Hard-to-heal wounds consensus: What this means in clinical practice

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During 2012/13:

- **2.2 million** wounds were managed by the NHS.
- **18.6 million** practice nurse visits
- **10.9 million** community nurse visits
- **7.7 million** general practitioner visits
- **3.4 million** hospital outpatient visits
- **Estimated cost with associated co-morbidities of £5.3 billion**

• 2.2 million wounds
• 1.5% of all adults over 18 years had a leg ulcer
• Mean NHS cost is £7,600 per VLU over 12 months (Guest, Fuller et al. 2018)
• Unhealed VLU 4.5 times more than healed VLU (£3,000 versus £13,500) (Guest, Fuller et al. 2018)
• Total annual NHS cost was estimated to be between £596 and £921 million (Guest, Ayoub et al. 2017)

• 6.5 million individuals with complex wounds (Sen CK, Gordillo GM et al. 2009)
• Average annual cost of treating chronic wounds is more than $25 billion per year (Tricco, Cogo et al. 2015 (Rice, Desai et al. 2014))
• 3% of total spend on health
• Over 1000 wound care clinics across the USA
• Skin scarring $12 billion annual market
The Burden of Wounds Patient numbers and associated costs in Primary care using and average 10% increase in prevalence
(Based on THIN Data set 2012/13)
Global wound healing market to reach over 35 billion US$ by 2025: US represents the world’s largest growing market! VLU care (Transparency market research, 2018)

Xie, T., et al. "The venous ulcer continues to be a clinical challenge: an update." Burns & Trauma 6(1): 18
Healing at 1 year

Guest, J. F., et al. (2015). "Health economic burden that wounds impose on the National Health Service in the UK." Downloaded from http://bmjopen.bmj.com/ on January 4, 2016 - Published by group.bmj.com
Wound Care: Unwarranted variation

- Poor assessment and diagnosis
- Underuse of evidence-based practice
  - Off loading
  - Pressure redistribution
  - Compression therapy
  - Venous intervention
  - Biofilm management
- Overuse of ineffective interventions
  - Compression less than 40 mmHg
- Variations in commissioning of services
- Variation in wound bed preparation
Chronic Wounds
Chronic wound

The word chronic:

• early 15c., of diseases, "lasting a long time," from Middle French chronique, from Latin chronicus, from Greek khronikos "of time, concerning time," from khronos "time".

• Vague disapproving sense (from 17c.) is from association with diseases and later addictions. Literal sense "pertaining to time".
Chronic wounds = Duration

American College of Surgeons Definition: “Chronic non-healing wounds are wounds that have the failed to progress through a timely sequence of repair”

Time:
• 2 weeks
• 6 weeks
• 3 months
Do we wait?
Chronic wounds = Classification

The World Union Wound Healing Society classifies chronic wounds into 4 major categories:

• pressure ulcers
• diabetic foot ulcers
• venous ulcers
• arterial insufficiency ulcers
International Wound Infection Institute (2016) defines as:

Chronic wound:

“a wound that has a slow progression through the healing phases, or shows delayed, interrupted or stalled healing due to intrinsic and extrinsic factors that impact on the individual and their wound”.

The process of wound healing

“A dynamic, natural and efficient process that involves the overlapping of various healing stages, with a continual sequence of regulatory mechanisms that bring about the ultimate healing of the wound”

Calvin (1998)
The Wound Healing

<table>
<thead>
<tr>
<th>STAGE OR PHASE OF HEALING</th>
<th>TIMESCALE</th>
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</thead>
<tbody>
<tr>
<td>Haemostasis (blood clotting)</td>
<td>Within a few seconds of tissue injury</td>
</tr>
<tr>
<td>Inflammation</td>
<td>1 - 5 days</td>
</tr>
<tr>
<td>Proliferation or reconstructive</td>
<td>3 - 24 days</td>
</tr>
<tr>
<td>Maturation or remodelling</td>
<td>21 days onwards but may take over 1 year</td>
</tr>
</tbody>
</table>
Haemostasis

