healing have been introduced; further knowledge of their role and contraindications is warranted. 'E' is also a reminder of the importance of evaluation as there is a sense that, after each specific clinical intervention (debridement, infection control or moisture management), a return to the wound should be made with an assessment of wound closure. The original TIME table supports this by suggesting that if the wound is not responding, a reassessment should be made with consideration of other adjunctive or corrective therapies.

Psychosocial issues

Patients with chronic wounds have been shown to suffer associated stress and anxiety. As well as the negative impact on patient well-being, stress and anxiety can also have a negative impact on wound healing (88). A questionnaire survey, investigating the prevalence of mood disorders among patients with acute and chronic wounds, found that pain (particularly associated with dressing changes), lack of control over treatment, and living with slow-healing chronic wounds caused stress and anxiety (88). Suggested, non pharmacological therapies for relieving pain in patients with

chronic wounds include cognitive behavioural therapy, hypnosis, acupuncture, distraction and meditation and prayer (89).

DISCUSSION

Although the major principles of the TIME wound bed preparation table remain the same, they are facilitated by many new developments (Table 3):

Tissue: non viable dead tissue and bacterial-related slough and debris

Debridement remains the quickest and most efficient method of removing these materials. Clinicians have a variety of debridement methods to choose from, depending on the individual requirements of the patient and the skill set of the practitioner. Autolytic debridement is most likely to be used in conjunction with other debridement methods, and can also be used alone if a slower, more conservative option is preferred. Newer modalities such as low-frequency ultrasound and hydrosurgical debridement may be selective, but require advanced clinician knowledge and further testing for appropriate and efficacious use. Regardless of which debridement option is chosen, healing potential and outcome goals must be determined before commencing with debridement.

Infection or inflammation

Infection and inflammation remain the major challenge to healing, particularly in chronic wounds. However, knowledge of the inflammatory process and its role in chronic wounds has increased since the TIME acronym was first developed. It is now known that reducing excessive inflammation can revitalise tissue with reduction in exudate and in the risk of infection. The understanding of biofilms – what they are and how to detect them – has improved considerably. Wound biofilm presents a clinical conundrum, and how to detect it remains a major issue; a diagnostic method for biofilm detection is required. Although a number of dressings such as silver, honey, cadexomer iodine and possibly PHMB have revealed some efficacy in disrupting biofilm, it is generally agreed that the best way to disrupt biofilm is by debridement. Once the biofilm has been disrupted, it is then possible to implement treatment with antiseptic agents, while the biofilm is more vulnerable to antimicrobials, and prevent its reformation (90). The use of antiseptic dressings and wound irrigants has been more widely reintroduced and represents another area that has revealed a great deal of growth. The increased recent use of antiseptics also probably reflects the concerns regarding antibiotic resistance, whereas concerns about microbial resistance to antiseptics appear unfounded.

Moisture imbalance

Understanding of wound moisture balance has increased, and clinicians are more aware of the importance of maintaining an appropriate level of wound moisture, as well as the differences between acute and chronic wound fluid. There are more dressings available to 'intelligently' manage exudate, and some of its contained constituents that can adversely affect wound healing. NPWT has also proved to be an increasingly valuable tool, particularly with its extension for wound management to the home environment.

Edge of wound

There have been considerable developments in the means of facilitating wound healing, with greater use of NPWT and new therapies, such as EMT, laser and ultrasound therapy. The original recommendation made by Schultz and colleagues in 2003, of a holistic approach with treatment of the whole patient, remains just as valid today. Causes of poor or delayed healing, and patient factors that might impede or facilitate healing, must be reconsidered at every assessment. What is new, however, is the raised awareness of patient concerns and the active effort to promote patients to act as advocates for their own care and concerns. One of the treatment modalities which has revealed the most development and interest since the TIME acronym was first developed is NPWT. From its introduction as a simple means of removing exudate and facilitating wound closure, it now also appears to have effects on biofilm reduction and to be effective in infected and hard-to-heal wounds. It may also facilitate wound debridement when used in combination with other debridement methods.

Using the TIME concept in practical wound care raises further questions – for example,

