Why don’t wounds heal?

The healing of a wound is achieved by way of the integrated phases of haemostasis, inflammation, proliferation, and remodelling [Table 1], which must occur in the proper sequencing and time period, without interference and at an optimal intensity, in order for a wound to heal normally\(^1\).

**Normal stages of wound healing**

**Rapid haemostasis**

Haemostasis begins as soon as the wound occurs, with constriction of the blood vessels and fibrin clot formation. The blood clot and surrounding tissues release pro-inflammatory cytokines and growth factors, such as platelet-derived growth factor (PDGF) \(^1\). These growth factors stimulate epithelial cells, recruit fibroblasts, and recruit neutrophils and monocytes, resulting in initiation of the inflammatory phase of wound healing\(^2\).

**Appropriate inflammation**

Once bleeding is controlled, the inflammatory cells migrate into the wound. This stage involves the sequential infiltration of neutrophils, macrophages and lymphocytes into the wound site\(^3-5\). Neutrophils are responsible for phagocytosing cell debris and microorganisms, ensuring defense against infection. As they die, neutrophils release intracellular enzymes (e.g. elastase), which further digest tissue. Macrophages also phagocytose bacteria and provide a second line of defence, as well as secreting extracellular enzymes (matrix metalloproteases [MMPs]) to degrade necrotic tissue at the wound site. Macrophages also secrete various cytokines and growth factors — such as fibroblast growth factor, epidermal growth factor, transforming growth factor-beta and interleukin-1 — which are important in the next stage of healing\(^6\).

The role of T-lymphocytes — which migrate into the wound following inflammatory cells and macrophages — is not completely understood, although several studies suggest that delayed infiltration and decreased concentration of T-cells at the wound site may be associated with impaired healing. Other studies report that subsets of T-lymphocytes have differential effects on wound healing, suggesting a positive role for CD 4+ cells in wound healing and an inhibitory role for CD 8+ cells\(^7-8\).

**Proliferation and re-growth of the epithelial tissue surface**

The proliferative phase, which usually overlaps with the inflammatory phase, is characterised by re-epitheliasation, whereby epithelial cells

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**Table 1: The phases of normal wound healing**\(^1\)[\(^2\)].

<table>
<thead>
<tr>
<th>Phase</th>
<th>Time frame</th>
<th>Cells involved</th>
<th>Function of activity</th>
<th>Cellular and bio-physiologic events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haemostasis</td>
<td>Immediate</td>
<td>Platelets</td>
<td>Clotting</td>
<td>Vascular constriction, Platelet aggregation, degranulation, and fibrin formation (thrombus)</td>
</tr>
<tr>
<td>Inflammation</td>
<td>Day 1 – 4</td>
<td>Neutrophils, Macrophages</td>
<td>Phagocytosis</td>
<td>Neutrophil infiltration, Monocyte infiltration, and differentiation to macrophages, Lymphocyte infiltration</td>
</tr>
<tr>
<td>Proliferation</td>
<td>Days 4 – 21</td>
<td>Macrophages, Lymphocytes, Angiocytes, Neurocytes, Fibroblasts, Keratinocytes</td>
<td>Fill defect, Re-establish skin function, Closure</td>
<td>Re-epithelialisation, Angiogenesis, Collagen synthesis</td>
</tr>
<tr>
<td>Remodelling</td>
<td>Day 21 – 2 years</td>
<td>Fibrocytes</td>
<td>Develop tensile strength</td>
<td>Collagen remodelling, Vascular maturation and regression</td>
</tr>
</tbody>
</table>

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proliferate and migrate over a provisional matrix within the wound[10].

In the reparative dermis, fibroblasts and endothelial cells are the most prominent cell types. These cells have a number of functions including supporting capillary growth, as well as formation of collagen and granulation tissue at the wound site. Endothelial cells are important during the process of angiogenesis, where they support regeneration of the capillary linings[11]. In the wound bed, fibroblasts produce collagen, glycosaminoglycans and proteoglycans, all of which are important components of the extracellular matrix[11].

**Synthesis, cross-linking and alignment of collagen**

Once fibroblast cells have secreted the collagen framework upon which further dermal regeneration can occur, the remodelling phase of the wound healing process can begin. The remodelling phase involves the realignment of this collagen tissue to develop tensile strength, and can take up to 2 years[12]. During this phase, the vascular density of the wound also returns to normal[11].

**When is a wound defined as non-healing?**

When these precise processes occur normally, a wound should reach re-epithelialisation within 4 weeks. However, the normal wound healing process is complex, involving multiple interlinked phases that must occur in a timely fashion, but are each vulnerable to interruption by external and internal inhibitory factors[9]. As such, some wounds fail to progress through this orderly and timely repair sequence, leading to delayed healing, also known as wound ‘stalling’. Where healing is delayed, wounds can become chronic, posing a number of difficulties to both the patient and healthcare system, including increased costs[9].

