Hard-to-heal wounds made easy

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Introduction

Most people have, at some stage in their life, experienced a wound. For the majority, healing is a simple and rapid process and, although the wound may leave a visible scar, it is not associated with persistent pain, excessive exudate, odour or distress. In some patients, healing is prolonged and accompanied by major symptoms, which adversely affects their quality of life. Clinicians therefore face the dual challenge to meet patient expectations of prompt and trouble-free wound healing, and to recognise and act appropriately for those patients in which wound healing may be prolonged.

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What is a hard-to-heal wound?

A hard-to-heal wound has been defined as one that fails to heal with standard therapy in an orderly and timely manner[1]. This definition applies equally to both acute and chronic wounds and is independent of the wound type and aetiology.

Many wounds, particularly those in an elderly population with significant comorbidities, prove challenging to manage. Audit data from both Bradford[2-5] and Hull[6,7] has demonstrated that delayed healing occurs in a variety of wound types. Although delayed healing appears to be common, it is frequently not recognised early enough and can pose a major problem, increasing clinical workloads and cost.

Why do some wounds not heal?

One of the characteristics of multi-celled organisms is the ability to replicate and self-repair. The normal healing process is a well-orchestrated, complex and interlinked series of four well-recognised overlapping phases.

Normal healing

The process starts with haemostasis, progresses through a destructive inflammatory phase and then a restorative proliferative phase. It finishes with remodelling of the wound area. In this process, components of the extracellular matrix, interacting with recruited cells, play an important role in coordinating key processes in healing[8]. The normal process can be interrupted at any stage and is vulnerable to a variety of intrinsic and extrinsic inhibitory factors.

Box 1 Factors for delayed healing[9]

- Patient-related factors (eg underlying pathology/comorbidities, severe pain, psychological factors, gender and reduced mobility)
- Wound-related factors (eg ulcer size >10cm^2, ulcer duration >6 months, anatomical location and wound bed condition)
- Clinical competency factors (eg skills and knowledge of healthcare professional)
- Resources and treatment-related factors (eg availability and suitability)

What factors affect healing?

Wound aetiology, patient age and the presence of significant comorbidities all impact on the healing process, as do factors such as wound size and depth, location of the wound, wound duration and the presence of a heavy bioburden[9].

Age and hard-to-heal wounds

Age affects healing in a number of ways. Elderly patients tend to have significant comorbidities and are more likely to be on multiple medications, which impact on healing. Ageing itself also affects both the rate and quality of the healing process. Large wounds often take longer to heal than small wounds and, as such, are more likely to develop complications such as infection, which may then slow healing[9]. For chronic wounds, size may relate to the severity of the underlying causative condition and the status of the surrounding skin, both of which have the potential to delay healing. In addition, the persistent inflammatory process associated with non-healing and long wound duration degrades the extracellular matrix and vascular supply to the wound, resulting in poor cellular function and senescence – a loss of a cell's power to divide and grow[9].

Comorbidities: diabetes

Patients with hard-to-heal wounds may have a number of comorbid conditions that affect the healing process. Diabetes is a significant factor and can affect healing in the following ways:

- **Cell membrane structure may be altered, affecting cell motility and deformability and the cellular response to local and systemic signalling proteins**
- **The extracellular membrane may be damaged by non-enzymatic glycosylation, affecting both its structure and function**
- **The inflammatory response and response to infection may be modified by changes in both chemotaxic and phagocytic function of white cells**
- **The blood supply to the wound area may be reduced by both occlusive arterial disease, changes in the distribution of blood flow (shunting) and a reduction in angiogenesis function (the growth of new blood vessels) affecting the ingrowth of new blood vessels to the wound**
- **The presence of a neuropathy allowing ongoing trauma to the wounded area.**

Ischaemia

As described, wound healing is dependent on cell replication, the formation of a new supporting matrix and the elimination of damaged, necrotic, foreign or infecting material. All of these processes are energy dependent and only occur effectively in the presence of an adequate blood supply and the delivery of nutrients and oxygen to the wounded area.

This process is impaired in the presence of systemic disease (cardiac and respiratory failure), regional ischaemia (peripheral vascular disease) and local ischaemia within the wound, secondary to poor neo-vascularisation and angiogenesis.

Infection and Inflammation

Inflammation is a necessary component of the healing process, but is detrimental if it continues at an inappropriate level beyond the initial phases of healing, or is stimulated by other events such as infection within a wound. Diseases such as rheumatoid arthritis and medication (eg steroids) alter the inflammatory process. This can have a detrimental effect on healing.