• Vasodilatation
• Infiltration of macrophages
• Cytokines releasing
  • → angiogenesis
  • → fibroblast activation
  • → B- and T-cells activation
  • → keratinocytes activation
  • → wound contraction
• Injured cells in wound area release clotting factors
• Further supported by vasoconstriction which is initiated by platelets
• Leukocytes migrate into tissue to initiate inflammatory response
• Fibrin clot formation

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Inflammatory Phase

• Lasts approximately 5 days post wounding
• Neutrophils, macrophages control bacteria and debris
• Macrophages also release chemicals to stimulate capillary growth
• Ending when fibroblasts become the main cellular component
Proliferative Stage

- Vascular integrity is restored
- Fibroblasts proliferate and secrete glycoproteins and collagen
- Wound defect is filled with new connective tissue (granulation)
- Wound surface covered by new epithelium (epithelisation)
Maturation/Remodelling Phase

- Continues for up to 1 year or longer
- Fibroblasts decrease in number
- Regression of many capillaries
- Collagen degeneration and synthetisation
- Organisation of cells
- Tensile strength increases – Max 80%
- Wound contracts increasing tissue integrity
Wound Healing

Inflammation

Proliferation

Maturation
Non Healing

Inflammation

- Degradation of ECM and growth factors
- Bacterial proteases and toxins
- Cytokines and free radicals
- Increased inflammatory response
- Excess proteases
- Imbalance

Damaged tissue

Cells produce excess proteases

Delayed wound healing

Proliferation

Maturation
Fail to heal

Transmission from inflammation to proliferation is precarious
CHRONIC WOUND MOLECULAR ENVIRONMENT

Acute (healing) wound

Initial phase:
1. Scab formation
2. Immune cell infiltration

Healing phase:
3. Re-epithelialisation
4. Angiogenesis
5. Fibroblast migration
6. Collagen deposition

Chronic (non-healing) wound

Chronic wound abnormalities:
1. Infection/biofilm
2. Hyperproliferative epidermis/stalled re-epithelialisation
3. Persistent inflammation
4. Fibroblast senescence
5. Impaired angiogenesis
6. Fibrin cuffs (barrier to oxygen)
7. Elevated MMPs

Key:
- Fibrin cuff
- Collagen/fibroblast
- Bacteria
- Immune cell
- Scab
- Epidermis
- Biofilm
- Blood vessels
- Dermis
- MMP (Matrix metallo-proteinases)
Cell Senescence

• Senescence is a cell state related to the number of cell divisions that a cell has experienced.
• During every cell division, a part of the chromosomal structure—the telomere—shortens until a limit is reached.
• The limit, known as the Hayflick limit, determines when a cell will be subject to programmed cell death (‘apoptosis’).
• As telomeres shorten, the cell’s proliferative potential is reduced.
Delayed transmission

Hard to heal
Hard to heal

• With appropriate care it is estimated that 93% of VLUs will heal in 12 months

• However, 7% remain unhealed after five years

(Franks et al, 2016).

