Basic Principles of Wound Healing

An understanding of the basic physiology of wound healing provides the clinician with the framework necessary to implement the basic principles of chronic wound care

BY

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Introduction

Wound healing is a complex and dynamic process, with the wound environment changing with the shifting health status of an individual. Knowledge of the physiology of the normal wound healing trajectory through the phases of hemostasis, inflammation, granulation and maturation provides a framework for understanding the basic principles of wound healing. Through this understanding, the healthcare professional can develop the skills required to care for a wound and the patient can be helped with the complex task of tissue repair.

Wounds that do not heal as expected should prompt the healthcare professional to search for unresolved underlying causes. A wound that does not heal as expected requires care that is patient-centred, holistic, interprofessional, collaborative, cost-effective and evidence-based.

This paper addresses the following topics: Why do wounds occur? How do they heal? What factors interfere with healing? When is a wound considered chronic? What is the nature of good chronic wound care? It is hoped that the explanations regarding these basic principles will provide a framework for further study and exploration into the complex area of wound management.

Why do wounds occur?

In any natural disaster, the damaging forces must be identified and stopped before repair work can begin. So, too, in wound care must the basic underlying cause(s) of a wound be identified and controlled as best as possible before wound healing can begin. Common underlying causes of tissue damage are listed in Table 1.

How do wounds heal?

Research regarding acute wounds in animal models demonstrates that wounds heal in 4 phases. It is believed that chronic wounds also undergo 4 basic phases of healing (although some authors combine the first 2 phases). These are:[1]

- hemostasis;
- inflammation;
- proliferation (also known as granulation and contraction); and
- remodelling (also known as maturation).

Kane's analogy to the repair of a damaged house provides a visual understanding of and connection to the basic physiology of wound repair (Table 2).[2]

Hemostasis

Once the source of damage to a house has been removed and before work can start, utility workers must cap damaged gas or water lines. So, too, in wound healing must damaged blood vessels be sealed. In wound healing, the platelets are the cells that act as utility workers sealing off the damaged blood vessels. The blood vessels themselves constrict

TABLE 1

Common underlying causes of tissue damage

- Trauma (initial or repetitive)
- Scalds and burns (thermal and chemical)
- Animal bites or insect stings
- Pressure
- Vascular compromise (arterial, venous, lymphatic or mixed)
- Immunodeficiency
- Malignancy
- Connective tissue disorders
- Metabolic disease, including diabetes
- Nutritional deficiencies
- Psychosocial disorders
- Adverse effects of medications

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TABLE 2

The 4 phases of wound healing

Phase of healing	Time post injury	Cells involved in phase	Function or activity	Analogy to house repair
Hemostasis	Immediate	Platelets	Clotting	Utility workers cap-off broken utilities
Inflammation	Day 1–4	Neutrophils Macrophages	Phagocytosis	Unskilled labourers clean up the site Contractors direct activity
Proliferation (granulation and contraction)	Day 4–21	Macrophages Lymphocytes Angiocytes Neurocytes Fibroblasts Keratinocytes	Fill defect Re-establish skin function Closure	Subcontractors start work: • framers; • plumbers; • electricians; and • roofers and siders
Remodelling (maturation)	Day 21–2 years	Fibrocytes	Develop tensile strength	Interior finishing

in response to injury, but this spasm ultimately relaxes. The platelets secrete vasoconstrictive substances to aid this process, but their prime role is to form a stable clot sealing the damaged vessel.

Under the influence of ADP (adenosine diphosphate) leaking from damaged tissues, the platelets adhere to the exposed type 1 collagen.[3] They become activated and secrete adhesive glycoproteins, leading to platelet aggregation. They also secrete factors that interact with and stimulate the intrinsic clotting cascade through the production of thrombin, which in turn initiates the formation of fibrin from fibrinogen. The fibrin mesh strengthens the platelet aggregate into a stable hemostatic plug.

