

Wound Healing and Perioperative Care

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Wounding or injury unleashes a tightly choreographed array of cellular, physiologic, biochemical, and molecular processes directed toward restoring the integrity and functional capacity of the damaged tissue. Healing in the orofacial region usually is taken for granted, yet a variety of local and systemic factors can hinder the process of tissue restitution and set the stage for adverse outcomes. Although surgical attention invariably focuses on local wound care, consideration of systemic factors is equally important. An understanding of the biologic underpinnings of the wound-healing continuum provides surgeons with a framework for developing the skills required to care for wounds and facilitate healing.

How do wounds heal?

Wound healing starts immediately after injury and generally progresses in an established sequence of overlapping phases: hemostasis, inflammation, proliferation, and remodeling. Kane's analogy of wound healing to the repair of a damaged house provides a simple framework for understanding the complex interplay of the cellular events that comprise healing (Table 1) [1].

As with a house destroyed by a natural disaster, the initial response is directed toward minimizing further damage by capping off the broken vascular

conduits. Functioning as utility workers, arriving platelets go about sealing off the damaged blood vessels. They secrete substances to augment the reflexive vasoconstriction of the injured vessels and aggregate rapidly at the wound site, adhering to each other and the exposed vascular subendothelial collagen to form a primary platelet plug organized within a fibrin matrix. The clot secures hemostasis and provides a provisional matrix through which succeeding reparative cells can migrate. Degranulating platelets initiate the subsequent reparative steps by releasing various cytokines and growth factors, including interleukins, transforming growth factor-beta (TGF- β), and platelet-derived growth factor. Unless there are underlying clotting disorders, hemostasis usually is complete within minutes of the initial injury.

Once hemostasis is secured, the inflammatory phase begins and lasts for up to 4 days post injury. Clinically, the inflammatory phase is characterized by pain, heat, redness, and swelling. Cytokines released at the wound site sequentially recruit neutrophils and monocytes to the site of injury. Arriving neutrophils or polymorphonucleocytes serve as the nonskilled laborers involved in site preparation. They swarm around the site and clean up the rubble. Aided by local mast cells, the neutrophils ingest tissue debris and microorganisms by phagocytosis and provide the first line of defense against infection. As they perish, the short-lived neutrophils release proinflammatory cytokines that continue to stimulate the inflammatory response. Around this time, the general contractor cell or macrophage is established at the site and begins to direct the subsequent activities of the specialized subcontractor cells. The macrophages, essentially activated monocytes, continue with the wound microdébridement initiated by the neutrophils. In ad-

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Table 1
Kane's analogy of wound-healing phases to house restoration

Healing phase	Time	Principal cells	House-building analogy
Hemostasis	Immediate	Platelets	Capping of damaged conduits
Inflammation	Day 1–4	Neutrophils	Unskilled laborers for site cleanup
Proliferation/ granulation	Day 4–22	Macrophages	Supervisor
		Lymphocytes	Specific site preparation
		Angiocytes	Plumbers
		Neurocytes	Electricians
		Fibroblasts	Framers
Remodeling	Day 22– 2 years	Keratinocytes	Roofers
		Fibrocytes	Remodelers

Adapted from: Kane D. Chronic wound healing and chronic wound management. In: Krasner D, Rodeheaver GT, Sibbald RG, editors. *Chronic wound care: a clinical source for healthcare professionals*. 3rd edit. Wayne (PA): Health Management Publications; 2001. p. 7–17.

dition, they release a slew of growth factors and cytokines (TGF- β , fibroblast growth factor, interleukin 1, insulin-like growth factor I and II, and so forth) that stimulate and direct the succeeding proliferative phase [2].

Beginning as early as the third day post injury and lasting up to 3 weeks, the proliferative phase is distinguished by the formation of pink, granular tissues containing inflammatory cells, fibroblasts, and budding vasculature enclosed in a loose matrix. Using a housing-building analogy, the framer cells or fibroblasts move into the cleared site and, working under the direction of the general contractor, begin the framing or reinforcing of the wound with collagen fibers. Concomitantly, specialized cells, such as the angiocytes and neurocytes, install new plumbing and wiring through the framework. As the framing proceeds, the epidermal cells begin their task as roofers and help provide a protective outside barrier through re-epithelialization.

