Innovations in hard-to-heal wounds

Roberto Brambilla¹, Jennifer Hurlow², Stephan Landis³, Randall Wolcott⁴

A well-established practical and predictive measure of complete wound healing over the longer term (24 weeks) is per cent change in wound area over the first 4 weeks⁵. However, certain conditions have the potential to delay healing and signs may indicate stalled healing: infection, ischaemia, or abnormal inflammation, with impaired inflammatory response often being self-perpetuating⁶. Non-healing wounds contain microbial, biochemical or cellular abnormalities that delay healing progression⁷, with biofilm presence often implicated⁸.

With the prevalence and incidence of wounds increasing due to aspects such as an ageing population and comorbidities including diabetes⁹, a high economic and humanistic burden is incurred (Table 1). In hard-to-heal wounds, this burden is compounded: complications occur, patients become more dependent and costs increase, typically driven by a need for increased healthcare professional time⁶.

Numerous factors may impact the complex and multifaceted process of wound healing⁶, including issues associated with the patient (i.e. comorbidities and medication), their wound (e.g. size, duration, location), clinical service delivery (i.e. competency of the healthcare professional) or various biophysiological factors (Figure 1)⁹,¹⁰. Recently, certain factors have gained recognition due to their considerable influence on outcomes. Biofilm is present in the majority of chronic wounds (at least 60%)⁴, they are often a precursor to overt infection with increasing tolerance to antimicrobial agents, including antibiotics, and tend to form where exudate is not under control⁸–¹².

Biofilm can impair healing by stimulating an inflammatory response that leads to abundant neutrophils and macrophages (in an attempt to remove the biofilm),

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Table 1 | Cost of wounds to the healthcare system, society and patient

<table>
<thead>
<tr>
<th>Category</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Economic</td>
<td></td>
</tr>
<tr>
<td>Hospital and other facility costs</td>
<td>Inpatient hospitalisation and readmissions, outpatient clinic visits</td>
</tr>
<tr>
<td>Specialist care or treatments</td>
<td>e.g. surgical procedures such as amputation</td>
</tr>
<tr>
<td>Healthcare professional time</td>
<td>e.g. for dressing changes, community care visits, travel</td>
</tr>
<tr>
<td>Materials, interventions, specialist equipment</td>
<td>Dressings, devices, medicines (e.g. antibiotics), other disposables, orthotics</td>
</tr>
<tr>
<td>Assessment tools</td>
<td>Diagnostic equipment, laboratory testing</td>
</tr>
<tr>
<td>Patient out-of-pocket payments</td>
<td>e.g. travel costs</td>
</tr>
<tr>
<td>Lost productivity</td>
<td>Patient or carer lost work time</td>
</tr>
<tr>
<td>Health-related quality of life</td>
<td></td>
</tr>
<tr>
<td>Physical wellbeing</td>
<td>Pain, impaired mobility and functioning, poor nutrition or sleep</td>
</tr>
<tr>
<td>Mental wellbeing</td>
<td>Depression, anxiety</td>
</tr>
<tr>
<td>Psychosocial wellbeing</td>
<td>Social isolation, difficulty with social interactions</td>
</tr>
<tr>
<td>Spiritual/cultural wellbeing</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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WOUND HEALING IS

COMPLEX AND

MULTI-FACETED

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THE IMPACT OF HARD-TO-HEAL WOUNDS

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WORLD UNION OF WOUND HEALING SOCIETIES

CLINICAL REPORT

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WORLD UNION OF WOUND HEALING SOCIETIES
which secrete high levels of reactive oxygen species and proteases (i.e. matrix metalloproteinases [MMPs])\[4\]. Numerous studies have shown the presence of biofilm promotes a sustained inflammatory state and delays wound healing\[13\], and elements of this response may actually facilitate their development\[14\]. Biofilm provides protection to the contained microorganisms and increases exudate production\[16\], supporting the inhibition of tissue granulation and epithelialisation.

**Box 1: Advances in care**

Changes to diagnosis and treatment of hard-to-heal wounds, using advanced technologies\[8\], could lead to improvements in:

- Patient quality of life
- Symptom control, where they are present
- Long-term outcomes, including traditional (i.e. healing rates), but also patient-reported outcomes, such as pain, malodour, or social functioning
- Cost of care, including reduced healthcare professional time.