Finally, platelets also secrete growth factors such as platelet-derived growth factor, which is recognized as one of the first factors in initiating the subsequent healing steps. These growth factors recruit neutrophils and monocytes (initiating the next phase of wound healing), stimulate epithelial cells and recruit fibroblasts. Hemostasis occurs within minutes of the initial injury unless the patient has underlying clotting disorders.

Inflammation

Clinically, inflammation (the second stage of wound healing) presents as erythema, swelling and warmth often associated with pain, the classic "rubor et tumor cum calore et dolore." This stage usually lasts up to 4 days post injury. In the damaged house analogy, once the utilities are capped the second job is to clean up the debris. This is a job for unskilled labourers. In a wound, these unskilled labourers are the neutrophils (polymorphonucleocytes).

The inflammatory response causes the blood vessels to become leaky, releasing plasma and neutrophils into the surrounding tissue.[4] The neutrophils phagocytose debris and microorganisms and provide the first line of defence against infection. As they digest bacteria and debris, neutrophils die and release intracellular enzymes into the surrounding matrix, which further digest tissue. As fibrin is broken down as part of this clean-up, the degradation products attract the next cells involved such as fibroblasts and epithelial cells. They are aided by local mast cells.

The task of repairing a house is complex and requires someone, such as a contractor, to direct this activity. Similarly, wound repair requires coordinated cell activity and good cell-to-cell communication. Cells communicate through soluble proteins call cytokines and growth factors. These cytokines and growth factors are released by 1 cell and bind to a receptor on a target cell. Once a cytokine binds to a target cell it stimulates the cell to move. Growth factors, on the other hand, stimulate the target cell to either divide and produce more cells or synthesize and release substances such as collagen, which is required to form the extracellular matrix. The extracellular matrix also plays an active role in wound healing by interacting with the cells through receptors called integrins, leading to platelet activation, epithelial migration and fibroblast movement.[5]

In wound healing, cells known as macrophages act as the "contractors." Circulating monocytes differentiate into macrophages after they exit the blood vessels and come in contact with the extracellular matrix. Macrophages are able to phagocytose bacteria and provide a second line of defence. Macrophages also secrete extracellular enzymes to degrade necrotic tis-

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TABLE 3

Differentiating inflammation from infection[7]

Inflammation	Factor	Infection
Coexisting systemic disease	**Comorbidity**	Decreased host resistance
Constant, onset	**Pain**	Increasing with lesions
Multiple sites, symmetric	**Location**	Single location, asymmetric
Palpable purpura, livedo pattern, rolled border, focal necrosis satellite lesions	**Morphology**	Classic or subtle signs of infection, soft tissue crepitus
Local	**Erythema**	Advancing
Normal or warm	**Skin temperature**	Warm or hot

sue at the wound site. These enzymes belong to a family of substances called matrix metalloproteases (MMPs). MMPs require calcium to form a functional shape and zinc for the active site.

About 20 different types of MMPs are secreted by many different cells — including neutrophils, macrophages, epithelial cells and fibroblasts — under the influence of inflammatory cytokines such as tumour necrosis factor-alpha and interleukin-1 and -6. MMPs act on all components of the extracellular matrix and are responsible for removing devitalized tissue, repairing lost or damaged tissue and remodelling. MMPs are balanced by tissue inhibitors of metalloproteases (TIMPs), which are released locally by cells and inactivate MMPs by reversibly binding to them. Uncontrolled MMPs can degrade newly formed tissue or destroy growth factors.

Macrophages secrete a variety of cytokines and growth factors — such as fibroblast growth factor, epidermal growth factor, transforming growth factor-beta and interleukin-1 – which appear to direct the next stage.[6]

Inflammation – the body's response to trauma — can be confused with infection. However, inflammation is a normal response to tissue injury, but with increased bacterial burden and decreased host resistance (Table 3).[7]

Proliferation

The proliferation phase starts approximately 4 days after wounding and usually lasts until day 21 in acute wounds, depending on the size of the wound and the health of the patient. It is characterized by angiogenesis, collagen deposition, granulation tissue formation, wound contraction and epithelialization. Clinically, proliferation is observed by the presence of pebbled red tissue or collagen in the wound base and involves replacement of dermal tissues and sometimes subdermal tissues in deeper wounds, as well as contraction of the wound. In the house analogy, once the site has been cleared of debris under the direction of the contractor, framers move in to build the framework of the new house. Subcontractors can now install new plumbing and wiring on the framework and siders and roofers can finish the exterior of the house.