Once the basic infrastructure of the wound is established, the wound enters the remodeling phase and most activity moves inwards. Through progressive remodeling and strengthening of the framework, the immature scar tissue eventually is replaced by a more refined and organized tissue that is closer to the native tissue. The fibroblasts are the principal

facilitators of the remodeling phase, which can last for several years. They act as the source of collagen and the proteoglycans that make up the extracellular matrix. Homeostasis of scar collagen and extracellular matrix is regulated to a large extent by serine proteases and matrix metalloproteinases under the control of regulatory cytokines. Tissue inhibitors of the matrix metalloproteinases provide a tight control of proteolytic activity within the scar. Any disruption of this orderly balance can lead to excess or inadequate matrix degradation and can result in either an exuberant scar or wound dehiscence.

Factors associated with impaired healing can be grouped into two classes, local and systemic. Local factors include the presence of foreign bodies, tissue maceration, wound ischemia, and increased bioburden. Systemic factors include advanced age, malnutrition, and coexisting diseases. Good surgical practice involves a proactive assessment of the impact of these cofactors on healing and, when possible, making use of clinical strategies to remove or reduce the impact of these factors.

What interferes with wound healing?

Wound bioburden

All bacteria impose a metabolic load on wounds because they compete with new tissue for nutrients and oxygen and produce byproducts that are harmful to the normal physiologic balance of the healing wound. The bacterial burden, also known as wound bioburden [3], provokes various degrees of inflammation in the wounded tissue through released endotoxins and metalloproteinases that can degrade fibrin and local wound growth factors. The fibrin matrix is essential for fibroblast migration and macrophage phagocytic activity. Newly formed cells and their collagen matrix, in particular, are susceptible to these breakdown products of wound infection. Depending on local tissue conditions and the quality of the host immune response, the wound bioburden can progress from a simple contamination to critical colonization and, eventually, frank infection. The clinical diagnosis of wound infection usually is made on the basis of the presenting signs (induration, pus, pain, and erythema) and can be confirmed by a wound culture that shows greater than 10^5 organisms per gram of tissue [4,5].

All wounds, in particular oral wounds, are contaminated, and the progression to frank infection in a contaminated wound can be visualized as a set of

scales. The beneficial effects of local wound care and host immunocompetence tip the scale in the direction of healing. Alternatively, the quantity and mix of the infecting microorganisms and infection-potentiating factors, such as hematoma, necrotic tissue, and foreign bodies, tilt the balance toward infection. Other local factors that may allow the wound-infection continuum to advance after oral surgery include continued tissue trauma from prostheses, avascular bone chips in fractures or osteotomies, and implanted biomaterials. Some bioimplants irritate wounds mechanically, whereas others solubilize in the biologic environment and provoke a chemical irritation. Even biocompatible devices, such as bone plate and screws, can act as a nidus for infection. Once an implant-associated infection develops, it is difficult to control without removal of the foreign body. To the extent possible, all elective incisions should be placed to avoid trauma under function.

A competent immune system and antibiotics are no substitute for meticulous surgical technique and proper wound toilet. To minimize the effects of the wound bioburden, the treatment should be based on sound surgical principles. Techniques include careful wound débridement, diluting the bacterial counts by copious wound irrigation before closure, and systemic antibiotics used, when necessary, in tandem with local antiseptics. If antibiotics are administered, they must be given before surgery or shortly after the injury, because adequate tissue levels of the antibiotic are not achieved for up to 90 minutes after an intravenous dose [6].

