Chapter 8
Wound Healing in the Elderly

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Introduction

Wound healing impairment in the elderly has been accepted as a medical reality for many years now. The most devastating wounds in the elderly include pressure ulcers, diabetic foot ulcers, venous stasis ulcers, and poorly healing surgical wounds. Recently, improved wound care products (see Table 8.1) and best practice guidelines (see Table 8.2) have helped to improve care of elderly patients with these types of wounds.

However, to date there is no compelling clinical study that proves that increased age impairs wound healing. The best evidence available is from studies, performed four decades ago which reported an increase in the incidence of wound dehiscence after laparotomy in older men [1, 2]. Likewise, the incidence of anastomotic complications was reported to increase with age [3, 4]. None of these studies is definitive owing to the variability of patient co-morbidities such as nutrition, vascular insufficiency, and the presence and severity of diabetes. Furthermore, human wounds cannot be precisely matched. These factors make it extremely difficult to carry out a conclusive clinical study. In contrast, animal studies have successfully demonstrated age related defects in wound healing.

However, these classical studies, along with fundamental histological findings and, more recently, in-depth descriptions of cellular functions and interactions remain the basis for future studies at a molecular and genetic level.

From a biological point of view, wound healing, tumor development and suppression, and aging are processes involving common mechanisms. Hayflick showed in 1961 that cultured cells in vitro had a limited lifespan, thus giving rise to the term cellular senescence [5]. New and powerful methods, which are now routinely available, have introduced the concepts of telomeric attrition and DNA damage by oxidative stress [6]. Despite the growing body of knowledge and exciting fundamental research, cellular senescence and its mechanisms in vitro have only tenuous links with the aging of a whole organism [7]. Therefore, animal models remain our best option to study the physiology of wound healing in the elderly.

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Physiology of Wound Healing

From the moment of injury, the body responds with a series of complex interactions that culminate in the restoration of integrity. Under normal conditions, healing can be divided into four specific stages: coagulation, inflammation, fibroplasia, and remodeling. Although described in a sequential fashion, healing is an active, dynamic process that proceeds through a series of mechanisms that are often redundant and simultaneous.

Coagulation

Coagulation initiates the process that leads to healing. Injury disrupts tissues and cells and induces local hemorrhage. Vasoconstriction occurs almost immediately as a response to catecholamine release to limit blood loss. Tissue destruction induces mast cells to release various vasoactive compounds including bradykinin, serotonin, and histamine, which initiate the process of diapedesis. Platelets from the hemorrhage help form the hemostatic plug by releasing clotting factors that produce fibrin and form the fibrin mesh onto which inflammatory cells migrate. Fibrin deposition is followed by fibrinolysis and the release of chemoattractive peptides, particularly fibrinopeptide E, which attracts monocytes, and fibrinopeptide B, which is angiogenic. In addition, platelet degranulation releases platelet-derived growth factor (PDGF), platelet factor IV, transforming growth factor 1 (TGF-1), and insulin-like growth factor 1 or somatomedin C (IGF-1), all of which stimulate fibroblast replication. Platelets

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Table 8.1 Wound care products categories

Product classification	Most common brands
Antimicrobial dressings	
Topical wound products derived from *silver, iodine*, *and/or polyhexethylene biguanide* Available in Foams Alginates Hydrogels Hydrocolloids Barrier layers May or may not need secondary dressing Use in draining, and non-healing wounds where protection from bacterial contamination is desired	Silver products Acticoat absorbent dressing *Aquacel Silver Contreet foam dressing Contreet Hydrocolloid Silva Sorb (silver hydrogel) *Silverlon *Silver Med (silver hydrogel) Iodines *Cadexomer Iodines *Iodosorb Gel Iodoflex Pad
Calcium alginate	
Absorbs moderate to heavy drainage Origin – brown seaweed Non-woven fibers Ropes or pads Absorbent and conforms to the shape of the wound Absorbs up to 20 times its weight	*Aquacel is a hydrofiber, not a Ca alginate but performs in a similar fashion Curasorb Kaltostat SeaSorb alginate 3M Tegagen Genteel calcium alginate Restore calcicare Sorbsan
Collagens	
Promotes the deposition of newly formed collagen fibers and granulation tissue in the wound bed. Stimulates new tissue development and wound debridement Available in Sheets Pads Particles Gels	Fibracol + collagen with alginate *Promogran Matrix *Promogran Prisma Matrix (collagen + silver)
Composite dressings	
Combination of two or more different products into one dressing, i.e., absorptive layer with an adhesive border for ease of application	*Alldress – low-adherent layer + absorbent pad + tape border Covaderm DermaDress Stratasorb 3M Tegaderm Plus
Compression	
Used to manage edema, promote venous return to the heart and manage wounds caused by venous insufficiency. Multilayered. Available in individual layers or packaged as a multi-layer system	Alto press (single-layer system) Coban2 compression system DYNA-FLEX (multi-layer system) Profore (multi-layer system) Seto press (single-layer system) *Zinc Unna Boot + cotton padding + Flex wrap or Coban
Debriding agents	
Debridement of necrotic tissue and liquefaction of slough Dry eschar must be scored before applying debriding gel Gels available by prescription only Mesalt available in: Squares Ribbons	*Accuzyme (gel Rx) Gladase (gel Rx) *Mesalt Panafil (gel Rx) Santyl (gel Rx)

(continued)

Table 8.1 (continued)

Product classification	Most common brands
Foams	
Absorbs moderate to heavy drainage Provide a moist environment and thermal insulation Primary dressing for absorption and insulation, or secondary dressing for wounds with packing. Also effective to treat hypergranulation tissue. May be used under compression Available: With adhesive border Without adhesive border Varied shapes and sizes	Allevyn *Biatain Curafoam Hydrasorb Polyderm PolyMem 3M Tegaderm Foam Tielle
Hydrocolloids	
Absorbs light to moderate exudates Occlusive or semi occlusive dressings composed of gelatin, pectin, and carboxymethylcellulose Provide a moist healing environment Promotes granulation in clean wounds Helps debride necrotic wounds autolytically Used as primary or secondary dressing Available in: Thin or thick Varied shaped wafers May or may not have transparent film border May be used under compression May be opaque or translucent Also available in pastes and powders	Combiderm Comfeel Plus *DuoDerm CGF or -DuoDerm Extra Thin RepliCare Hydrocolloid Restore *3M Tegasorb *3M Clear Acrylic Dressing – new product that performs similar to a hydrocolloid. Absorbs more than a hydrocolloid. Clear acrylic that allows visualization of the wound. May extend wear time due to visualization
Hydrogels	
Can absorb minimal drainage. Water or glycerin-based gels. Helps to maintain moist wound environment. Promotes granulation and epithelialization and facilitates removal of necrotic tissue or slough by autolytic debridement Available in: Amorphous gels Impregnated gauze Sheets	Curafil Gel Curasol Gel *DuoDerm Gel IntraSite Gel Purilon Gel SAF-Gel TenderWet Gel Pad Curagel DermaGel Hypergel Normlgel *Restore Hydrogel SoloSite Wound Gel 3M Tegagel
Non-adherent layer	
Wound contact layers used to prevent dressing from sticking to the wound bed May or may not be impregnated with gel, petroleum jelly, or other compounds Also used over hydrogel to keep gel in place and prevent secondary dressing from absorbing gel	*Adaptic Mepitel *Vaseline gauze *Xeroform Gauze
Transparent films	
Non-absorbent Adhesive, semi permeable, polyurethane membrane dressings that vary in thickness and size Waterproof and impermeable to bacteria and contaminants, yet permit water vapor to cross the barrier Maintain a moist healing environment, promoting granulation tissue and autolysis of necrotic tissue Not recommended for infected wounds Available in varied sizes	Clearsite Dermaview OpSite *3M Tegaderm