The "framer" cells are fibroblasts, which secrete the collagen framework on which further dermal regeneration occurs. Specialized fibroblasts are responsible for wound contraction. The "plumber" cells are the pericytes, which regenerate the outer layers of capillaries, and the endothelial cells, which produce the lining. This process is called angiogenesis. The "roofer" and "sider" cells are the keratinocytes, which are responsible for epithelialization. In the final stage of epithelialization, contracture occurs as the keratinocytes differentiate to form the protective outer layer or stratum corneum.

In a healing wound, the cells under the influence of growth factors divide to produce new cells, which migrate to where they are needed under the influence of cytokines. There is a balance between the MMPs and TIMPs so that there is a net production of new tissue. In chronic wounds, in contrast, in which healing is stalled, cell division and migration are suppressed, there are high levels of inflammatory cytokines and MMPs, and low levels of TIMPs and growth factors. Cells are often senescent and unresponsive to the growth factors. This lack of response is characteristic of a chronic inflammatory state. It may be caused by an increased bacterial burden, the presence of devitalized tissue, chronic ischemia or repetitive trauma.

Infection = (number of organisms × virulence of organisms) ÷ (host resistance)

Remodelling

Once the basic structure of the house is completed, interior finishing may begin. Similarly, in wound repair, the healing process involves remodelling and realignment of the collagen tissue to produce greater tensile strength. In addition, cell and capillary density decrease. The main cells involved in this process are the fibroblasts. Remodelling can take up to 2 years after wounding. This explains why closed wounds can quickly breakdown if attention is not paid to the initial causative factors.

Defining the wound care process

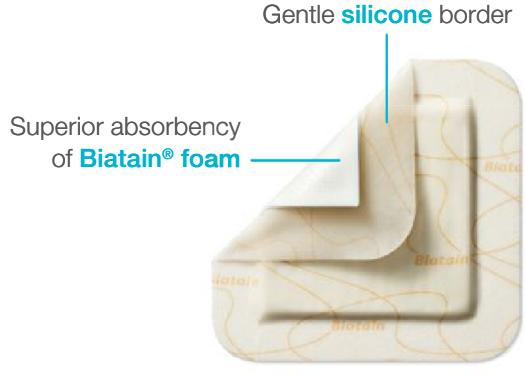
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TABLE 4

Healability of wounds

Type of wound	Characteristics	Examples
Healable	• Causes and cofactors that can interfere with healing have been removed • Wound healing occurs in a predictable fashion • May be acute or chronic	Pressure ulcer, where pressure and other factors such as shear are managed
Maintenance	Causes and cofactors that can interfere with healing are removable but have not been removed due to patient or system factors	Pressure ulcer, where pressure is not managed
Nonhealable	Causes and cofactors that can interfere with healing cannot be removed	Gangrenous foot or malignant wound

determine the type of wound they are caring for to set realistic goals:

- *Acute wounds:* Heal in a normal, orderly sequence of repair as described above.
- *Chronic wounds:* Fail to progress through a normal, orderly and timely sequence of repair, usually because of unresolved factors that interfere with healing. These wounds may eventually pass through the repair process without restoring sustained anatomical and functional results.

Factors that can interfere with healing

Louis Pasteur stated: "The germ is nothing. It is the terrain in which it is found that is everything." It is very similar with wounds! Factors that interfere with wound healing must be addressed in a holistic fashion looking, as Pasteur suggested, at the terrain in which the wound is found. The individual with a wound has a wide terrain, from the local wound environment to the environment in which he or she lives, and that terrain may determine healability. In other words, wounds do not exist in isolation from the patient as a whole.