Age

As people age, the entire healing process occurs more slowly. The major components of the healing response in aging skin or mucosa are deficient or damaged with progressive injuries [7]. As a result, free oxidative radicals continue to accumulate and are harmful to the dermal enzymes responsible for the integrity of the dermal or mucosal composition. In addition, the regional vascular support may be subjected to extrinsic deterioration and systemic disease decompensation, resulting in poor perfusion capability [8]. Beyond the gradual decline in the physiologic processes, elderly patients have a greater incidence of chronic conditions, including cardiovascular disease, pulmonary disease, and diabetes. The systemic disease frequently compounds the deterioration in the regional vascular support and the restricted tissue perfusion can impair healing. In elderly patients undergoing maxillofacial surgery, preemptive steps to prevent complicated healing include mini-

mizing, where possible, extensive stripping of the periosteal and soft tissue envelope [9].

Poor tissue perfusion and oxygenation

Oxygen plays a critical role in all phases of the wound-healing cascade—inflammation, fibroplasia, epithelialization, angiogenesis, and remodeling [10,11]. Poor oxygenation interferes with the synthesis of collagen because oxygen is required for the hydroxylation of lysine and proline [12]. Wounds in hypoxic tissues are infected more easily and heal poorly as leukocytic, fibroblastic, and epithelial proliferation is depressed by low oxygen concentration. Delayed movement of neutrophils, opsonins, and the other mediators of inflammation to the wound site further diminishes the effectiveness of the phagocytic defense system and allows bacteria to proliferate. Most healing problems associated with diabetes mellitus, irradiation, small vessel atherosclerosis, chronic infection, and cardiovascular disease can be attributed to local tissue ischemia.

The local microcirculation after injury influences the wound's ability to resist the inevitable bacterial proliferation. Tissue traumatized by rough handling, or desiccated by cautery or prolonged air drying, tends to be poorly perfused and susceptible to infection. Similarly, tissue ischemia can be produced by tight or improperly placed sutures and poorly designed flaps. Hypovolemia, anemia, and peripheral vascular disease all affect wound healing adversely. Especially in trauma patients, therapy must be focused on keeping the wounds perfused with oxygenated blood. Cold, pain, and fear all induce catecholamine release, leading to increased sympathetic tone and increasing the peripheral vasoconstriction and tissue hypoxia. Peripheral blood flow can be improved by keeping patients warm and controlling pain and anxiety. It is important to maintain patients' cardiac output and intravascular volume. Anemia per se is not a cofactor in impaired healing; however, severe anemia (<20 mg/dL) should be corrected by transfusion. Patients evidencing clinical hypovolemia require fluid replacement therapy, because the depleted intravascular volume reduces the transport oxygen and nutrients to the tissues and has an impact on the cellular activities needed for healing.

Smoking tobacco is another common contributor to decreased tissue oxygenation [13]. After every cigarette, the peripheral vasoconstriction can last up to 1 hour; thus, a pack-a-day smoker remains tissue hypoxic for most of each day. Cigarette smoke contains carbon monoxide, which binds to hemoglobin, reducing the oxygen-carrying capacity of the blood.

Whenever possible, smokers should be asked to abstain from smoking for a minimum of 1 week before and after surgical procedures.

Concomitant disease

Wound healing can be impaired by a variety of systemic conditions, including diabetes mellitus, peripheral vascular disease, and immune compromise. Diabetics are predisposed to atherosclerosis and microangiopathy, which are associated with tissue hypoxia. There is impaired wound healing and an increased rate of wound infection in diabetics. The tissue hyperglycemia in poorly controlled diabetes affects the immune system adversely, including neutrophil and lymphocyte function, and increases the risk of infection [14]. Uncontrolled blood glucose hinders red blood cell permeability and impairs blood flow through the critical small vessels at the wound surface. The hemoglobin release of oxygen is impaired, resulting in an oxygen and nutrient deficit in the healing wound. The wound ischemia and impaired recruitment of cells resulting from the small vessel occlusive disease renders the wound vulnerable to bacterial and fungal infections. Well-controlled diabetics have a far lower incidence of wound-healing problems. Improving diabetic control before elective surgery reduces the incidence of wound-healing problems, although it does not reverse the microangiopathy.