When writing orders, refer to the product classification and not the brand name

Table 8.2 Pressure ulcer prevention best practices

Interventions	Reason
Get resident out of bed if condition allows. Residents with skin breakdown, should be up a maximum of 2 h at a time	Redistributes weight bearing sites and minimizes the risks of immobility
Teach and encourage resident to shift weight every 15 min, assisting as necessary, while up in chair	Prevents pressure points from developing and allows blood flow to return. Helps prevent pressure ulcers from developing on the lower portion of the buttocks
Assist or provide resident with devices to maintain mobility, i.e., passive ROM, splint, hand cones	Lessens resident's risk for development of a pressure ulcer or contracture
Turn and/or reposition non-ambulatory residents every 2 h minimum	Rotates the sites of pressure and allows blood flow to return to an area where blood flow had been restricted
• Lift resident off bed, do not drag when moving, especially heels and sacrum • Use a draw sheet to help when moving or turning resident • Place socks or heel protectors on resident • Place pajama top or elbow protectors on resident to protect elbows	Minimizes shear and friction which can tear the skin and damage the capillaries supplying blood to the skin
Elevate heels by placing a pillow lengthwise under the residents calves	Decreases pressure on the heels and may decrease shear and friction
Place resident on pressure reducing mattress	Reduces effects of pressure
Place resident on pressure reducing cushion in chair	Reduces effects of pressure
Use maximum of two incontinent pads under resident in bed	Too many layers of linen between resident and pressure reducing mattress, will decrease the effectiveness of the mattress
Avoid incontinent pads over wheelchair cushion, use drawsheet or pillowcase for cover	Incontinent pads reduce effectiveness of pressure reduction provided by cushion
Inspect resident's skin during bath, when changing clothes, etc.	Identify any redness or skin break so that appropriate treatment or prevention measures can begin immediately
Apply lotion to bony prominences, back, and dry, flaky skin at bath time and prn	Keeps skin soft and supple
Apply moisture barrier ointment to the skin of an incontinent resident	Helps prevent incontinence from making the skin soft and prevents burning of the skin
Report frequent incontinence to ensure that appropriate methods of containment or treatment will be promptly implemented	Decreases the chance of complications from incontinence
Encourage resident to drink prescribed supplements and adequate amounts of water between and/or with meals. Report if resident refuses supplements	Helps maintain and/or improve nutritional status and hydration
Keep linen neat and wrinkle free	Helps prevent shear and friction

Prevention is part of every aspect of wound care, regardless if a wound exists or not. Many recommended practices regarding pressure ulcer prevention are nothing more than "good old common sense." Prevention requires a holistic approach from all members of the health care team
Source: Reprinted with permission from the Wound Care Education Institute

are critical in wound healing because they are the first to produce several essential cytokines thought to modulate many subsequent wound healing events [8].

Inflammation

The inflammatory stage is characterized by an increased migration of mast cells, polymorphonuclear leukocytes (PMNs), and lymphocytes into the wound. Within 24 h of injury, PMNs predominantly populate the wound area. Their role is more important for antibacterial defense than for repair. These cells are progressively replaced by macrophages, which are predominant by 48 h after injury. Macrophages stimulate replication and movement of fibroblasts and vascular endothelial cells, which in turn regulate the repair of the connective tissue. When stimulated by injured tissue, fibrin, foreign bodies, low oxygen, and high lactate concentrations, macrophages have been shown to secrete IL-1 (Interleukine-1), IL-6, IL-8, tumor necrosis factor-α (TNF-α), transforming growth factor-β (TGF-β), IGF-1, and fibroblast growth factor-like molecules (LDGF). These factors regulate cell growth and chemotaxis of inflammatory cells, new fibroblasts, and endothelial cells. Inflammation is aggravated by the release of free radicals. The damaging effect of free radicals is enhanced by reactive hyperemia.

Fibroplasia

Fibroplasia is the stage where wound strength increases and integrity is restored. Fibroblasts originate locally, and

replication rates are proportional to oxygen availability. By 72 h fibroblasts migrate into the wound and synthesize collagen and proteoglycans. The latter are important extracellular compounds that stabilize and support cells and fibrous components of tissue. Collagen synthesis starts as early as 10 h after injury and reaches a peak between the first and second week before stabilizing. Initially, the collagen within a wound is comprised of large amounts of type III collagen but relatively little type I collagen. Collagen III provides strength during the late phase of wound healing by cross-linking. Vitamin C plays an important role in this process.

During this stage, the production of ground substance in the matrix increases, and vessels proliferate. Neovascularization occurs along the steep oxygen gradient that characterizes wounds. Regrowth of sympathetic nerve fibers is also associated with angiogenesis. Along with invading fibroblasts, fibronectin appears and promotes cell adhesion and phagocytosis, and it may be involved in matrix remodeling. Fibrinogen, laminin, and fibronectin constitute a framework from which new vessels can form and reepithelialization can occur. Reepithelialization is a complex phenomenon in which resting G_0 cells (cells in the inactive phase of mitosis) are recruited from the margins of the wound, followed by migration of epidermal cells. This process is essential for reconstitution of cutaneous barrier function [9]. It has been suggested that as the wound epithelializes, inflammation is downregulated owing to the presence of apoptotic cells at the advancing epithelial wound edge [10–12].

Remodeling

Remodeling is an extensive phase during which collagen is produced and remodeled to reach an equilibrium between collagen formation and destruction by collagenases. The type III/type I collagen ratio decreases allowing the mature type I collagen fibers to cross-link, organize, and rearrange along the tension lines of the skin. Acute and chronic inflammatory cells gradually diminish, and fibroplasia ends. Fibronectin that guided the migration of multiple cells during earlier phases is removed within a few weeks [13].

The first migration of epithelial cells has been observed 6–48 h following an injury, and epidermal proliferation reaches maximum values at 12–48 h. Neovascularization regresses, and a mature scar is formed.

Aging and Wound Healing

While clinical studies have not been able to clearly demonstrate an isolated age related defect in healing in humans, animal studies have shown this age related defect. In human studies, confounding variables of nutrition and vascular insufficiencyand the difficuty in identifying sufficient numbers of identical wounds, make a definitive study impossible. On the other hand numerous animal studies demonstrate very clearly an impairment of wound healing in the elderly compared to the young.

Coagulation and Inflammation

Specific age-related alterations in both the coagulation and immune system have been shown to influence wound healing. Older patients show signs of vascular fragility or risk of hemorrhage. However, the cellular and molecular events that could support these clinical findings are unclear. Frequent comorbidities and impaired renal function are the primary reasons for hemostasis dysfunction [14–16].

Platelet and macrophage adhesion to substrates within the wound increases while macrophage function declines [17]. Old mice display a slower wound healing rate when compared to young mice [18]. Furthermore, wound healing is accelerated when macrophages from young mice are added locally to wounds of old mice. It is possible that the migratory capacity of macrophages in addition to other macrophage functions are affected by age, and the correction of such dysfunction might stimulate wound healing [19]. In accordance with the above reports, Ashcroft et al. observed a similar phenomenon. At 7 days after injury, wounds of young animals consisted of mature granulation tissue and scattered inflammatory cells, whereas the wounds of middle-aged and old mice showed persistent inflammation and immature granulation tissue [20].

Any study of macrophages is affected by their source (spleen, liver, brain, bone, mice, humans) and their state of activation and the experimental conditions (circulating macrophages, peritoneal exudates, in vivo, in vitro) leading to contradictory results in the cellular functions like chemotaxis and phagocytosis. However, there is a general consensus that macrophages are impaired by aging at a molecular level including a decrease in cytokine production and dysfunction of intracellular signaling pathways like NF-KappaB [21].