**Figure 1 | Carrying out an initial assessment for recognising hard-to-heal wounds. Adapted from Vowden, 2011\[2\]**
Infection and biofilm

Microorganisms are commonly divided into two distinct phenotypes: single cells (i.e. planktonic) or sessile aggregates (i.e. the biofilm mode of growth). Research into bacterial pathogenesis has previously focused primarily on acute — or planktonic — infections, which result from invasion by free-floating, solitary microorganisms, as has the development of prevention and treatment control measures. However, a new category of chronic infection caused by microorganisms growing as biofilm has become an increasingly important focus in wound care [16].

Hard-to-heal wounds are often chronically infected, producing a distinct pattern of growth associated with biofilm [17], which can be 500 to 5,000 times more tolerant to antimicrobials [18]. Chronic biofilm-based infections:

- Have a slower progression than acute infections
- Are characterised by an adaptive inflammatory response
- Are typically extremely resistant to antibiotics and many other conventional antimicrobial strategies
- Have an innate ability to evade the host’s defences [16].

Regardless of phenotype, microbial cells have multiple mechanisms to attach to specific host epitopes [19–21]. Within minutes, over 800 biofilm genes may be expressed [20], providing genetic capability for microbial cells to communicate and co-operate (quorum sensing) [22–24], develop protection (self-secreted matrix polymers) [25,26], and secrete molecules preventing host immunity counter measures [27–29] (Figure 2).

Uncontrolled exudate

Poorly managed wound exudate can harm the wound healing trajectory, as it can slow down or prevent cell proliferation, interfere with growth factor availability, or contain high levels of proteases and pro-inflammatory cytokines that degrade the host extracellular matrix [40].

Chronic wound fluid also challenges skin integrity around the wound — intact periwound skin has been shown to have a five-fold decrease in barrier function simply by virtue of the underlying tissue inflammation [41]. Moreover, prolonged moisture exposure leads to maceration [42], which increases likelihood of friction and shear. In combination with the decrease in periwound barrier function, maceration increases the risk of chemical irritation from inflammatory exudate and bacterial invasion.

Box 2: How does biofilm protect microorganisms?

Biofilm enhances the tolerance of microbes to factors that would easily kill the same microbes when growing in an unprotected state, including the immune system, antimicrobials and environmental stressors [43].

The biofilm matrix (or the extracellular polymeric substance) forms a physical barrier preventing removal of waste products from around the microbial cells [38], creating regions of metabolic waste and low oxygen tension, and blocking large molecules such as antibodies and inflammatory cells from penetrating deep into the biofilm matrix [44].

These anoxic cores influence surrounding microbial cells, providing unique cooperative and protective effects (such as secretion of protective enzymes that protect neighbouring non-antibiotic-resistant microorganisms), and making them dormant (metabolically quiescent) and so more tolerant to antibiotics and biocides [39].

At a molecular level biofilms require:

- Attachment
- Rapid development of a microcolony
- Secretions of molecules to produce host cells senescence (loss of cells’ power to divide and grow)
- Hyper-inflammation to produce plasma exudate; achieved via release of outer membrane vesicles, release of planktonic cells, and subversion of host immunity

At a biochemical and cellular level, biofilms produce:

- Excessive neutrophils (i.e. lysozyme, myeloperoxidase, Cathepsin G, etc.)
- Elevated pro-inflammatory cytokines (IL-1, IL-8, gamma interferon, TNF-α)
- Elevated MMPs (MMP-2, MMP-8, MMP-9, elastase)

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INNOVATIVE APPROACHES TO TREAT HARD-TO-HEAL WOUNDS

Innovation in assessment, diagnostics and treatment

The key to effective diagnostics is how efficiently they are used in practice. Although point-of-care technologies, such as a test allowing practitioners to measure elevated protease activity [43], may offer the best opportunities for real-time decision-making, these have yet to be implemented within daily care.
The TIME framework (Tissue, Infection/Inflammation, Moisture, Edge of wound) is a well-established assessment and management method, and remains the typical wound bed preparation paradigm in practice[44]. Since its original presentation, substantial developments in our understanding of wound care have occurred; in particular, regarding the bacterial continuum through contamination, colonisation and infection, as well as the presence of biofilm. TIME remains relevant, but there is a need to ensure these developments are incorporated into assessments[15].