Similarly, patients who have chronic renal failure and uremia have a disrupted immune response as manifested by depressed neutrophil function, leucopenia related to complement activation, diminished T and B lymphocyte function, and a reduction in natural killer cell activity. The attenuation of the inflammatory response makes these patients more susceptible to infection [15].

Patients who have a debilitated immune system include those who have HIV or AIDS and are in advanced stages of the disease, those on immunosuppressive therapy, those who have cancer or chronic disease, and those taking high-dose steroids for extended periods [16]. Immunocompromised patients are unable to mount an adequate immune response and all phases of healing are delayed. Studies indicate that HIV-infected patients who have CD4 counts less than 50 cells/ μ L are at significant risk of poor wound outcome [17].

Poor nutrition

Various nutrients are required for different phases of the healing process. Nutritional deficiencies severe

enough to lower serum albumin to less than 2 g/dL are associated with a prolonged inflammatory phase, decreased fibroplasia, impaired neovascularization, collagen synthesis, and wound remodeling. In malnourished patients, protein is diverted from cellular repair to providing the glucose required for cellular maintenance, further compounding the healing process. Lack of vitamin A depresses the inflammatory response, whereas the B-complex vitamins and cobalt are essential cofactors in antibody formation, white blood cell function, and bacterial resistance. Inadequate vitamin C can cause a lysis of collagen, such that fresh wounds have delayed collagen formation and healed wounds can break down. Trace minerals, including copper, iron, and manganese, are required as cofactors for producing enzymes necessary for all phases of wound healing. Data suggests that zinc repletion, in states of deficiency, returns healing to its normal rate [18]. Alternatively, exceeding the zinc levels can exert a distinctly detrimental effect on healing by inhibiting macrophage migration and interference with collagen cross-linking.

If possible, elective surgery should be postponed until nutritional deficiencies are corrected. Even a few days of repletion ameliorates wound-healing problems in malnourished patients [19]. Postoperatively, it is important to resume enteral feeding as soon as possible. If there are difficulties with swallowing or oropharyngeal wounds, a feeding tube can be useful. Total parenteral nutrition may be necessary if the gastrointestinal system must be bypassed.

Radiation injury

The effects of therapeutic radiation are permanent and related directly to the dose [20]. Impaired surgical wound healing can be seen at total doses above 5000 cGy. There is damage to the small blood vessels of the dermis and submucosa, with obliterative endarteritis and a decrease in overall vascular supply. The epithelium becomes thinned and fragile. Radiated tissues are traumatized easily, producing ulcers that are slow to heal. The dermis and submucosa become thickened and fibrotic with damaged fibroblasts [21]. Hypoxic, fibrotic tissue is less able to support normal wound healing and is predisposed to infection.

Hence, surgeons always must anticipate the possibility of a complicated healing after surgery or traumatic injury in irradiated tissue. Wound dehiscence is common and wounds heal slowly or incompletely. Even minor trauma may result in ulceration and colonization by opportunistic bacteria. If patients cannot mount an effective inflammatory

response, progressive necrosis of the tissues may follow. Healing can be achieved only by excising all nonvital tissue and covering the bed with a well-vascularized flap. Because of the relative hypoxia at the irradiated site, tissue with intact blood supply may need to be brought in to provide oxygen and the cells necessary for inflammation and healing.

Medications

Many drugs can impair the wound-healing process and, when possible, should be discontinued before elective surgery. Nonsteroidal anti-inflammatory drugs and other platelet inhibitors affect hemostasis and predispose to hematoma formation. They are best stopped 1 week before surgery. Depending on a patient's international normalized ratio, coumadin usually is stopped 2 or 3 days before surgery and substituted by low molecular weight heparin until hours before surgery. Anticoagulants are resumed as soon as the risk of surgical bleeding is over. Although a short course of perioperative steroids (used to reduce intracranial pressure or decrease surgical edema) has minimal effect on wound healing, chronic steroids inhibit almost every phase of wound healing and increase the risk of infection. Steroids suppress the inflammatory response, reduce immunocompetent lymphocytes, and decrease fibroplasia, collagen formation, and neovascularity [22]. Fibroblasts reach the site in a delayed fashion, and wound strength is decreased by as much as 30%. Epithelialization and wound contraction also are impaired. Unfortunately, chronic steroids rarely can be discontinued for surgery.