T cell-mediated immune function also deteriorates during aging. There is a loss of T cell proliferative capacity, a decline in the synthesis and release of IL-2, and a decrease in IL-2 receptor expression. A major factor responsible for the loss of T cell function is the inability of the T cell to respond to activation signals transmitted through the membrane binding of specific stimulatory signals [22]. An IL-2 deficit alone cannot explain these effects because exogenous administration of IL-2 does not completely restore the decreased T cell proliferative response of the elderly. A defect in the IL-2 receptor

expression or function may exist. In addition to IL-2, T cells have an increased ability to produce interferon-γ (IFN-γ), IL-4, IL-6, and TGF [23, 24]. Aging is associated with a decrease in cytotoxic lymphocyte activity and a reduction in lytic capacity. A significant portion of the age-related decline in $CD8^+$ T cell-mediated cytotoxic activity is secondary to age-related alterations in the $CD4^+$ T cell subset. The well-documented diminution in IL-2 production with age may contribute to the defect seen in the $CD4^-$ cells [25].

Proliferation

Cell proliferation is affected by aging in a number of ways. Fibroblast migration in vitro is reduced, but the number of cells within an acute wound is not altered. Fibroblast proliferation declines as well. It seems that the mitogenic and stimulatory effects of growth factors, hormones, and other agents are significantly reduced during aging [26, 27]. The in vitro loss of responsiveness to specific stimulatory cytokines also occurs, with no changes in response to inhibitors [28]. In addition, fibroblast cultures from premature aging syndromes such as Werner syndrome, show a significantly reduced mitogenic response to PDGF, fibroblast growth factor (FGF), and serum [29, 30].

In addition to these intrinsic alterations, a detrimental microenvironment such as hypoxia has been demonstrated to have a dramatic effect on the migration of fibroblasts impeding even further the healing capacity of the elderly [31].

Studies show that epidermal behavior in elderly subjects differs from that of young subjects. Reepithelialization has shown to be delayed in wounds of old mice [32]. The rate of epithelialization of open wounds is slowed in elderly patients compared to that in young individuals [33, 34]. This is due, in part, to a longer migration time for the keratinocytes to migrate from the basal layer to the epidermal surface [35].

Moreover, in vitro studies have revealed a decline in keratinocyte responsiveness to stimulatory cytokines, an increased response to inhibitory cytokines, and a decline in IL-1 production in elderly patients. This physiologic delay, when coupled with other factors that impair epithelial repair, may result in significant healing problems in the elderly.

Several studies have described changes in angiogenesis during aging. Elements of the microvasculature in young rats are periodic acid-Schiff (PAS)-negative and become increasingly PAS-positive beyond the halfway life-span. This observation reflects an increase in the carbohydrate content of blood vessels with aging. During acute wound repair in old animals the microvasculature is PAS-negative after injury and intensely PAS-positive after 8 weeks, reproducing the process of aging in an accelerated manner [36].

Aged endothelium may exhibit an increased adhesive response to leukocytes and TNF-α. Furthermore, IL-1 production increases and subsequently endothelial cell proliferation declines but vascular smooth muscle cell proliferation increases.

Recent work may guide the way to understanding the precise biological processes that are impaired in the elderly. Instability of hypoxia inducible factor I alpha (HIF) seems to be involved in the impairment of neovascularization and wound healing in elderly mice [37, 38]. HIF is a transcription factor that upregulates the expression of numerous angiogenic peptides including vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), Angiopoietin 1 and 2, as well as placental growth factor [38, 39]. Delivery of a constitutively stable form of HIF can improve wound healing in diabetic mice (see Fig. 8.1), and this improvement in wound healing is associated with increased angiogenesis [38]. Recently it has been shown that aged mice had significant upregulation of hydroxylases

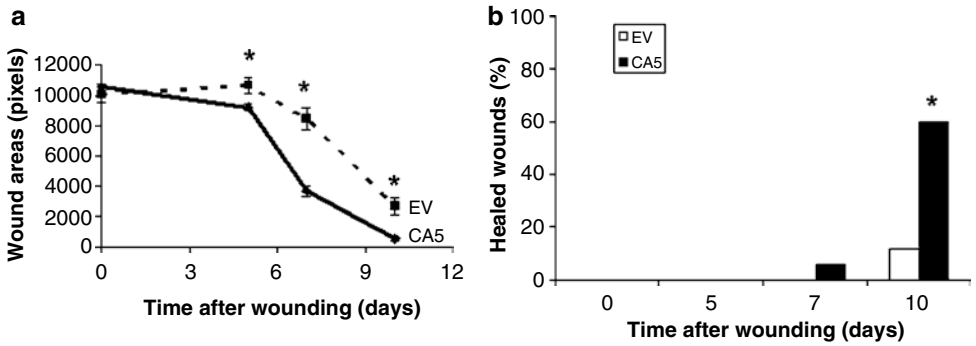


Figure 8.1 Wound closure in db/db mice after electroporation-facilitated DNA transduction of CA5 (constitutively active form of HIF) versus Empty Vector (EV). (**a**) Open wound area (in pixels) was determined on the indicated day after wounding and transfection with gWIZ-CA5 (CA5) or gWIZ-EV (EV). Mean ± SEM is shown ($n = 48$ for CA5; $n = 20$ for EV). *$P < 0.05$, ANOVA with Tukey Test. (**b**) Percentage of wounds achieving ≥95% closure after transfection with CA5 versus EV is shown. *$P < 0.001$, Mann–Whitney Rank Sum Test (from [38], with permission).

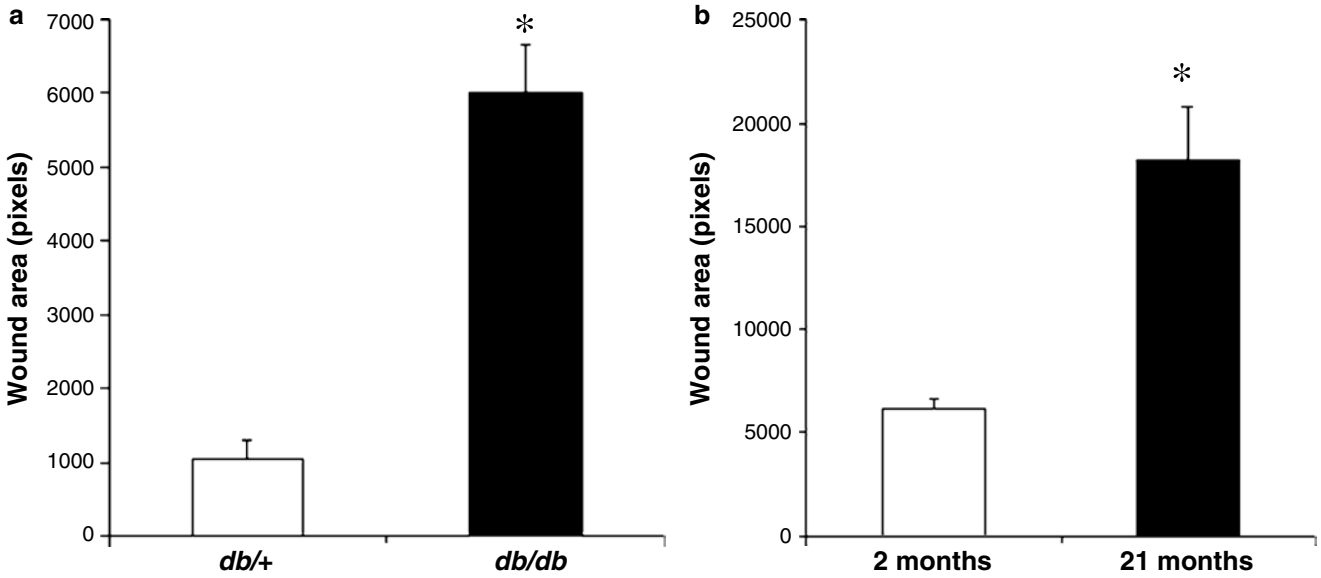


Figure 8.2 Wound healing characteristics of *db*/*db* mice. (**a**) Excisional wound closure in 2-month-old diabetic mice (*db*/*db*) and their heterozygous littermates (*db*/+). The bar graph shows the wound area (in pixels) measured by computer assisted plannimetry on day 9 (mean ± SEM, $n = 20$ for each group). $^*P < 0.01$, Student's t test. (**b**) The effect of age on wound healing in *db*/*db* mice. For mice of the indicated age, the bar graph shows wound area on day 9 (mean ± SEM, $n = 20$ for each group). $^*P < 0.01$, Student's t test (from [38], with permission).