Table 3 Summary table of new developments within the TIME concept

Clinical observations	WBP	Developments	Factors to consider
Tissue	Debridement	New methods ● Low-frequency ultrasound ● Hydrosurgery ● Debriding wipes Advances in use of existing methods ● Larvae ● Autolytic (honey and hydrogels) ● Use of enzymes (collagenase) ● Sharp/surgical (new guidelines) ● Chemical (antiseptics, i.e. silver and PHMB) NPWT – as add-on with existing debridement methods	Use of maintenance debridement Considerations around safe practice ● Knowledge ● Skills ● Competence ● Evidence of efficacy
	Wound cleansing	Microbicidal irrigation solutions	
Infection/inflammation	Bacterial balance	Biofilm ● Improved understanding of biofilms and their role in non healing wounds ● Management – combination strategy to disrupt biofilm and prevent reconstitution (debridement and antiseptic agents) ● Detection of biofilm Use of Polymerase Chain Reaction (PCR)/pyrosequencing techniques to identify bacteria/fungi in wounds	Increased bacterial tolerance to topical/systemic agents Mixed flora living synergistically Quiescent state of some bacteria in biofilms reduces effectiveness of antibiotics Diagnostic for biofilm detection needed
	Persistent inflammation	Improved understanding of the role of persistent inflammation in chronic/stalled wounds ● Role of MMPs and other proteases (diagnostics and inhibitors) ● Role of biofilms in promoting wound inflammation	
	Managing infection/inflammation	● Increased use of antiseptic agents ● Role of nanocrystalline silver as an anti-inflammatory ● Combination of surfactants with antimicrobials – biofilm disruption ● NPWT combined with instillation of microbicidal solutions to reduce levels of planktonic and biofilm bacteria ● Alternative use of new or existing agents – for example, using nanocrystalline silver to dampen down inflammation ● Improved healing of wounds treated with custom formulations of topical antibiotics/antiseptics based on bacterial profiles	Diagnostic tests – when and how often? Point-of-care detection Review of appropriate antimicrobials Rotation of products Microbial resistance (particularly to antibiotics)

Table 3 (*Continued*)

Clinical observations	WBP	Developments	Factors to consider
Moisture	Moisture balance Exudate	Improved awareness of need to maintain appropriate moisture levels Improved understanding of exudate composition – differences between acute and chronic wound fluid ● Damaging proteolytic activity of chronic wound fluid Relationship of exudate with bacterial burden and biofilm formation Selection of appropriate dressings or devices for exudate management (i.e. new super-absorbers) Greater emphasis on moisture management NPWT – for removal and containment of large exudate volumes	Dressing selection – what do we need to consider? ● Absorption ● Retention ● Patient comfort ● Bacterial pool ● Skin sensitivity or allergy Revisiting existing therapies Alternative use of products, for example, using NPWT to splint wounds Role of diagnostics/theranostics
Edge of wound		Epithelial edge advancement Improved state of surrounding skin *Evaluation* – check whether wound is closing Use of NPWT to encourage contraction Adjunct therapies (EMT, laser, ultrasound, systemic oxygen therapy)	

how moist should a wound be? Knowledge of exudate management has improved considerably but, as discussed above, that question cannot be answered simply but depends on many factors, including the type of wound, its location and the type of exudate associated with it. Wound infection and patient comfort are also important considerations, as are other issues relating to patient needs. Clinicians have developed an increased awareness of psychosocial issues relating to wound care – chronic wounds in particular can cause patient stress and anxiety, not just in relation to pain, but in the complexities of caring for a non healing wound, and concerns about social aspects such as appearance and malodour. Clinicians, industry, research and health care organisations often focus on complete wound healing as a key outcome measure, while people living with a chronic wound may have different priorities. This criticism has also occasionally been levelled at the TIME acronym itself, focussing as it does on the wound bed, as opposed to patient-centred concerns. More emphasis may need to be undertaken within the TIME framework to encompass patient-centred concerns and promote a holistic approach to patient well-being in wound care.

The TIME acronym could be redefined from its first, assessment stage to become a second, management stage consisting of treatment, implementation, monitoring and evaluation:

i. *Treatment:* An appropriate treatment plan is important, based on the objectives of care to be achieved, and the objectives of the original TIME framework.
ii. *Implementation:* Agreed treatment plans should be implemented consistently for optimal, effective objectives with evaluation of outcomes.
iii. *Monitoring:* This should include detection of any local or systemic adverse events and ensure that clinical practice and products used achieve the best performance.
iv. *Evaluation:* All treatments should be regularly and objectively evaluated to include, for example, a wound healing curve, a validated pain assessment tool, a debridement index or other symptom measurement, and assessment of impact on quality of life.

CONCLUSION

Complete and timely wound closure is the main objective of all aspects of wound care, although this is not always possible. Chronic wounds, in particular, present a challenge to effective wound care. Since the TIME acronym was first published a decade ago, the understanding of wound bed preparation and the inflammatory and infective pathways has increased considerably, as have available treatment options. Of necessity, most clinical guidelines represent 'work in progress' because of the continuous changing and understanding of wound pathology, healing and therapeutic agents. Although the basic principles of the TIME concept have not changed greatly since its first inception, the application of these principles has expanded, with developments in knowledge and interventions for wound management. It is important to consider that, while the TIME concepts provide a valuable framework for wound assessment and management, they are also inextricably linked.

So, 10 years on – is TIME still relevant to clinical practice? Although there are many new developments in the field of wound therapy and our understanding of wounds, the basic concepts of tissue, infection/inflammation, moisture and edge of wound still remain important in guiding clinical practitioners in their approach to wound management.

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SUPPORTING INFORMATION

The following Supporting information is available for this article:

Appendix S1: Spanish translation of this article.

Additional Supporting Information may be found in the online version of this article:

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