### Cost of non healing: economic and Quality of life

<table>
<thead>
<tr>
<th>Economic(^{[5,6]})</th>
<th></th>
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<tbody>
<tr>
<td><strong>Hospital and other facility costs</strong></td>
<td>Inpatient hospitalisation and readmissions, outpatient clinic visits</td>
</tr>
<tr>
<td><strong>Specialist care or treatments</strong></td>
<td>e.g. surgical procedures such as amputation</td>
</tr>
<tr>
<td><strong>Healthcare professional time</strong></td>
<td>e.g. for dressing changes, community care visits, travel</td>
</tr>
<tr>
<td><strong>Materials, interventions, specialist equipment</strong></td>
<td>Dressings, devices, medicines (e.g. antibiotics), other disposables, orthotics</td>
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<tr>
<td><strong>Assessment tools</strong></td>
<td>Diagnostic equipment, laboratory testing</td>
</tr>
<tr>
<td><strong>Patient out-of-pocket payments</strong></td>
<td>e.g. travel costs</td>
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<td><strong>Lost productivity</strong></td>
<td>Patient or carer lost work time</td>
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<th>Health-related quality of life(^{[7]})</th>
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<td><strong>Physical wellbeing</strong></td>
<td>Pain, impaired mobility and functioning, poor nutrition or sleep</td>
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<td><strong>Mental wellbeing</strong></td>
<td>Depression, anxiety</td>
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<tr>
<td><strong>Psychosocial wellbeing</strong></td>
<td>Social isolation, difficulty with social interactions</td>
</tr>
<tr>
<td><strong>Spiritual/cultural wellbeing</strong></td>
<td>Difficulty connecting with one’s self and others, impact of cultural nuances and personal values on physical, mental and psychosocial wellbeing</td>
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Fail to heal
How does this feel? The patient perspective

“I am upset about the life I could have had, the career I should have had and for the person that I should have been. I always thought I would be somebody and achieve something in life but I feel like I have had that opportunity stolen away. I hate feeling self-conscious, disabled and unattractive and I hate that this leg ulcer has taken away my self-confidence”
Impaired Healing

• Not a single factor
• Multiple contributing factors at play.
• Remember there are overlapping mechanisms in normal wound healing that prevent a single factor from disrupting the process
• However, when the wound healing process is disrupted non-healing will develop.
• Non-healing wounds share similar characteristics: high level of proteases, elevated inflammatory markers, low growth factor activity, and reduced cellular proliferation
Wound Complexity

Patient-related factors

Wound-related factors

Healthcare professional-related factors

Resource/treatment-related factors

Wound complexity
Hard to heal: Risk Factors

Where can wound care go wrong?
Fundamental aspects of care

**Holistic assessment:** International/local guidelines/best practice statements, Patient risk factors of a hard-to-heal wound, additional assessment (e.g., venous duplex, biopsy)

**Wound assessment:** volume, extent, area, exudate

**Diagnosis:** refer on if appropriate/required

**Treatment:** standard to best practice, including wound bed preparation, initiation of biofilm prevention/treatment, TIMERS wound assessment, control oedema, refer to local formulary

**Patient-centred outcomes:** healing or maintenance (this needs to be a multidisciplinary team approach)
Confirm Diagnosis

What has caused the skin to breakdown?

- Arterial
- Venous
- Trauma
- Pressure
- Malignant
- Infection
- Autoimmune
- Rheumatoid
- Other
# Adequate Wound Bed Preparation

<table>
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<tr>
<th>T: Tissue</th>
<th>E: Inflammation/Infection</th>
<th>M: Moisture</th>
<th>E: Edge</th>
<th>R: Repair</th>
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<td>Observation: devitalised tissue</td>
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<td>Observation: Incorrect moisture balance</td>
<td>Observation: edge rolled, epithelial/callus. Poor advancement of wound edge</td>
<td>Observation: Slow/stalled closure falling conservative therapy</td>
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| Outcome: Clean wound bed, debride devitalised tissue | Outcome: inflammation, infection and biofilm controlled | Outcome: Manage moisture wound environment conducive to healing | Outcome: Reduced wound size Epithelialisation | Outcome: wound closure, repair tissue |
Systematic approach: Structure, methodical, ordered and coherent

Tissue non viable or deficient

Infection or inflammation

Moisture imbalance

Edges of wound – non advancing or undermined

Repair
Tissue

- Observation: devitalised tissue
  - Debridement options:
    - Autolytic
    - Sharp
    - Surgical
    - Mechanical
    - Including:
      - Hydrosurgery
      - Debridement pads
      - Enzymatic
      - Larval
      - Ultrasound
      - Laser CO₂
      - Concentrated surfactants

- Outcome: Clean wound bed, debride devitalised tissue
T = Tissue - Debride?