which degrade HIF. The aged mice had significantly delayed wound healing (see Fig. 8.2) with reduced levels of HIF and downstream transcription products (see Fig. 8.3) as well as decreased neovascularization, compared with younger mice. Inhibitors of hydroxylation of HIF tended to improve wound healing in the older mice [37]. These studies provide an interesting insight into the biology of impaired wound healing in the elderly and suggest strategies for directly addressing the problem with targeted treatments. In addition to this recent work on the role of HIF in the impairment of wound healing in the elderly, defects in other aspects of wound healing have also been demonstrated.

Remodeling and Collagen Deposition

The structure of the extracellular matrix changes with age. Aging is associated with significantly reduced levels of wound matrix constituents, including collagen, basement membrane components, glycosaminoglycans, and fibronectin [40].

It is assumed that anastomotic strength and collagen metabolism are primarily determined by assessing collagen synthesis and content [36]. Collagen metabolism also seems to be altered by aging, with decreased production and increased degradation, although animal studies have reported conflicting findings and no general agreement has been reached [40–42]. In healthy human volunteers, intrinsic aging can be studied excluding extrinsic aging like UV light exposure. In covered skin, age will show a decrease in collagen content when, in contrast, this content will be increased in exposed tissue. In both situations, age will constantly show a disorganization of the collagen and elastin fibers and architecture [43].

Wounds have been reported to change with age. The tensile strength of skin is positively correlated with collagen fiber diameter. During normal wound healing, the tensile strength of wounds increases with time, despite a decrease in the rate of collagen synthesis. The breaking strength of wounds in old animals has been found to be lower than that of young animals [44, 45]. This difference is believed to be due to less organized collagen fiber arrangement [46]. Tensile strength and energy absorption of abdominal incisional wounds are lower in old rats than in young rats by the fourth postoperative day. If wound strength is in fact impaired in the elderly, collagen might not be the only element involved in this phenomenon. A defect in the synthesis of noncollagenous proteins such as glycosaminoglycans, laminin, enzymes, and cytokines may affect the mechanical properties of wounds in the elderly. Imbalance between matrix metalloproteinases and their inhibitors [tissue inhibitors of metalloproteinases (TIMPs)] has been shown in humans but, to complicate things further, this phenomenon seems tissue and cell type dependent [27, 47].

Skin Stem Cells

Different types of adult stem cells have been found in the skin and are protected within a specific niche by a group of

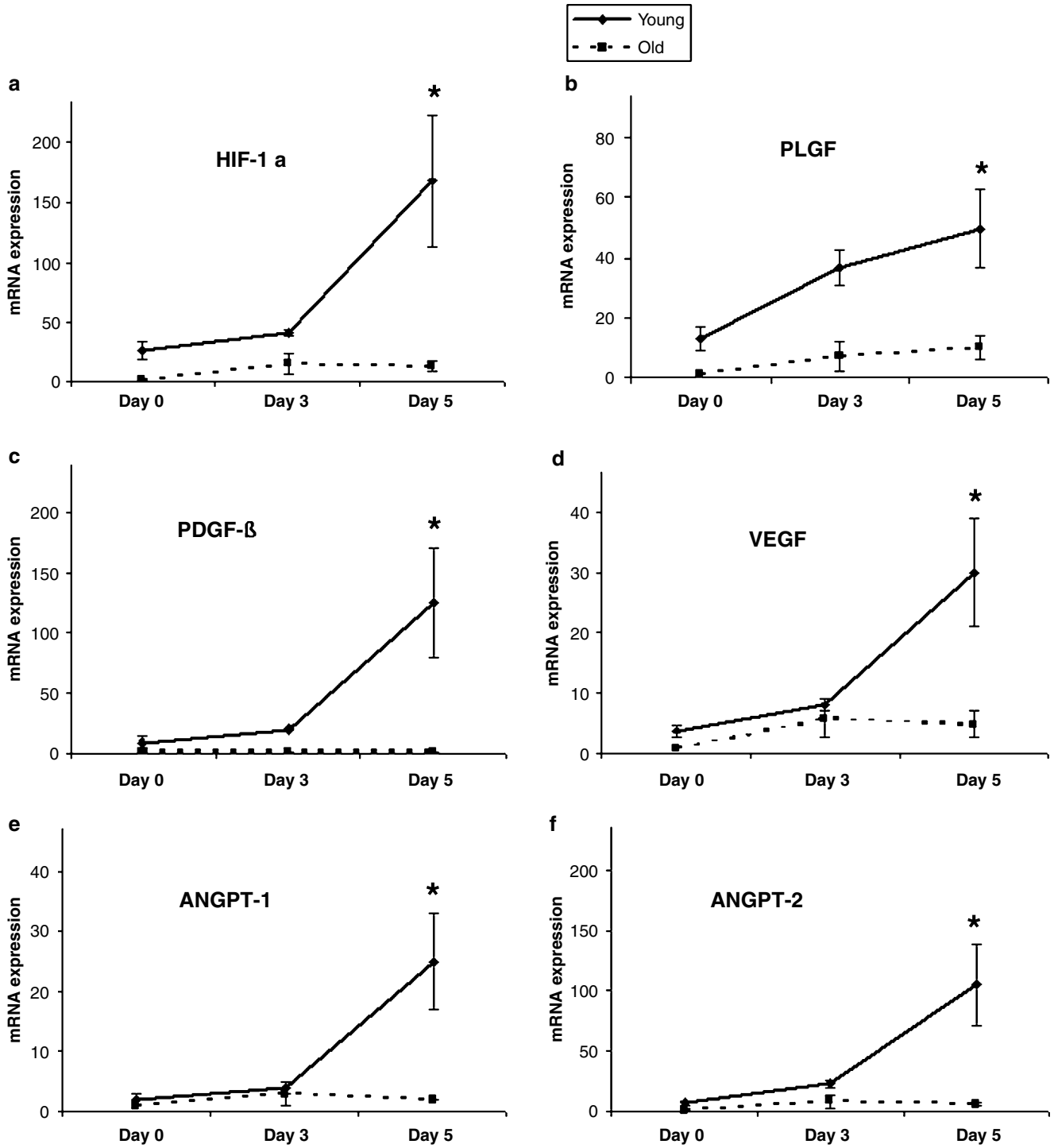


Figure 8.3 Expression of mRNAs for HIF-1α (alpha) and angiogenic cytokines in wounds of 2- and 6-month-old db/db mice. Total RNA was extracted from normal skin (day 0) and wounds on day 3 and day 5 and assayed by qRT-PCR for each mRNA. (**a**) HIF-1α (alpha); (**b**) PLGF; (**c**) PDGF-B; (**d**) VEGF; (**e**) ANGPT1; (**f**) ANGPT2. *$P<0.01$, ANOVA with Tukey Test, $n=3$ for each group (from [38], with permission).

specialized niche-cells from extrinsic trauma. It has been observed that the number and self-renewal capacity of these stem cells are not affected by age, but their specific role, which is the ability to produce differentiated effector cells, declines [48].

