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

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Updating TIME\textsuperscript{1}

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the TIME acronym

Aimed to describe the observable characteristics of chronic wounds within the framework of wound bed preparation

Developed by the International Advisory Board on Wound Bed Preparation
## TIME: the principles of wound bed preparation (first published 2003)^2

<table>
<thead>
<tr>
<th>Clinical observations</th>
<th>Proposed pathophysiology</th>
<th>WBP clinical actions</th>
<th>Effect of WBP actions</th>
<th>Clinical outcomes</th>
</tr>
</thead>
</table>
| **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 extracellular 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  
- anti-inflammatories | 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 |
Evidence based medicine
David Sackett

- conscientious, explicit and judicious use of current best evidence in making decisions about care of individual patients
- integrating individual clinical expertise with the best external evidence from systematic research involves:
  - evidence
  - experience
  - patients and carers
  - (and health economics?)
- critical in dressing selection
Developments over past 10 years

1. Increased understanding of the role of biofilms in chronic wounds
2. Use of devices such as negative pressure wound therapy (NPWT)
3. Topical antiseptics and their impact on biofilms (particularly silver, cadexomer iodine, PHMB, honey)
4. Advances in diagnostics, theranostics, molecular biology therapies
TIME: Tissue³-⁷

• Maintenance debridement
• Reintroduction of traditional non-surgical debridement methods (i.e. larval, enzymatic agents)
• New debridement methods (i.e. hydrosurgery and low frequency ultrasound devices)
• Use of NPWT in combination with debridement
Rationale for debridement

• Thick adherent eschar/necrosis in extensive ulcers
• Rapid wound cleansing
• Reduce bacterial load (cellulitis/pus)
• Produce best wound environment
• Wound bed preparation for skin grafts/myocutaneous flaps

in conjunction with other therapy
Debridement: methods

Autolytic
Enzymatic
Mechanical
  Hydrosurgery
  Wound irrigation
Larval (maggot) therapy
Surgical
Chemical
  collagenases
  wet-to-dry
  cold steel
  antiseptics/
  hypochlorites
Conservative sharp
NPWT in TIME\textsuperscript{1,4}

- NPWT use has become increasingly prominent in wound management
- Advances in technology and more portable devices mean NPWT is more accessible
- NPWT applied to a wound via a sealed foam or gauze dressing facilitates wound drainage, reduces oedema and rate of infection, while increasing wound perfusion
- Advances in debridement technologies such as low-frequency ultrasound, hydrosurgery in combination with NPWT have led to more efficacious outcomes
TIME: Infection and inflammation

- Greater understanding of the type and behaviour of bacteria in the wound
- Importance of biofilms in wound management
- Enhanced understanding of the action of antimicrobial agents (i.e. PHMB, iodine, honey, silver-containing dressings)
Determinants for infection

- host resistance
- bacterial quantity and virulence

bacterial balance

always consider any underlying pathology
Signs of acute infection

Aulus Aurelius Cornelius CELSUS (25BC-50AD)

- Calor (localised raised temperature)
- Rubor (redness)
- Dolor (pain)
- Tumor (swelling)

Systemic Inflammatory Response Syndrome (SIRS)
Signs of clinical infection: chronic wounds\textsuperscript{1,19,20}

\begin{itemize}
  \item Increased discharged
  \item Delayed healing
  \item Wound breakdown
  \item Pocketing at base of wound
  \item Epithelial bridging
  \item Unexpected pain or tenderness
  \item Abnormal granulation tissue
  \item Discolouration of the wound bed
  \item Abscess formation
  \item Malodour
\end{itemize}

infected? biofilm?
sepsis related to a chronic wound

SIRS + documented infection
Chronic wounds\textsuperscript{21}

Bacterial burden:
• Increased metabolic load
• Production endotoxins and proteases
• Stimulation of pro-inflammatory wound environment
• Wounds don’t heal
Critical colonisation\textsuperscript{18-20,22}

• Critical colonisation has yet to be definitively quantified
  – increased bacterial burden
  – bacterial imbalance
  – covert/local/topical infection

• Signs and symptoms appear to vary between wound types

• Is critical colonisation a transitional stage between colonisation and overt infection?

• Is it indicative of chronic inflammation?

• Is it indicative of biofilm?