- Removes physical barrier to epidermal resurfacing, contraction or granulation
- To reduce bacterial burden by removing dead tissue
- To convert chronic wound to an acute wound by stimulating healing cascade
- To facilitate action of wound dressings
Wound Debridement

• Wound bed preparation key
• Wound debridement poorly completed in the UK
• Clinicians mostly believe this is about applying a dressing
• Evidence and practice in management of DFU not transferred to VLU.
Evidence

Key Study Finding: Patients were 3x more likely to heal at 12 weeks with adequate debridement.
Inflammation/infection

I: Inflammation/Infection

Observation: Inflammation and/or infection, bioburden

Treatment options:
- Antimicrobials
- Antibiotics
- Biofilm pathway
- Bacterial binding dressings
- Fluorescence biomodulation
- Gas plasma
- Oxygen therapy (hyperbaric and topical)
- MMP/TIMP management
- Surfactants

Outcome: Inflammation, infection and biofilm controlled
Wound colonisation continuum

Contamination  Colonisation  Local infection  Spreading infection  Systemic infection

Vigilance required  Intervention required

No antimicrobials indicated  Topical antimicrobial  Systemic and topical antimicrobials

Increasing microbial virulence and/or numbers

**Biofilm**

• Bacteria – not new
• Biofilms – relatively new!

What is a biofilm:

*Any group of microorganisms in which cells stick to each other and adhere to a surface using a self-produced matrix of extracellular polymeric substance (EPS)*
Biofilm

- Biofilm has been recognised as an important contributor to the hard-to-heal status of chronic wounds
- Endogenous tissue-breakdown mechanisms, common to all skin ulceration: tissue-destructive enzymes; an oxidative environment; impaired endogenous control mechanisms that modulate enzyme activity
How quickly do biofilms form?

Planktonic bacteria typically:

• Attach within minutes
• Form attached micro-colonies within 2–4 hours
• Develop initial extracellular polymeric substance and are tolerant to biocides within 6–12 hours
• Evolve into mature biofilm colonies within 2–4 days
• Rapidly recover from mechanical disruption and re-form mature biofilm within 24 hours

How Does a Biofilm Delay Healing?

• The EPS protects the microbial community from the external environment and other substances (e.g. antibiotics and other antimicrobials)

• Biofilm delays healing because they cause:
  • Inflammation
  • Increased exudate
  • Host cell senescence (a state of permanent cell-cycle arrest)
Suggested signs of biofilm in chronic wounds

- Delayed wound healing
- Visible, slimy gel like shiny cover on wound bed, which detaches easily and can be peeled off wound without trauma to wound bed
- Rapid reforming of slough/slimy covering
- Increase exudate
- Poor/Fragile granulation tissue
- Signs of local infection
- Persistent recurring infection
- Slow or no response to antimicrobial dressings
- Low level chronic inflammation
- Low level erythema
Clinical issue
Biofilm management
Moisture

Observation: Incorrect moisture balance

Treatment options:
- NPWT
- Compression
- Absorbent dressings

Outcome: Manage moisture
Wound environment conducive to healing
Moisture

Natural response in healing:

- Haemostatic phase – platelet factors, vascular response factors.
- Inflammatory phase – cytokines and protease
- Proliferative phase – Angiogenesis, extracellular matrix formation and epithelisation

Prolonged inflammatory phase leads to increased levels of cytokines and proteases and decreased levels of growth factors.
Moisture

• Optimal condition for wound healing
• Enhances autolytic process
• Increases rate of epithelisation
• Increases cell proliferation
• Optimum levels of exudate – contains vital proteins and cytokines and MMP’s
• Aids cell migration
• Provides essential nutrients for cell metabolism
• Enables diffusion of immune and growth factors
Moisture imbalance

• Eliminate of underlying cause
• Manage moisture
• Prevent further tissue damage
• Control bacteria
• Compression/NPWT
Edge