Muscle and hepatic production of progenitor cell also decline with age. Exposure to young animals' systemic factors (serum) has increased, in vitro, the capacity of niche-cells from liver tissue of aged animals to proliferate and increased the gene expression of specific remodeling pathways to levels seen in younger animal tissues [49]. These findings, together with the study of dermal gene expression, suggest that epidermal stem cells are resistant to intrinsic aging, but sensitive to changes in the local environment. Recently, strong data supports the new idea of stem cells within hair follicule bundles homing into epidermal scar tissue. This finding opposes a common paradigm that hair follicules do not regenerate [50]. This whole new field in medicine holds great promise for future treatment in tissue repair and cell-based therapies.

Co-morbidities

Co-morbidities can further impair the healing process in the elderly. Often co-morbidities appear to be the primary impediment to successful wound healing. Careful clinical evaluation of the patient can reveal the presence of disease processes that require intervention.

Nutrition

Frequent minor deglutition accidents, loss of appetite, and loss of social interaction are the major causes of malnutrition in the aging population. Poor nutrition is associated with impaired wound healing [51], with decreased wound tensile strength, decreased T-cell function, decreased phagocytic activity, and decreased complement and antibody levels.

However, the nutritional status will affect the healing course differently depending on the type of wound. A wound such as a surgical incision or colonic anastomosis that heals by primary intention could heal in a malnourished patient in a reasonable time if protected from infection. On the contrary, a wound like a bed sore or a large burn that heals by secondary intention will be severely affected by a poor nutritional status and could trigger a state of catabolism [52].

Animal studies have helped us understand this relation. A commonly encountered degree of malnutrition, insufficient to affect nutritional indices used for clinical assessment, may interfere with colonic healing. Early feeding to enhance nutrition during the postoperative period may be able to reverse this effect [53]. Daly et al. showed that rats deprived of protein for only 1 week exhibited a 17% reduction in mean bursting strength of colonic anastomoses compared to that of controls. They also observed a correlation between serum albumin and bursting strength with prolonged malnutrition [54]. These studies were later confirmed by Irving, who showed that severe protein deprivation reduced the breaking strength of abdominal wall wounds. A recent animal study from 2009 confirmed these original findings. Malnutrition impairs the healing of colonic anastomosis and a proper food intake given to malnourished rats 7 days prior to surgery will normalize the anastomosis tensile strength and its collagen contents [55].

In humans the wound healing response has been assessed by measuring the collagen content (hydroxyproline) of subcutaneously inserted Gore-Tex tubes. In this respect, a delay in the wound healing response is also seen in malnourished elderly surgical patients; but contrary to what happens in animals, it occurs even with mild degrees of protein–calorie malnutrition [56]. In addition, low serum levels of nutritional markers such as albumin and transferrin correlate with a high incidence of wound complications in elderly patients undergoing vascular operations [57].

The wound healing response, measured by hydroxyproline accumulation, is improved by intravenous nutrition in surgical patients. This improvement is seen after only 1 week of nutritional therapy and before the indices of nutritional status are significantly changed [58]. In the latest meta-analysis update from the Cochrane collaboration on nutritional supplementation for hip fracture aftercare, oral multinutrient feeds seem to reduce the risk of unfavourable outcomes, but data are insufficient to recommend nasogastric feeding, whereas protein-rich supplementation may reduce long-term complications and the number of days spent in hospital [59]. ESPEN guidelines on parenteral nutrition are in agreement with this review and conclude that a time limited parenteral support is beneficial only to severe malnourished patients and should be quickly replaced by intraoral intake [60].

Diabetes

Diabetes has been shown to impair wound healing and increase the potential for infection. Cruse and Foord demonstrated that diabetic patients have five times the risk of infection in a clean surgical wound compared to nondiabetic patients. Obesity, insulin resistance, and hyperglycemia all contribute significantly and independently to the wound impairment observed in diabetics [61, 62].

In experimental animals, insulin restores collagen synthesis and granulation tissue formation to normal levels if given during the early phases of healing [63]. However, this is not

the case in phenotypically obese mice [38, 64]. In humans with juvenile-onset diabetes, insulin treatment ensures normal wound collagen accumulation. Specific phases of wound healing involving collagen metabolism and cellular proliferation as well as chemotactic, phagocytic, and adherence properties of neutrophils have been shown to improve with insulin administration or lowering of the blood glucose level below 200 mg/dl. Careful preoperative correction of blood glucose levels can improve the outcome of wounds in diabetic patients [65].

Future approaches in diabetic wound treatments will probably take into account the critical role played by advanced glycoxidation products that seem to act negatively both on the vascular and peripheral nerve injuries sustained by diabetic patients [66].

Hypoxia and Hypoperfusion

Local tissue perfusion and oxygenation are key elements in wound healing [67]. Unfortunately, the elderly experience a progressive decline in health and are more prone to develop diseases that compromise tissue perfusion. Diabetes, arteriosclerosis, venous insufficiency, and cardiac failure are among the major diseases that can affect local oxygen delivery. It is even possible that a substantial portion of surgical patients are hypoperfused [68]. Healing of ischemic wounds in old animals is impaired by 40–65% (wound shrinkage) compared to similar wounds in young animals [69]. Tissues from older animals are less tolerant to ischemia with increasing age. Consequently, limiting ischemia time during surgical procedures in older patients is beneficial [70].

Collagen synthesis requires oxygen as a cofactor, especially during hydroxylation of proline. Oxygen tensions in surgical wounds are often below what is desirable [71]. Perfusion during the first postoperative days seems to be crucial for collagen accumulation. In fact, collagen deposition is directly proportional to wound oxygen tension and other measurements of perfusion [72]. Interestingly, moderate anemia does not influence collagen deposition. Thus replacing fluid postoperatively based on the results of tissue oxygen tension measurements rather than clinical criteria may improve the overall wound healing response [67, 73]. The use of a transcutaneous oxymeter device has proven useful in predicting a successful wound closure but no consensus has been reached in clinical practice [74].

Infections

Infection of surgical sites and healing of secondarily infected wounds, are two wound problems commonly affecting aged patients with various co-morbidities.

Surgical site infection is the most frequent nosocomial infection in hospitalized patients and will affect at least 2% of all surgical patients and up to 20% of patients undergoing some specific surgical procedures. Local wound infection represents the most frequent cause of defective wound healing. These numbers are very likely underestimated because of a lack of documentation concerning patients prematurely discharged in the context of private insurance coverage [75]. The transfer of the cost of disabilities, depression, and death due to these infections to the community is therefore very high [76].

For classification purposes, these infections have been classified according to the initial incision (superficial, deep, organ/space) and the preexisting infectious risk (clean, contaminated, dirty, infected). This classification is now essential to determine a risk index, to study various risk factors, and suggest specific practice guidelines [77] including the use of general measures, skin preparation, and surgical environment and eventually antimicrobial prophylaxis. These measures can be found in extensive reviews [78, 79].

The clinical examination is the first most important element to recognize a wound that is being challenged by a bacterial infection. The loss of bacterial balance can affect the wound superficially or within deeper tissues. The most important evidence of this imbalance is the delay in wound closure and the presence of an exudate. Odor, pain, and surrounding tissue inflammation will indicate uncontrolled infection, but these signs may be less obvious in the elderly patient [80]. Therefore, it may be necessary to study the bacterial contents of the wound.

The mere presence of organisms in a wound is less important than the level of bacterial growth. Experimental data have shown that bacterial growth of more than 100,000 organisms per gram of tissue is necessary to delay or inhibit wound healing. The bacterial growth can be measured in the clinic by performing a biopsy for culture. It is more reliable than a bacterial swab that can isolate superficial noninvasive bacteria and miss the anaerobes responsible for the infection [81].