Antineoplastic agents exert their cytotoxic effect by interfering with the cell cycle. The reduction in protein synthesis or cell division manifests as impaired proliferation of fibroblasts and collagen formation in the healing wound. Attendant neutropenia also predisposes to wound infection by prolonging the inflammatory phase of wound healing. Chemotherapy also affects wound healing indirectly when nausea and vomiting produce malnutrition. Fortunately, the effects of these agents on wound healing are confined to the treatment period and immediately thereafter. Elective surgery often can be scheduled between cycles of therapy.

Intravenous bisphosphonates, zoledronic acid and pamidronate disodium, are used to prevent pathologic fracture in patients who have multiple myeloma or tumor metastases to bone. Their antiangiogenic properties and their capacity to abrogate the normal bone remodeling can produce recalcitrant osteonecrosis of the jaws. Affected patients should not have

incisions in the tissues overlying the jawbones. Although there is no direct effect on wound healing, exposed bone becomes necrotic and wounds in the overlying tissues fail to close. Stopping the drug for as long as 6 months does not seem to reverse the pathologic process.

Principles of wound care

Most simple wounds, such as surgical incisions or clean lacerations, heal rapidly by primary intention. Complex wounds, such as burns, avulsions, and infected or contaminated injuries, may heal more slowly by secondary intention and may require skin grafts or flaps before they can heal. Current wound management focuses on three principles: control or elimination of causative factors, systemic support to reduce existing cofactors, and maintaining a physiologic local wound environment. An increased understanding of the wound-healing processes, however, has led to greater interest in manipulating the wound microenvironment to facilitate healing. Traditional passive ways of treating wounds rapidly are giving way to approaches that enhance healing beyond its normal maximal inherent rate through the use of growth factors, extracellular matrix components, living skin equivalents, and bioabsorbable collagen scaffolds.

Wound closure

The basic principles of wound closure are important particularly in the head and neck, where the goal is a mechanically sound wound closure and a cosmetically acceptable scar. All wounds should be rendered clean as possible, debriding them of nonviable tissue or foreign bodies. In some instances, wet-to-dry dressings are preferable to surgical débridement. Copious saline irrigation should be used to dilute bacterial and other particulate contaminants. Ragged wound margins must be revised. Undermining of wound margins may be required to achieve a tension-free closure. With revised wound margins and undermining, the dermal (subcutaneous) sutures should approximate the wound. All dead space should be eliminated. Depending on the nature of the wound, sutures, suction drains, or pressure dressings may be used for this purpose.

Where appropriate, closure of wounds should be performed in a layered manner. Deep sutures are placed best in strong, fibrous tissue: fascia or dermis rather than muscle or fat. Wound tensile strength depends on suture integrity in the first few weeks,

until new collagen is remodeled sufficiently. Hence, polyglycolic acid sutures work well for this purpose. Nonresorbable sutures may be indicated in cases where a wound is under tension. Catgut is obsolete for most deep wound closures because it resorbs rapidly. Closure of the dermal (subcutaneous) layer is the key to esthetic wound closure. Dermal sutures should be inverted to avoid extrusion of the knots. Depending on the skin thickness, they are not necessarily placed as close as possible to the surface. Sutures that are too close to the surface can become extruded or cause a stitch abscess. These sutures should be placed in the vascular, collagenous dermis and should reach no higher than the lowest level of the epidermis. Maintaining the deeper portion of these sutures wider than the superficial portion encourages eversion and approximation of the epidermis. Wound margins needing revision should be beveled slightly away from the surface to help evert and approximate the epidermis. A mismatch in suturing this level is noted easily in the subsequent scar and should be avoided if esthetics are important. Inversion of wound margins delays wound healing and produces a wider scar.