Factors that may interfere with healing in the local wound environment include infection, necrotic tissue and the vascular supply. In addition, coexisting physical and psychological factors such as nutritional status, disease states (e.g. diabetes, cancer, arthritis) and mental health problems can all impact wound healing.

The next environment is the home in which the patient lives. This may raise concerns regarding immobility, cleanliness and family support. The broader community environment can also impact wound healability through the availability of support services such as personal care in the home, the financial cost of supplies and services, and the availability of skilled personnel and facilities.

Once healability is determined, wounds can be classified as healable, maintenance or nonhealable (Table 4).

When is a wound considered chronic?

In healthy individuals with no underlying factors, an acute wound should heal within 3 weeks with remodelling occurring over the next year or so. If a wound does not follow the normal trajectory then it may become stuck in 1 of the 4 phases, becoming chronic. Chronic wounds are thus defined as wounds that have "failed to proceed through an orderly and timely process to produce anatomic and functional integrity, or proceeded through the repair process without establishing a sustained anatomic and functional result."[8]

The presence of a chronic wound should trigger the clinician to search for underlying causes that may not have been addressed. Better yet, an understanding of the causative factors should lead clinicians to proactively address these factors in at-risk populations so that chronic wounds are prevented.

Best practice and wound healing

Wound healing is a science, but due to the complex nature of the patient it is also an art. The care required to support wound healing needs to be guided by both the available evidence and clinical judgment. Clinical decision-making also involves considering patient preferences, circumstances, values and rights.

Once the clinical problem has been identified and a wound-healing outcome determined, there are 3 key steps:[9]

1. Identify the best evidence available for treatment.
2. Evaluate the client, patient or resident risk factors.
3. Recognize limitations in: available resources; staff and human resources; equipment and supplies; and assessment tools and techniques.

Best practice = consideration of the best evidence + patient risk + available resources

Evaluation of healing

Clinicians must remember that wound closure is only 1 outcome parameter. Patients with wounds that are unlikely to heal (e.g. maintenance or nonhealable wounds) must have alternative outcome expectations. These might be wound stabilization, reduced pain, reduced bacterial load, decreased dressing changes or a return to normal daily routines and activities.[10]



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Figure 1. An elderly patient who suffered trauma when she banged her leg on a coffee table. She is on warfarin, which contributed to the injury becoming a large black hematoma. What is the safest way to support the healing of this wound?

Figure 2. A young spinal-cord-injured patient with a chronic pressure ulcer surrounded by erythema. Is the erythema caused by infection, irritation of wound fluid, incontinence or continual pressure to the area?

Figure 3. Chronic ulcers in a frail elderly woman with a long history of lower leg edema related to decreased mobility. The ulcer drains copious amounts of chronic wound drainage causing irritation to the surrounding skin. The patient sits for most of the day, which worsens the leg edema. Although compression is now reducing the edema, how can the wound fluid be controlled to enable healing?

Wound-healing challenges

The clinician working in wound care needs to become a detective. All possible factors and cofactors that may influence healing must be identified. Due to the multifactorial nature of chronic wounds, a thorough health and physical assessment is mandatory (Figures 1, 2 and 3).

Summary and conclusions

The wound-healing approach must incorporate the following themes:

- *Patient centred:* The clinician should remember that he or she is treating with a person who happens to have a chronic wound. A comprehensive wound-management plan can be developed, but without patient buy-in it is doomed to fail.
- *Holistic:* Best practice requires the assessment of the "whole patient," not just the "hole in the patient." All possible contributing factors must be explored.
- *Interprofessional:* Wound care is a complex business that requires skills from many disciplines. Nurses, physiotherapists, occupational therapists, dietitians, chiropodists or podiatrists, orthotists and physicians (both generalists and specialists) should all be included in the team. In some clinical settings, other professionals such as social workers or rehabilitation specialists may also be involved in care. Management and administration should be a further part of the team to support the team and provide required resources or practice change.
- *Evidence-informed:* In today's healthcare environment, treatment must be informed by the best available evidence and demonstrate cost-effectiveness.

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