Recently, the pathophysiology of infections associated with chronic wounds has begun to be better defined. Many more microorganism species have been identified [such as methicillin resistant *Staphylococcus aureus* (MRSA)] but most of them develop in the form of biofilms. This complex structure supports colony growth, retention of nutrients, and formation of water channels and allows cell–cell communication and even gene transfer through transduction [82]. In addition, bacterial cells in these structures are protected from antimicrobial agents and host defenses, explaining the frequent inability to eradicate them in infections. In addition, developing molecular microbiology techniques (nucleic acid amplification-PCR and metagenomic methods) have shown that chronic wounds from different

etiologies will display a different microorganism population and therefore require different treatment regimens. These molecular techniques are indeed reserved for the research community but should become a standard for resistant wounds [83].

Drugs

The major effect of steroids is to inhibit the inflammatory phase of wound healing. The stronger the anti-inflammatory effect of the steroid used, the greater is the inhibitory effect on wound healing [84, 85]. Large doses of steroids reduce collagen synthesis and wound strength. Dexamethasone increases the frequency of colonic anastomotic rupture 5 days postoperatively [86]. In addition, long-term perioperative steroids have a deleterious effect on colonic anastomoses and skin healing [87, 88]. Short-term high preoperative and postoperative steroid therapy does not decrease the strength of the anastomoses as measured by bursting pressure. Treatment with a single preoperative high dose of methylprednisolone may improve pulmonary function and reduce the inflammatory response without having a detrimental effect on collagen accumulation in the wound [89].

Cancer therapies have long been known to affect wound healing adversely. Chemotherapeutic antimetabolite drugs inhibit early cell proliferation, which is crucial to the onset of successful wound repair. Radiation therapy also has unwanted effects, as it can induce fibrosis, strictures, and ischemia in adjacent tissues. It can also generate an early decrease in seromuscular blood flow in colorectal anastomoses, although single preoperative doses may not compromise healing [90].

Other drugs may also have unexpected adverse effects on wound healing. Octreotide, a somatostatin analogue commonly used in surgical patients, has been shown to decrease wound breaking strength in experimental animals; these effects are comparable in magnitude to those caused by steroids [91].

Therapeutic Approaches

The healing impairment in aged individuals is a combination of intrinsic and extrinsic factors that act at multiple levels of the healing cascade. As a result, a multifaceted therapeutic approach is necessary. In addition, the incomplete success in translating animal research results to human clinical applications demonstrates the complexity of human biology in which, identification of relevant subtypes will be the next avenue to explore.

The correct assessment and correction of co-morbidities will be the first major step to take to achieve success. Each co-morbidity will have a specific age-related treatment to render with the relevant medical specialties.

Nutritional Support

Nutritional support will have to be adapted to the degree of malnutrition, the urgency in closing the wound, and the ability of the patient to tolerate nutritional intake. General nutritional support can be started by mouth if there is no deglutition problem, which generally manifests itself as a pulmonary infection in the elderly. Enteral nutrition is a very effective way to correct malnutrition and should not be delayed for patients with even a moderate 10% weight loss. Specific nutritional supplementation such as arginine, vitamin A, vitamin C, and zinc have been shown to be effective experimentally, but their mechanisms of action are still unclear. Again, subpopulations of patients have responded differently to specific supplements depending on their comorbidities and the type of wound.

Growth Hormone

In wound healing research studies, growth hormone (GH) has been shown to increase the strength of incisional wounds [92]. Rats treated with preoperative and postoperative GH experienced an increase in breaking strength and collagen content of colonic anastomoses. The increments in these parameters were accompanied by an increase in collagen deposition in the anastomotic segment. These effects were seen only when GH was given during the healing phase [93]. GH seems to stimulate structural organization of the anastomotic collagen fibrils into fibers [94]. In addition, GH administration significantly improves skin wound strength in malnourished rats [95].

GH appears to exert its favorable effect in part by stimulating IGF-1 synthesis; in turn, IGF-1 mediates the anabolic effects of GH. IGF-1 is released early during wound healing by the lysis of platelet alpha granules and later by fibroblasts. This molecule stimulates fibroblast and endothelial cell proliferation as well as collagen synthesis [96]. IGF-1 appears to be critical for effective wound healing.

Rats depleted of IGF-1 experience a 50% decrease in wound protein, DNA, hydroxyproline, and macrophage concentrations. Moreover, infusion of IGF-1 into the wounds restores these variables [97]. Similar to GH, IGF-1 increases wound breaking strength in rats. However, its

effect is evident only when it is combined with one of its specific binding proteins, such as IGFBP-1 [98, 99].

In clinical studies including those on burn patients, growth hormone can significantly reduce wound closure times and the length of hospitalization. In addition, it may accelerate donor site wound healing rates by 25%. With this increase in healing, patients with massive (>60% total body surface area) burn wounds can undergo further skin grafting procedures earlier [100–102]. The good results obtained with GH therapy in terms of the healing rates for donor sites and burn wounds are encouraging. The adverse effects of GH are multiple and potentially severe: carpal tunnel syndrome, peripheral edema, joint pain and swelling, gynecomastia, glucose intolerance, and possibly increased cancer risk. Caution should be exercised when considering treatment with growth-hormone [103–105].

Oxygen

Chronic wounds are hypoxic and arterial and venous diseases are not sufficient to fully explain the phenomenon. Using new models, mathematical models [106], hypoxia chambers models [39, 107], or local ischemia animal models [108], new tools to improve oxygen availability in wounds are being developed.

In a systematic review of human trials hyperbaric oxygen has been found to be efficient in treating diabetic foot ulcers but has not proven effective on arterial ulcers [109]. Reports of successful topical application of oxygen are encouraging but not completely convincing [110–112].

Gene Therapy

Growth factors are proteins that act as regulators of the cellular mechanisms and are intensely involved in the wound healing process. As some of these growth factors have been found deficient in elderly animal wounds, it has been postulated that the addition of growth factors should be sufficient to stimulate an adequate healing response. Topical application of growth factors has been shown to have a healing effect in animal experiments. PDGF (Regranex, Ortho-McNeil) has been approved by the FDA for the treatment of diabetic neuropathic ulcers [113]. Because of the presence of the wound eschar and proteases, daily application is required and only a marginal effect has been demonstrated, compared to placebo (50 versus 37% of complete healing). Direct injection of naked DNA in the wound requires repeated injections of high doses, which can actually impair wound healing [114].

In some instances topical application and direct injection can be inappropriate, and hence new methods of delivering the DNA into the cells had to be developed. These methods can be classified as chemical, mechanical, and virally mediated methods. Liposomes directly interact with the cell membranes to transfect the plasmid load [115]. The Gene Gun uses high air pressure to fire gold beads coated with DNA plasmids through the skin [116]. Liposomes and Gene Gun techniques have shown very variable transfection results. Electroporation might be the delivery method, which will be used in clinical settings in the near future. With the application of an electrical field through the skin, the cell membranes are made transiently permeable to charged macromolecules such as plasmid DNA. The cellular uptake is less than with a viral vector but better than the other chemical or mechanical methods and has not shown any associated risk. Electroporation has been used in human beings to treat specific cancers and to improve the efficacy of DNA vaccines [117–119]. Virally mediated transfer (called transduction) has a high transduction efficacy but there are serious concerns about its safety and pathogenicity [120]. The use of Lentiviruses instead of adenoviruses might reduce these risks.

Tissue Engineering

After more than a decade of progress in biomaterials and cell cultures, bioengineered skin substitutes are now available. Different types can be used: Cultured epidermal graphs (Epicel* Genzyme Tissue Repair), dermal substitutes (AlloDerm* LifeCell), dermal and synthetic epidermal substitutes (Integra*, Integra Life Sciences), and bilayered living skin constructs (Apligraph*, Novartis). The primary indications are life-saving immediate coverage of burn wounds, reducing the need for autographs, and closing chronic wounds. The products will improve as the understanding of their mechanism of action increases [121].