Esthetic closure of the epidermal layer can be achieved in many ways. With proper dermal closure, skin sutures (and their cross-hatches) can be avoided in favor of porous tape. A running subcuticular suture can be placed. Skin sutures can be placed for 1 or 2 days and then replaced by tape. Fast resorbing catgut sutures can be placed. When the type and location of a wound calls for a strong epithelial closure, there are other options. Mucosa can be closed with either permanent or resorbable sutures. Skin can be closed with permanent sutures or staples. If the deeper portion of the suture is wider than the portion that crosses the surface, there is slight eversion of the wound margins. The design of skin staples also fosters wound eversion. Depending on an individual wound, simple sutures, horizontal or vertical mattress sutures, half-buried mattress sutures, or running sutures can be used.

Partial-thickness wounds

Partial-thickness injuries include those caused by abrasions and by the harvesting of skin or mucosal grafts. Such injuries heal by epithelialization from wound margins and from epidermal appendages, such as hair follicles, ducts, and pores in the wound bed. After hemostasis, partial-thickness wounds of the skin form a scab. Epithelialization takes place beneath the scab. In the moist environment of the mucosa, similar wounds form a fibrinous pseudo-

membrane. Dressings may be useful in making partial-thickness wounds more comfortable and in aiding epithelialization. Gauze dressings impregnated with various antibacterial substances and occlusive plastic films often are used for this purpose. The risk of dressings is that bacteria can proliferate beneath them; hence, dressings should be used with care to avoid infection. Wet-to-dry dressings are effective in débriding partial-thickness wounds that become infected. The bacterial count in a wound should be reduced below 10^5 per gram. Healing then can proceed normally. Systemic antibiotics do not work well for this and should be used only if there is cellulitis in the surrounding tissues [23].

Full-thickness wounds

Full-thickness injuries imply a complete loss of the epithelium and its appendages. Subcutaneous (submucosal) tissues, fat, fascia, muscle, bone, cartilage, organs, and other tissues may be exposed in the wound bed. Full-thickness wounds can be caused by tumor resection, trauma, burns, infection, radiation, or vascular compromise. Left alone, these injuries heal gradually by granulation and epithelialization. This process is slow and can be uncomfortable. Infection may intervene before the protective epithelium is restored. Full-thickness wounds heal more rapidly if they are covered by epithelium. If the wound bed is clean and well vascularized, a full- or partial-thickness skin graft can be placed. Depending on the location, a flap that carries its own blood supply could be a better choice. As with split-thickness wounds, the bacterial count in infected or contaminated wounds must be reduced below 10^5 per gram before they can be closed. Systemic antibiotics do not lower these bacterial counts significantly; dressing changes and topical antibacterial agents are more useful.

Scars

Scarring is an inevitable consequence of healing. The strength and appearance of scars differ, depending on the location and type of injury and the presence of intrinsic and extrinsic factors in the host. If wound healing is problematic or takes place under excessive tension, the esthetics of the scar is affected. Such scars tend to be thick, wide, raised, and a poor color match with the surrounding tissues.

Every region of the body has relaxed skin tension lines. The placement of elective incisions parallel to these lines improves the appearance of the ultimate

scar. In the case of traumatic wounds or of incisions that cross these lines, the appearance of the ultimate scar is worse. Z-plasty or other techniques that reorient the wound can be useful in improving the appearance of the scar.

Keloids are scars that grow beyond the boundaries of the original wound, bulging above and invading the surrounding tissue. Keloids are caused by uncontrolled deposition of collagen (that is not balanced by collagen lysis) in an otherwise healed wound. Africans and dark-skinned people especially are prone to forming keloids. A variety of intralesional and topical steroids, antihistamines, pressure, surgical excision, and radiation all are used to treat this condition with varying degrees of success. Scars that are thickened so that they bulge above the level of the surrounding tissue are called hypertrophic scars. In contrast to keloids, hypertrophic scars do not extend beyond the boundaries of the original wound and they soften and flatten over time. Hypertrophic scars respond to treatment far better than keloids. Surgical reorientation within the relaxed skin tension lines and intralesional steroids are effective in managing hypertrophic scarring.

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