**What factors may contribute to delayed healing?**

Wound healing can stall for numerous reasons, related to the individual patient, their specific wound, and to a variety of biophysiological factors. In order to recognise that a wound is non-healing, the wound itself, the surrounding area, and the systems of care in place must be carefully assessed so that any precipitating factors acting as a barrier within the healing process can be quickly identified and resolved[9].

**Patient-related factors**

Patients with underlying pathologies and comorbidities, such as coronary artery disease or diabetes mellitus, may experience compromised healing. Studies have shown that vascular insufficiency is a common cause of arterial, diabetic, pressure or venous ulcers, affecting the lower extremities of the body[10].

Patients with diabetes mellitus are well documented to exhibit poor wound healing, and are prone to developing chronic diabetic foot ulcers (these are estimated to occur in 15% of all patients with diabetes). Multiple mechanisms, including decreased cell growth and local angiogenesis, contribute to this poor healing. In addition, people with diabetes have a number of additional risk factors, such as neuropathy and an impaired ability to fight infection, and are largely unable to mount an adequate inflammatory response to wounding. All of these factors increase the risk of delayed healing and can lead to sepsis and limb amputation. Indeed, there are over 100 known physiologic factors that contribute to wound healing deficiency in diabetic patients[11].

Patients undergoing treatments or taking certain medication for other conditions, such as radiotherapy, may also be at risk of delayed wound healing. In the case of radiation therapy, the immune system is suppressed, which can cause ulceration either during treatment or once the treatment is completed[15]. Many medications, particularly those that affect blood clot formation or platelet function, also disturb healing; commonly, glucocorticoid steroids, non-steroidal anti-inflammatories, and chemotherapeutic drugs interfere with normal wound healing[1].

Healing may also be impeded by a number of systemic factors that appear to bare no relation to the wound itself, such as age, body type, alcohol consumption, and nutritional status [Figure 1][16].

The age of a patient can affect the healing trajectory of a wound. Older patients may have a number of comorbidities that increase the risk of skin breakdown and delay healing, such as poor nutrition, altered hormonal response and problems with the immune, circulatory, or respiratory systems[16]. Differences in healing capacity of older patients compared with younger patients can be seen at each stage of the process, including enhanced platelet aggregation, delayed macrophage and lymphocyte infiltration, delayed re-epithelialisation and reduced collagen remodelling[1].
Lifestyle choices also play a role in wound healing success, with nutrition, smoking and alcohol consumption all affecting outcomes. Good nutritional status is essential for wound healing to take place. Ignoring nutritional status may compromise the patient’s ability to heal and subsequently prolong the stages of wound healing. For example, an obese patient may experience compromised wound healing due to inadequate blood supply to adipose tissue or protein malnutrition, whereas patients who are emaciated may lack the oxygen and nutritional stores required for normal wound healing. These studies highlight the importance of assessing a patient’s nutritional status to ensure that, regardless of visual appearance, they are not malnourished.

Studies have also shown that alcohol exposure impairs wound healing and increases infection incidence, with intoxication at the time of wounding a risk factor for infection susceptibility. A review of the effect of alcohol on host defense showed that short-term alcohol exposure leads to suppressed pro-inflammatory cytokine release. Moreover, the higher rate of infection in patients with acute alcohol exposure correlates with decreased neutrophil recruitment and phagocytic action. The association between cigarette smoking and delayed wound healing is also well recognised. Nicotine is a vasoconstrictor that reduces nutritional blood flow to the skin, resulting in tissue ischaemia and impaired healing of injured tissue. Proliferation of red blood cells, fibroblasts, and macrophages are also reduced by nicotine. Additionally, carbon monoxide in cigarette smoke leads to tissue hypoxia, and hydrogen cyanide impairs cellular oxygen metabolism.

Wound-related factors
There is evidence to suggest that a number of wound-specific factors play an important role in healing processes. In a study of 30,000 patients with diabetic foot ulcers, the three most important wound-related factors that affected healing outcome were size, depth, and duration of the wound. A study by Margolis and colleagues indicated patients with wounds larger than 2 cm², of more than 2 months’ duration and with penetration through to exposed tendon, ligament, bone or joint, had only a 22% chance of healing by 20 weeks.

Wound duration is a recognised indicator for non-healing across a variety of wound types, relating perhaps to the development of senescent cells that are unable to replicate. An accumulation of greater than 15% senescent fibroblast cells has been described as a threshold beyond which wounds become difficult to heal. In addition, it is expected that large wounds will take longer to heal than small wounds, and the longer a wound is open, the greater the risk of complications, such as infection. If infection is present — as evidenced by signs such as pain, heat, swelling, erythema, and loss of function — it is important to treat appropriately to accelerate healing.