Conclusion

It is apparent that the wound healing response is altered in the elderly compared to that in young individuals. Inflammation, angiogenesis, epithelialization, and remodeling show changes that may consequently impair wound healing. However, in elderly patients not suffering from concomitant diseases, the rate of wound healing is normal or slightly

reduced. It is still difficult to reach definite conclusions on certain wound healing processes such as collagen metabolism, and the influence the above changes may have on morbidity and mortality.

Nonetheless, a clear relation is observed between wound healing and certain disease states (i.e., malnutrition, infections, hypoxia and reoxygenation, diabetes, and drug interactions). Patients with these conditions should be carefully evaluated and supplementation with growth factors and nutrient supplements considered. The potential uses of these factors may be of importance for wound healing in critically ill patients.

Local Wound Management in the Elderly

This chapter has reviewed the patho-physiology of wound healing impairment in the elderly and outlined systemic approaches to improve wound healing by improving blood flow, nutrition, oxygenation, and metabolic status. Now attention is turned to the local management of the wound. There are now consensus-based practice guidelines which provide a basis for management of all the major wound types in the elderly. Pressure ulcers are of such importance that the staging system for categorizing these wounds and guidelines for their prevention are included (see Fig. 8.4 and Table 8.1). In addition, we have categorized frequently used wound dressings in Table 8.2. The best practices for the care of chronic wounds including pressure ulcers, diabetic foot ulcers, and venous ulcers are available on line at the website of the Wound Healing Society [122–124]. The best practices in caring for acute wounds and avoiding impediments to wound healing in the elderly are currently only available as a journal article [125]. These guidelines are based on the consensus of experts and the authors of this chapter consider them to be the best guidance available for the care of wounds in patients of any age.

As surgeons, the most important principle to follow is the complete debridement of necrotic tissue. Adequate debridement of a large pressure ulcer often requires a trip to the operating room with adequate anesthesia to debride not only skin, but muscle and frequently bone as well. The days of performing these types of debridements at the bedside, or in the clinic should be behind us. Inadequate debridement will doom an elderly patient to failed healing, chronic wounds, and associated morbidity and mortality.

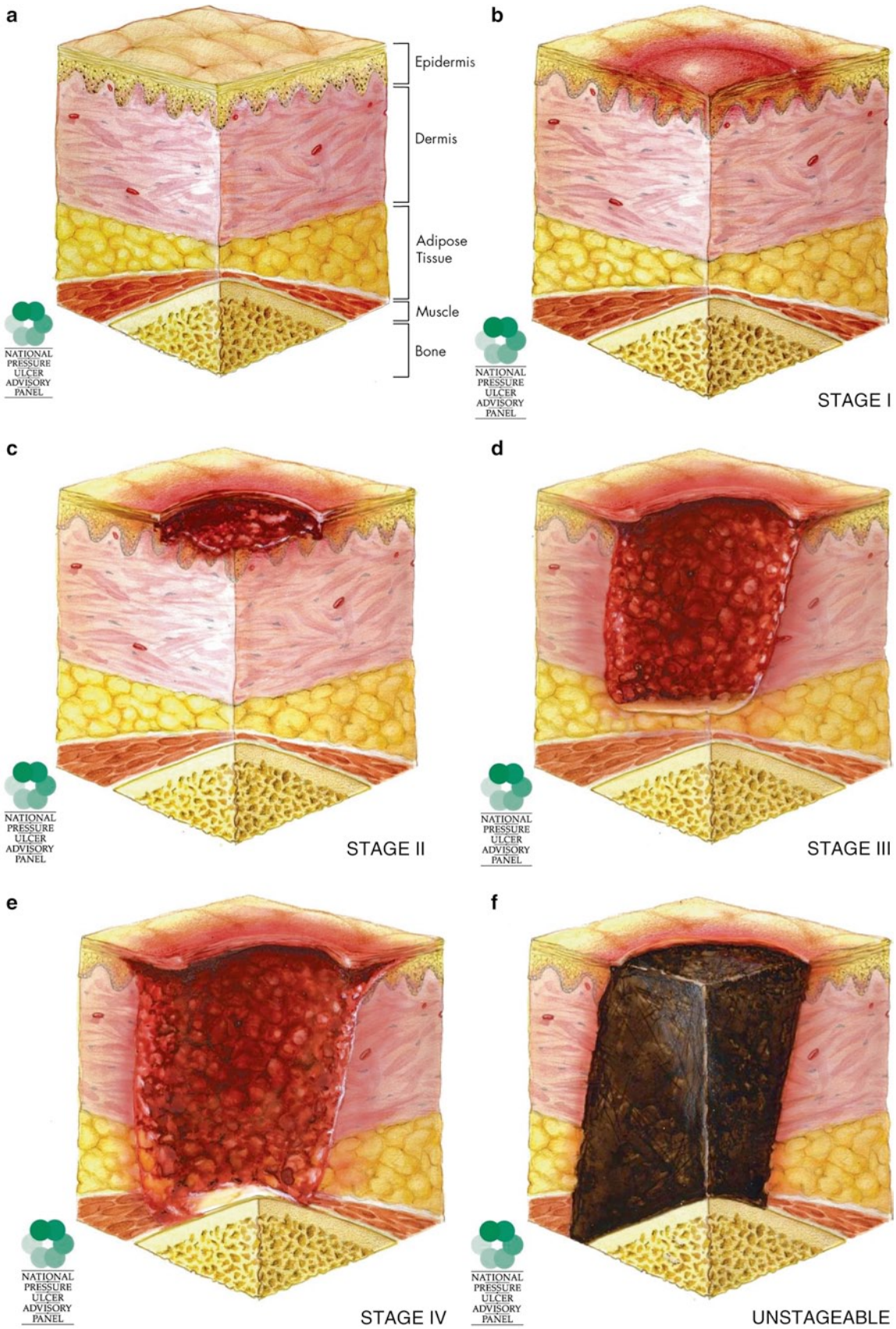
Surgeons also have to be vigilant in identifying and treating deep necrotizing soft tissue infections. Here, the decision to go to the operating room and excise the area of infection can be lifesaving. Erythema, pain, and swelling may be all that are required to make the diagnosis. Performing a CT scan, which shows air bubbles in muscle, or a needle aspiration to identify bacteria by gram stain or culture can waste valuable time and lead to poor outcomes, including mortality.

The availability of new dressings has improved outcomes for elderly patients with wounds. The important features of these new dressings include the capacity to hydrate the wound with a gel or alginateand antimicrobial effectiveness based on the presence of silver ion in the dressing. User choice determines which of the many types of dressings is preferable for a given patient.

Negative pressure dressing is an important advance that has been introduced over the past decade. Negative pressure dressing has been engineered to be applicable to open wounds ranging from small to large, including even the open abdomen. The system has revolutionized the nursing care of wounds, making the three times a day dressing changes a thing of the past. Negative pressure dressing can be applied and left in place for up to 3 days with good results. Importantly infection must be controlled in the wound prior to deploying it. Negative pressure dressing does not replace the need for surgical debridement. The wound must be debrided and clean for the negative pressure dressing to be effective. Infection can advance under such a dressing, even with a silver antimicrobial in place, if adequate debridement has not been performed.