Observation: edge rolled /epibole/ callus. Poor advancement of wound edge

Treatment Options:
- See also debridement
- Cyanoacrylate
- Periwound protectants
- Excision of sclerosed margins
- Fluorescence biomodulation
- Wound fillers (e.g. collagen)

Outcome:
- Reduced wound size
- Epithelialisation
Edge

Advancing or non-advancing?
- Undermining
- Cliffs or beaches
- Rolled
- Macerated
- Callous

Wound edge refashioning
- Removal of rolled edge/callous
- To pin point bleeding to stimulate keratinocytes
Refashioning the edge

Pre

Post
Repair

**Observation:** Slow/stalled closure failing conservative therapy

**Treatment options:**
- Amnion/chorion membrane
- Cell scaffold
- ECM-based technologies
- Growth factors
- Platelet-rich plasma (PRP)
- Bioengineered substitutes
  - NPWT
- Oxygen therapy (hyperbaric and topical)
- Stem cell therapy
- Autologous skin graft

**Outcome:** Wound closure, repair tissue
S: Social and patient factors

- Social situation
  - Patient understanding
  - Patient adherence
  - Patient choice
  - Psychosocial

- Engage the patient with the care plan

- Patient education
  - Understanding belief system
  - Motivational literacy
  - Active listening
  - Psychoeducation
  - Patient’s own goals
  - Patient’s family/caregiver education
Patient Engagement

1. Discuss plan of care
2. Reason for chosen plan of care
3. Patient's role in this plan of care
4. Overview signs and symptoms of complications & how to report
5. Review behavior that works against desired outcome
6. Motivation for healing potential / modify feelings
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TIME becomes TIMERS:

- **T**: tissue viability
- **I**: infection/inflammation
- **M**: moisture balance
- **E**: wound edge
- **R**: repair/regeneration
- **S**: social- and patient-related factors.
Fig 3. Timeline for suggested treatment and referral

First presentation: Day 1

A wound of four-week duration (including four weeks of treatment) and identification as ‘hard-to-heal’
Same timeframe/indications for specialist complex clinics

At four weeks/30 days 40-50% decrease
Indicators to failed treatment include: Clinically ↓, ↑ Exudate, ↑ Devitalised tissue, ↑ or new onset Pain, progression or recurrent Infection, ↑ Maceration

Referral required

Individual specialist (limited skill-set/access to therapies)

Complex wound clinics: multidisciplinary teams
Fundamental aspects of care

• Early intervention
• Accurate assessment and diagnosis of the patient and wound
• Optimal patient and wound management strategy
• Appropriately-skilled health professionals
• Early referral to specialist
The Evolution of Wound Therapies

MOIST WOUND HEALING
- Hydropolymers
- Hydrocolloids
- Collagen dressings
- Gels
- Saline wet gauze

ENVIRONMENT

ACTIVE HEALING
- Growth factors
- Interactive Biopolymers
- GF/Device combinations
- Pharmaceuticals
- Tissue Engineering

PASSIVE
- Gauze
- Sponges

TRADITIONAL

70 + Years - First Wave

15+ Years - Second Wave

80’s 90’s 00’s ’10 ’20 ’30

Third Wave

Improved Outcomes
Dressing cost

Cost of non-healing

- Patient quality of life
- Ability to work
- Cost of prescription
- Cost of dressings
- Clinician time
- Antibiotic spend
- Analgesic spend
- Service capacity

Total cost of managing 2.2 million patients with a wound: £5.3 billion

Percentage of total NHS cost associated with each wound type

Time for change

• Timely assessment
• Appropriate diagnosis
• Evidence based treatments
• Early escalation when failing to heal
• Actively preventing chronic wounds!
• Spells out the fundamental aspects of care linking to the importance of underlying pathophysiology identification and management

• Identification of those hard to heal

• Biofilm based wound care

• Importance of wound debridement

• Early referral to specialist centres

Aiming to win the race against hard-to-heal wounds
Thank You

Questions?