Other factors

The reason for delayed healing may not be related solely to an abnormality within the wound itself (Box 1). Available healthcare resources, product availability and the skill and knowledge of healthcare professionals may also influence outcome and healing time, as will the complexity of the wound itself[9].

Can you predict when a wound is hard to heal?

In most wounds, healing progress should be visible within a four-week period[1]. Figure 1 outlines the process of recognising a hard-to-heal wound and provides a useful check list to allow for the early identification of potentially slow healing wounds.

Much can be gleaned from a detailed initial wound and patient assessment when issues such as ischaemia, associated comorbidities and infection, amongst others, may be identified and a broad idea of healing potential derived. Such assessments must, however, be accurate and reproducible if treatment is to be delivered effectively[10].

Recognition of non-healing demands a careful reassessment of both the wound, the region of the wound, the patient and the systems of care so that both extrinsic and intrinsic barriers to healing may be identified. For many wounds one or more of the following three key intrinsic abnormalities will be present and delay or prevent healing:

- **Ischaemia**
- **Infection**
- **Abnormal or persistent inflammation.**

In addition, the presence of exposed bone or tendon, on which it is difficult to establish healthy granulation tissue, are recognised as obstacles to rapid wound healing[11,12].

The more complex the wound in relation to the underlying pathology and comordibites, the greater the likelihood that the wound will be hard to heal[9].

Biomarkers to predict hard-to-heal wounds

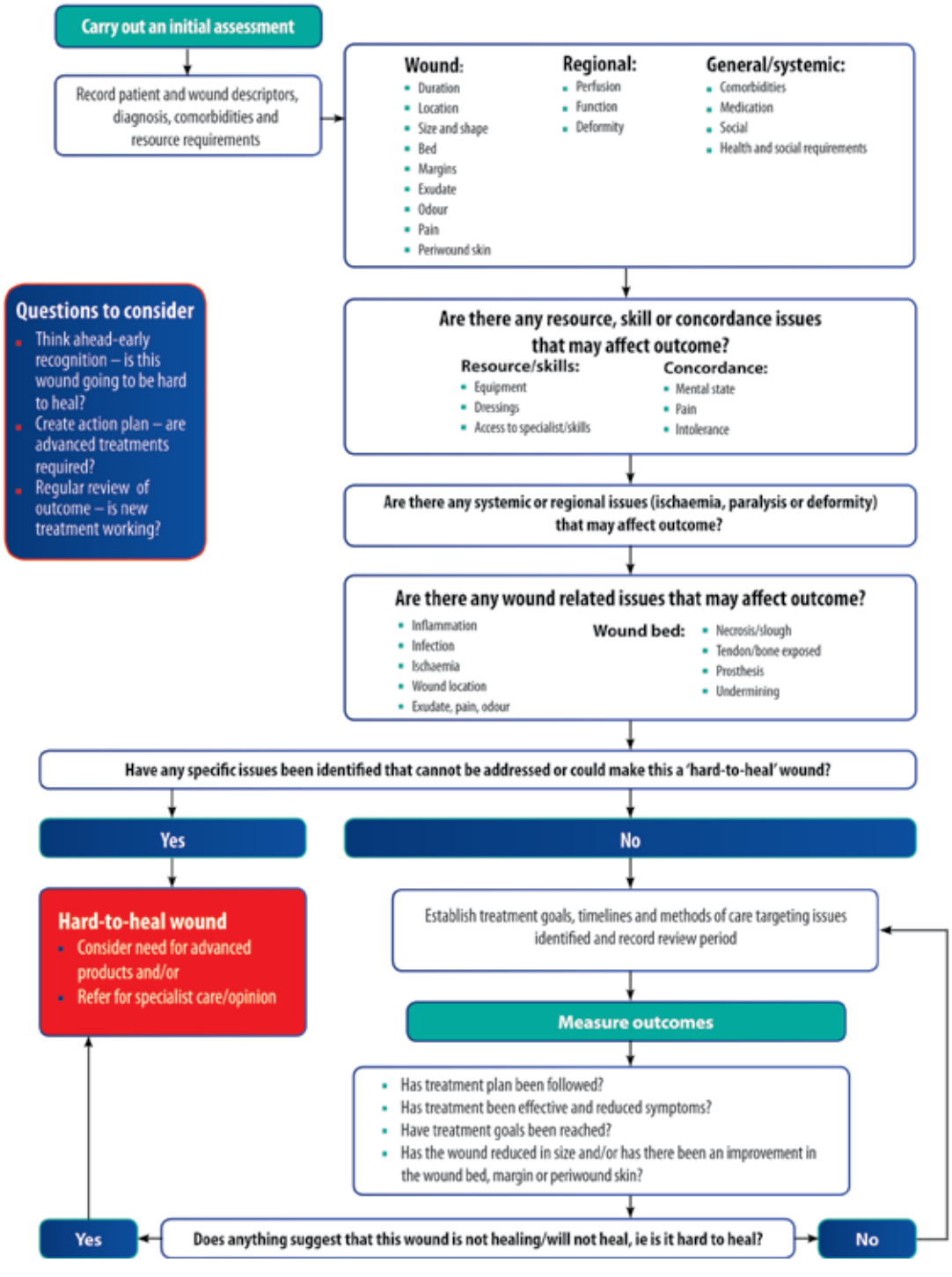
A non-healing wound contains a number of microbial, biochemical and cellular abnormalities that will prevent or slow the healing progression. This often occurs despite a seemingly adequate wound bed. As our knowledge of the processes and biochemistry of wound healing has progressed, it has become clear that, in a number of non-healing wounds, a range of biomarkers are abnormal and that some wounds are 'locked' into a self-perpetuating inflammatory process. Diabetic patients, for example, experience a substantial deficit in wound healing with a marked pro-inflammatory reaction[13].