Other diagnostics are in development with the potential to address gaps, providing further objective means to improve the healing trajectory.

An innovative, advanced strategy that targets local barriers to healing

Management of microbial load is vital in the prevention of infection. Moreover, although moist wound healing strategies are no more likely to promote infection than earlier dry wound healing strategies[51], the combination of pooled exudate associated with fully saturated dressings[9] and the corrosive nature of chronic wound exudate may be linked to biofilm development and resulting infection.

Prior to the discovery that keeping wounds moist would improve healing[52], the traditional approach was to soak up fluid and leave the wound to dry. As understanding increased regarding the optimum wound healing environment, the first film dressings with polyurethane technology were developed[53], followed by alternatives such as alginates and hydrocolloids[54], and later, Hydrofiber™ Technology.

As shown in Figure 3, since the first Hydrofiber™ Technology was developed 20 years ago, various products have been developed based on its unique physicochemical properties.
Table 2 provides an overview of in vitro, in vivo and real-life, clinical evidence for the recent addition of Ag+ Technology to Hydrofiber™ Technology.

<table>
<thead>
<tr>
<th>Year</th>
<th>In vitro data showed:</th>
<th>In vivo data showed:</th>
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<tbody>
<tr>
<td>2014</td>
<td>Biofilm eradication with a single dressing application — mature <em>Pseudomonas aeruginosa</em> (4 days) and community-associated <em>methicillin-resistant Staphylococcus aureus</em> (CA-MRSA) biofilm (5 days)</td>
<td>Consistently decreased <em>P. aeruginosa</em> counts, and improved wound healing relative to inactive vehicle and active control wounds (p &lt; 0.05)</td>
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<td></td>
<td>Bacterial counts significantly reduced (p &lt; 0.05), and improvements in bacterial burden/healing in polybacterial wounds (p &lt; 0.05)</td>
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<td></td>
<td>Ability to prevent reformation (bioburden control after a simulated contamination event)</td>
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<td></td>
<td>Hydrofiber™ Technology’s effect on biofilm enhanced by ionic silver, and further by Ag+ Technology, which increases removal and disrupts the structure of the residual biofilm, improving the antimicrobial effect of the ionic silver</td>
<td></td>
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<tr>
<td></td>
<td>Ability of technology to confer efficacy</td>
<td></td>
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<tr>
<td>2015</td>
<td>The antimicrobial efficacy of ionic silver against biofilm is substantially improved by ionic silver with a metal chelating agent and a surfactant, which produce a synergistic effect (Ag+ Technology)</td>
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<tr>
<td></td>
<td>Wound generally shifting from stagnant to improved, exudate levels improving, and tissue type moving from largely suspected biofilm to largely granulation tissue</td>
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</table>

Summary

Wound healing normally occurs in a predictable sequence, however, in some instances healing is prolonged or never achieved. The healing process is a complex interaction involving patient- and wound-related factors, the treatment used, and the skills and knowledge of healthcare professionals. Careful initial assessment and repeated evaluation of therapy are needed to recognise and assess the potential factors relating to wound complexity. In recent years, certain factors have been seen to have a considerable influence on healing, including wound infection, biofilm and exudate.

For healthcare professionals, initiating effective therapeutic strategies in a timely and cost-effective manner to reduce wound complexities, manage the patient’s symptoms and expectations and, where possible, achieve healing, remains a challenge. Indeed, the drive towards securing funding for efficacious and cost-effective wound care therapies continues apace.

Innovative strategies for diagnosis and treatment are critical. Making changes in approach to wound care could lead to improved symptom control and long-term outcomes, reduced economic costs, and better patient quality of life. Exciting developments in the field of point-of-care diagnostic testing, which have been identified above, have the potential to facilitate improvements in practice and offer a more targeted and effective approach to wound management. The evolution of Hydrofiber™ Technology in dressings with the addition of anti-biofilm Ag+ Technology also presents the case for an innovative advanced technology for hard-to-heal wounds that combats certain factors with a considerable influence on healing: biofilm, exudate and risk of infection.

AUTHORS

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