• We need a diagnostic
Reducing bioburden\textsuperscript{11,20}

- Bacteria cause a continuum of effects
- These may progress through contamination, colonisation, local and systemic infection

**Diagram:**
- **Contamination**
  - Topical antimicrobial dressings are not indicated because bioburden is not causing clinical problems
- **Colonisation**
  - Topical antimicrobial dressings indicated
- **Localised Infection**\textsuperscript{*}
  - Systemic antibiotics + topical antimicrobial dressings indicated
- **Spreading Infection**
- **Systemic Infection**

**French Phrase:** speed of kill
frapper fort et frapper vite
(hit hard and early)
The two week challenge

The silver consensus group (2012) recommended that first two weeks of treatment with an antimicrobial dressing can be seen as a ‘challenge’ period during which the efficacy of the antimicrobial dressing can be assessed.
Biofilms\textsuperscript{23} (Koch’s postulates upside down)

- Complex microenvironment - bacteria and glycocalyx
- Intercellular communication (quorum sensing)
- Resist host-defences and antibiotics
- Exist in acute and chronic wounds?
Infection and inflammation: biofilms\textsuperscript{9,23-26}

- Biofilms are a major contributing factor to persistent, chronic wound inflammation.
- Almost all chronic wounds are thought to contain biofilm communities.
- Bacteria form strongly attached microcolonies in 2-4 hours.
- Bacteria develop EPS in 6-12 hours and a mature resistant biofilm in 2-4 days.
- Following disruption, biofilms can reform in 24 hours.
Are biofilms visible?\textsuperscript{27}

Technically no unless...
- left undisturbed – dental plaque
- Pseudomonas produces the quorum sensing molecule pyocyanin which is green in biofilm phenotype

Is slough a biofilm?\textsuperscript{23}

- Biofilms stimulate inflammation
- Increased vascularity and wound exudate
- Deposition of fibrin slough
Biofilm management

- static healing
  - undertake comprehensive wound assessments

- suspected biofilm
  - static healing
  - slough
  - ‘slime’

- reduce biofilm burden
  - frequent sharp or other debridement
  - vigorous cleansing
  - cadexomer iodine, silver etc

- suppress biofilm reformation
  - topical antiseptic dressings and solutions
  - cadexomer iodine, silver etc
  - systemic antibiotics
biofilms...we could do with a diagnostic\(^1\) (swabs and biopsies unhelpful)

**structural analysis**
- confocal laser scanning microscopy

**molecular analysis**
- DNA extraction
- Denaturing Gel Gradient Electrophoresis (DGGE)
- Polymerase Chain Reaction (PCR)

**Pseudomonas aeruginosa** (PsaerFITC green)

**Staphylococcus aureus** (Cy5 red)
Antimicrobial dressings$^{1,10}$

Antimicrobial prevention and treatment

- May reduce bioburden and impact of bacteria on healing (diabetic foot ulcers, venous ulcers, pressure ulcers, open acute wounds)
- Debridement with lower toxicity than hypochlorites
- Aid in infection control (act as a barrier?)
- Reduced costs and hospital interventions
- Action on biofilms – can we define them?
Infection: antimicrobial agents\textsuperscript{11,16,23,28-32,33}

Silver

- Elemental, inorganic, organic
- Nanocrystalline silver dressings are effective against a broad spectrum of wound pathogens, including multiple MRSA strains and NDM-1 Carbapenemases (\textit{in-vitro})
- Different silvers have different outcomes – use evidence to help choose the most effective dressing
- May be effective against biofilms

Iodine

- Available in different presentations
- Cadexomer iodine may generate higher healing rates
- Cadexomer iodine shown to be effective against biofilms (\textit{in-vitro}) and assists debridement
Infection: antimicrobial agents\textsuperscript{11,16,23,28-32,33}

Honey

- Lowers infection
- Promotes debridement
- May be effective against biofilms

PHMB (polyhexanide/polyhexamethylene biguanide)

- Available in different presentations
- May be effective against biofilms
Silver and silver dressings

- Silver in use for hundreds of years in wound care
- Now a wide range of wound dressings available that contain silver as:
  - elemental silver
  - inorganic compound of silver
  - organic silver complex
- Silver component of the dressing may be:
  - a coating
  - within the dressing
  - a combination of these
Mechanism of action of antiseptics\textsuperscript{29}
(an alternative to antibiotics?)

- Changes DNA
- Blocks cell respiratory processes and membrane proteins
- Blocks efflux pumps
- Denaturation of proteins and enzymes
Risk of antiseptic use

• Selection of pathogenic bacteria from environment?
• Selection of resistance to antiseptics?
• Selection of antibiotic resistance (and emergence)?
• Promotion of transmission of resistant forms?
• All unproven in human pathogens and clinical practice
• Relates to non-specific action of antiseptics
TIME: Edge\textsuperscript{1,36,37}

- The importance of accurate wound measurement is critical in relation to the other clinical actions of time
- Consider using adjunctive therapies
  - NPWT
  - electrical stimulation
  - oxygen
  - ultrasound
  - low level laser therapy
The importance of accurate wound measurement is critical in relation to the other clinical actions of time.