Assessment of acute wound fluid and chronic wound exudate has shown marked differences between the wound fluid from the two wound types. Exudate from non-healing chronic wounds has been reported to have destructive properties, with abnormally high levels of proteases and reduced levels of important growth factors[14]. If left unchecked, sustained excessive protease activity in wounds start to destroy the extracellular matrix and damage newly formed tissue, preventing the wound from progressing to the proliferative stage[15].

The recognition that metalloproteases (MMPs) constitute one group of potential markers for delayed healing has led to work developing a point-of-care diagnostic[15] and targeted therapeutic interventions[16] that may assist in the management of hard-to-heal wounds. Ongoing work has identified other potential biochemical markers for delayed healing that may allow other targeted advanced wound therapies to be developed in the future. Molecular pathogen diagnostics now allow a comprehensive evaluation of the microbial bioburden[17], and targeted interventions based on this data have been shown to improve outcome[18]. It remains to be seen how clinically and cost-effective such interventions will be and how early in the cycle of healing/non-healing, persistent biochemical abnormalities can be detected.

The earlier the wound healing problems are detected, the better the outcome will be for the patient[19,20].

Figure 1 Carrying out an initial assessment for recognising hard-to-heal wounds



What practical actions can assist early recognition of hard-to-heal status?

Recognition of a hard-to-heal wound requires regular reassessment with measures taken towards healing. It does, however, also demand that:

- **The assessment and diagnostic process is correct**
- **Appropriate treatment has been applied to deal with both the requirements of the wound and the management of any underlying medical conditions that may impact on healing**
- **The outcome of treatment has been evaluated within a timeframe that is appropriate for a specific wound type.**

Wound measurement

Perhaps the most important element of the initial assessment in terms of predicting subsequent healing and hard-to-heal status, is to carefully map and measure the wound.

Changes in wound size during the initial phase of treatment have been shown to be a potential indicator of subsequent response to treatment and ultimately healing[9]. These measurements will help to identify wounds that are not progressing according to predicted healing times with the standard therapy for a specific wound type.

Troxler et al[1] have reviewed the potential of wound measurement to predict hard-to-heal status. Such measurements can be combined with other wound and periwound skin characteristics to give a score indicating healing potential[21]. Digital photography can also be used to document the wound size.

Whichever technique is used, recognition of delayed healing is important and can only really be achieved by careful, detailed and repeated wound assessment and measurement.

Laboratory data

In patients with significant comorbidities, optimising the management of the underlying medical condition can markedly improve a wound's healing potential. In such a situation, measuring and acting on the results of biochemical parameters such as blood glucose, renal and hepatic function can be useful. Monitoring inflammatory markers and wound culture as well as wound biopsy may also assist in diagnosis and allow targeted treatment.

Using clinical criteria alone to accurately predict which wounds are unlikely to heal in a timely manner is difficult[22]. Accurate detection of elevated protease activity or other biomarkers would aid early diagnosis and appropriate use of treatments aimed at optimising the wound environment[15].

However, diagnostic tests directing treatment and predicting outcomes are not yet widely available or of proven efficacy. They may however be the key to improvements in outcome for the slow or non-healing wound.