Delayed or non-healing may also be due to a number of other local factors, including desiccation, maceration, necrosis, pressure, or oedema. A moist environment is essential to healing, with moisture first appearing during the inflammatory phase when the fibrin clot is degraded and capillaries dilate and become permeable. Indeed, the process of epithelialisation — whereby new skin cells form over the wound — is dependent on the presence of moisture. However, excessive wound exudate can be detrimental to wound healing, particularly in chronic wounds, where exudate can contain cellular debris and enzymes that harm the wound bed and periwound skin. Conversely, in a dry environment, a wound can become desiccated and cells will typically dehydrate and die; such wounds heal more slowly and painfully than moist wounds.

Necrotic tissue results from the accumulation of dead cells and debris following haemorrhage. Necrotic tissue can impair assessment attempts and will act as a focal point for infection. As such, dead or

Figure 1. Patient factors that affect wound healing.
devitalised tissue should be removed before repair and healing can occur. If pressure at the wound site is excessive or sustained, this can also impair healing since the blood supply to the area may be disrupted. Additionally, any wound that is deprived of an adequate blood supply as a result of trauma or oedema may also be at risk of non-healing.

Bio-physiological factors

The biochemistry of a non-healing wound is stuck in a state of perpetual inflammation; it is necessary to break this cycle in order for a wound to heal. The elevated levels of inflammatory cytokines, free radicals, and proteases found in chronic wounds create an environment not conducive to healing, and while a wound remains in a stalled state, this hostile environment is sustained and non-healing continues to be perpetuated. Although inflammation is a normal part of the wound healing process, where elevation of pro-inflammatory cytokines continues and elongates the inflammation phase, healing can be delayed. Prolonged inflammation leads to increased levels of serine proteases, such as elastase and plasmin, and MMPs, a group of proteases that break down the extracellular matrix, and a decrease in naturally occurring protease inhibitors. This shift may cause degradation in growth factors, which are important in the proliferation stage of healing. In addition, the presence of bacteria may increase the inflammatory response and intensify an already hostile healing environment.

Clinical competency and service delivery

Although factors affecting wound healing have often only been described from a patient perspective, there are also numerous factors relating to clinical competency and environment of care that may influence wound healing. The healthcare professional’s knowledge and attitude can have a great impact on clinical outcome; for example, quality of assessment, their ability to control a patient’s symptoms and management of underlying comorbidities. Healthcare professionals providing patient-centred care will take into consideration the patient’s individual needs, discuss potential barriers to healing, and provide support while calling on other professionals and agencies where needed, aiming to ensure the care they provide is holistic.

How does non-healing manifest itself in clinical signs and symptoms?

The longer a non-healing wound is left without appropriate treatment, the worse it is likely to become. Therefore, it is important to recognise a number of symptoms and clinical signs that may be manifest when a wound is failing to heal within the proper sequence and time. Table 2 lists a number of signs and symptoms that may indicate that a wound is failing to progress along a normal healing trajectory. These symptoms and signs of non-healing indicate a need to re-evaluate the underlying cause of the wound and look for factors that could be contributing to non-healing. Indeed, they may provide the stimulus needed to properly treat an underlying condition or address inadequacies in service delivery, thereby enabling the healing process to proceed in an orderly fashion.

Conclusion

The normal sequence of wound healing, which comprises four interlinked phases, can often be compromised and prolonged. If the intricate building blocks of normal wound healing are disrupted, complete healing may never be achieved. Some barriers to healing may be obvious, such as identifiable comorbidities and concomitant treatments, but other factors may not be immediately apparent. As such, effective wound assessment must look at a wound’s complexity, ability to heal and potential barriers to healing, as well as taking into account clinical signs and symptoms of non-healing, so that problems within the healing cycle can be quickly resolved. Treating early and appropriately is vital, considering use of advanced therapies if standard of care
is not enough to heal a wound, since the longer a compromised wound is left without appropriate treatment, the higher the risk of delayed or non-healing.

References


Table 2: How does non-healing manifest in clinical signs and symptoms?

<table>
<thead>
<tr>
<th>Description</th>
<th>Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>The wound is large in size; expanding or there is a failure to decrease in size over time</td>
<td></td>
</tr>
<tr>
<td>The wound bed is in poor condition with little healthy granulation tissue and little improvement is seen over time</td>
<td></td>
</tr>
<tr>
<td>There are higher than expected levels of exudate, which itself can lead to the healthy surrounding skin becoming macerated or ulcerated</td>
<td></td>
</tr>
<tr>
<td>There is evidence of critical colonisation or local infection, with signs such as pain, swelling, redness or loss of function</td>
<td></td>
</tr>
<tr>
<td>There is abnormal or persistent inflammation, which clinically can be difficult to differentiate from infection in a chronic wound</td>
<td></td>
</tr>
</tbody>
</table>