Consider using adjunctive therapies:
- NPWT
- electrical stimulation
- oxygen
- ultrasound
- low level laser therapy
TIME to expand the focus

- Tissue Debridement
- Moisture Balance
- Inflammation
- Infection

**Wound Bed Preparation**

- Epithelial Edge

**Surrounding Skin**

**Therapeutic Services Environment**

**Cost Benefit & QoL Issues**

**Holistic & Systemic Evaluation**

**Healing Environment**

**Patient Environment**
<table>
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<th>Tissue characteristic</th>
<th>WBP goal</th>
<th>Considerations</th>
<th>Practicalities</th>
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<tbody>
<tr>
<td><strong>TISSUE</strong></td>
<td>Debridement</td>
<td><strong>New debridement methods</strong>&lt;br&gt;Low-frequency non-contact ultrasound&lt;br&gt;Microbicidal irrigation solutions&lt;br&gt;Synthetic fibre wipes that entrap debris</td>
<td><strong>Review existing methods</strong>&lt;br&gt;Larvae / Autolytic / Conservative sharp / Enzymes – collagenase / Hydrosurgery&lt;br&gt;Honey / Mechanical (therapeutic irrigation) / Chemical / Surgical&lt;br&gt;<strong>Frequent maintenance debridement</strong>&lt;br&gt;Consider safe practice:&lt;br&gt;Knowledge&lt;br&gt;Skills&lt;br&gt;Competence&lt;br&gt;Evidence of efficacy</td>
</tr>
<tr>
<td><strong>INFECTION / INFLAMMATION</strong></td>
<td>Bacterial balance</td>
<td>Biofilm&lt;br&gt;Increased bacterial tolerance to topical/systemic agents&lt;br&gt;Mixed flora live synergistically&lt;br&gt;Quiescent state of some bacteria in biofilms reduces effectiveness of antibiotics&lt;br&gt;Not all antiseptives effective in eliminating biofilm</td>
<td><strong>Managing inflammation</strong>&lt;br&gt;Nanocrystalline silver helps reduce bacterial load which causes prolonged inflammation&lt;br&gt;Role of MMPs and other proteases (diagnostics and inhibitors)&lt;br&gt;Identification of bacteria and fungi in wounds using PCR or pyrosequencing techniques to detect unique genetic sequences of micro-organisms&lt;br&gt;<strong>Choose effective anti-biofilm antimicrobial</strong>&lt;br&gt;Use appropriate antimicrobials&lt;br&gt;Regular debridement and antimicrobial use&lt;br&gt;NPWT combined with instillation of microbicidal solutions reduces levels of planktonic and biofilm bacteria&lt;br&gt;<strong>Use of new (or revisited) agents</strong>&lt;br&gt;If no progress of wound in two weeks, reassess treatment pathway&lt;br&gt;Diagnostic tests – determine when required&lt;br&gt;Improved healing when MMP levels detected by point-of-care protease status test&lt;br&gt;Improved healing with custom formulations of topical antibiotics/antiseptics based on bacterial profiles</td>
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<tr>
<td><strong>MOISTURE</strong></td>
<td>Maintain moisture balance</td>
<td>Dressings that donate or retain fluid for dry wounds (eg foams, gelling fibres)&lt;br&gt;Superabsorbers for heavy exudate absorption&lt;br&gt;NPWT for exudate management</td>
<td><strong>Determine the efficacy of dressings for:</strong>&lt;br&gt;Absorption&lt;br&gt;Moisture vapour transmission rate&lt;br&gt;Retention&lt;br&gt;Patient comfort</td>
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<tr>
<td><strong>EDGE</strong></td>
<td>Advance closure</td>
<td>NPWT to promote granulation and contraction&lt;br&gt;Adjunct therapies – electrical stimulation: oxygen, ultrasound, low level laser therapy</td>
<td><strong>Alternative use of products e.g. NPWT to ‘splint’ wounds</strong>&lt;br&gt;Role of diagnostics / theranostics in the future</td>
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Summary

• TIME continues to provide a useful framework for guiding the assessment and treatment of chronic wounds
• Use TIME within a holistic approach
• Consider all the evidence
• Keep up to date with new technologies
• Review article to be published in IWJ
TIME 10 years on

Tissue (debridement and biofilm)
Infection/inflammation (bioburden)
Moisture (maintain balance)
Edge (advance closure)

Treatment
Implementation
Monitoring
Evaluation
References

1. Leaper D, Schultz G, Carville K et al. Extending the TIME concept: what have we learned in the last 10 years? Int Wound J 2012; 9 Suppl 2
References

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