What impact does delayed healing have on the patient?

Chase et al[23] introduced the concept of 'forever healing' and other work has led to the concept of permanent 'wounding'. For the patient this requires learning to live with the pain, emotional problems and social isolation associated with delayed healing[24,25]. Wissing et al[26] and Persoon et al[27] both concluded that patients with chronic leg ulcers have a poorer quality of life. Similar findings have been found for people with diabetic foot and pressure ulcers[9].

Although it is possible to measure the direct health costs of wound care, the implications for individual patients and their family are more difficult to measure.

Treatment of a non-healing wound is demanding on both the patient and carers' time, and frequently requires multiple clinic visits or weekly dressing appointments over many months. For younger patients this may involve time off work or loss of employment with significant financial implications for them and their families. This can also affect patients' mobility and ability to drive a car as well as their general health and social wellbeing.

The more wound healing is delayed the more it impacts on the patient. Symptom control is important in all wounds, but particularly for those of long duration. Pain management, exudate control and odour management are some of the main issues that impact on both the patient and his/her family's quality of life[28, 29]. Failure to control these issues will adversely affect concordance and increase the chance of non-healing[9].

Pragnell and Neilson[30] emphasise the extreme psychological impact that hard-to-heal wounds have on the patient, as well as the challenge they pose to the clinical team in terms of resource expenditure. Non-healing can also have a psychological influence on clinicians who are providing care, who may be emotionally overwhelmed by their inability to alleviate suffering and achieve wound healing[31].

Impact of hard-to-heal wounds on resources

Reducing health costs is a recurring global issue. Wound management is a major area where there is a drive for improved cost-effectiveness[9]. Costs are higher for hard-to-heal and long duration wounds as the frequency of therapy, staff time and product use increases[32, 33].

Reducing costs while optimising quality of life for patients with delayed wound healing requires the following:

- **Early identification of hard-to-heal wounds**
- **Targeted use of advanced wound care products.**

The latter must involve a plan to address specific issues within the wound, a defined goal and a timeline for use.

What is the role of advanced therapies?

Using the principles of wound bed preparation, which is now well established and forms the basis for much of modern wound management[34], together with advanced therapies may help to promote healing by restoring or preventing the breakdown of the extracellular matrix. This may be achieved through the addition of deficient components, such as growth factors and collagen, or the introduction of a temporary matrix[35,36].

However, without maintenance debridement and normalisation of proteases and the inflammatory process, an effective extracellular matrix cannot be restored and healing is unlikely to progress[37]. This process, which establishes a stable wound environment, is therefore necessary before the addition of active wound management components such as growth factors, collagen and cellular constructs can be effective.

Advanced therapies may be considered following:

- **Comprehensive assessment of the patient and the wound to identify/ address known risk factors for delayed healing**
- **Clinical observation/ documentation over a 3-4 week period, with failure to respond to standard therapy.**

Benefits of using advanced therapies

Improved healing rates and a reduction of symptoms from a non-healing wound are of benefit to the patient, but does come with additional cost burdens for healthcare providers. The introduction of advanced therapies can, if used appropriately, result in long-term savings despite initial increased treatment costs. A number of economic studies have demonstrated the cost and clinical benefits that may be derived from the appropriate use of advanced products, both in relation to the wound and the periwound skin[38, 39]. The potential advantages of advanced wound care products, include:

- **Earlier control of symptoms**
- **Promotion of wound closure**
- **Improved quality of life**
- **Reduced healthcare costs.**

Monitoring the response

For all patients with wounds, it is important to monitor healing progress and measure outcomes according to the treatment goals set.

If the wound fails to reduce in size or there is no improvement within the expected timeframe using standard therapy, it is essential to reassess the patient and alter the treatment regimen accordingly[9]. This should include a review of the treatment plan to ensure the therapy has been applied correctly and the patient has been concordant. Involving patients in the decisions about their treatment requires the establishment of a good alliance between the patient and clinician to ensure priority is given to achieving symptom control, with the elimination of pain and tolerance of the therapy[9].

Summary

In managing those patients with hard-to-heal wounds, it is important to get the basics right and recognise and address potential barriers to healing early in the treatment cycle. If that is achieved most wounds will progress towards healing. This includes the need to review the assessment and diagnosis, confirm that treatment is both appropriate and has been applied correctly. Once these issues have been addressed there is undoubted benefit for the targeted use of advanced products, which aim to address specific wound problems. For those few wounds where healing is an unrealistic goal, it is important to ensure good symptom control and address patient quality of life issues.

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