Pressure ulcers remain a significant problem in the elderly and preventive methods can decrease their incidence. For this reason the pressure points where bony prominences lie under the soft tissue are highlighted in Fig. 8.5 (see Fig. 8.5). These areas must be carefully protected using the best practice guidelines in Table 8.1. When a stage I ulcer appears with erythema, this is a dangerous signal that ulceration is about to begin. Efforts should be re-doubled to avoid weight bearing on the vulnerable tissue. Pressure reducing strategies include frequent turning and off-loading with pillows as well as the other modalities listed Table 8.1. Prevention of pressure ulcers requires diligent nursing care and may sometimes be impossible for the extremely vulnerable patient with poor nutrition, cachexia, and contractures. Pressure reducing and air-flow mattresses are expensive and their cost effectiveness is unclear. These beds play a role in the management of the very vulnerable patient. Occasionally a colostomy is required to prevent tissue maceration in patients with incontinence. This strategy will sometimes achieve healing of a recalcitrant ulcer, or it may be performed prior to a major surgical tissue transfer procedure to cover a particularly severe pressure ulcer.

Absent from the list of treatment options, is a means to specifically accelerate wound healing. The only FDA approved treatment option of this type is Regranex*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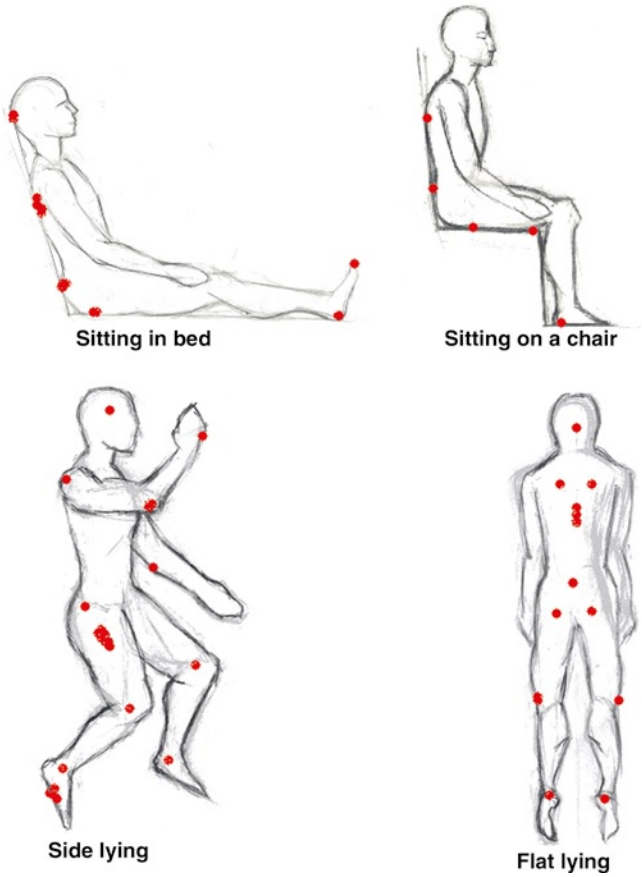

Figure 8.5 Pressure points.

(Becaplermin), Systagenix Wound Management, Gargrove England, which is platelet derived growth factor in a gel for topical application. Most clinicians have found it to be only minimally effective, but it may have a place restoring healing, particularly of a diabetic foot ulcer where healing has stalled, and all efforts necessary to off-load weight-bearing and restore blood flow have been exhausted. There are a number of promising agents including VEGF, KGF, and hypoxia inducible factor 1 alpha that are in preclinical and clinical trials. The delivery of these agents as well as PDGF, using DNA plasmids, or even viral vectors, has the potential to keep therapeutic levels elevated over relevant time periods without requiring frequent applications. In addition these types of delivery systems can place the agent deep in the wound tissue, obviating the need for transfer across a wound eschar. In the coming years as more studies are performed, some of these promising agents will be available in clinics.

Figure 8.4 Staging system for decubitus ulcers. (**a**) Normal tissue. (**b**) Stage I: An observable pressure related alteration of intact skin whose indicators as compared to the adjacent or opposite area on the body may induce changes in one or more of the following: skin temperature (warmth or coolness), tissue consistency (firm of toggy feel), and/or sensation (pain, itching). The ulcer appears as a defined area of persistent redness in lightly pigmented skin, whereas in darker skin tones, the ulcer may appear with persistent red, blue, or purple hues. (**c**) Stage 2: Partial thickness skin loss involving epidermis, dermis, or both. The ulcer is superficial and presents clinically as an abrasion, blister, or shallow crater. (**d**) Stage III: Full thickness skin loss involving damage to, or necrosis of, subcutaneous tissue that may extent down to, but not through, underlying fascia. The ulcer presents clinically as a deep crater with or without undermining of adjacent tissue. (**e**) Stage IV: Full thickness skin loss with extensive destruction, tissue necrosis, or damage to muscle, bone, or supporting structures (e.g., tendon, joint capsule). Undermining and sinus tracts may also be associated with Stage IV pressure ulcer. (**f**) Unstageable: Eschar: Thick dry black necrotic tissue.

CASE STUDY: GERIATRIC WOUND HEALING

Background

Medical History

This 67-year old gentlemen was referred to our service with a complex wound. Two years prior to admission he had a sigmoid colectomy for removal of a polyp at an outside hospital. He developed MRSA wound infection requiring extensive debridement and reoperation. He was left with the bowel covered with skin graft with a 20 cm diameter ventral hernia (Fig. 8.6). His abdominal wound was complicated by the fact that he has alcoholic cirrhosis with ascites. His co-morbidities include coronary artery disease with a myocardial infarction managed with four coronary artery stents. He has COPD with periodic bronchitis requiring hospitalization. He does not use home oxygen, but he is severely short of breath after climbing one flight of stairs.

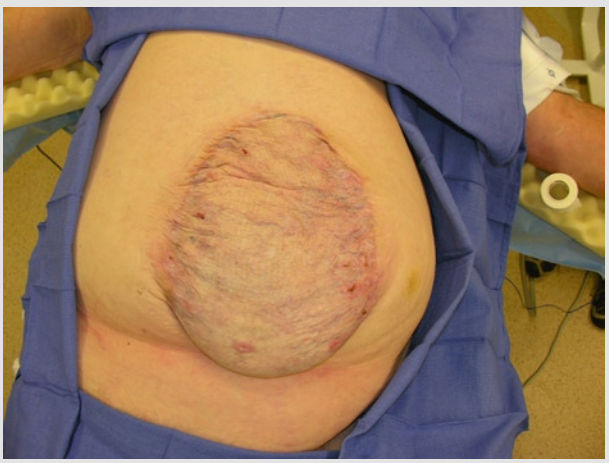

Figure 8.6 Case report: The ventral hernia with skin graft. There was an ascites leak through a punctuate ulceration in the skin graft.

He has insulin dependent Type 2 diabetes.

Considering his life threatening co-morbidities, and the benign status of his hernia, our initial approach was to simply monitor his situation and treat his hernia with a binder. But when he developed an ascites leak we proceeded to urgent repair of the hernia. The repair was carried out excising the skin graft from the bowel

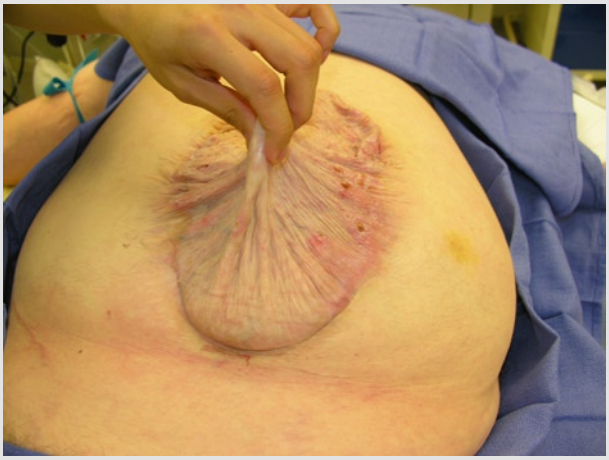

Figure 8.7 Case report: "Pinch Test" showing that the skin graft was not densely adherent to the underlying bowel.

(Fig. 8.7). This meticulous dissection was carried out without creating an enterotomy. A subcutaneous flap was raised to the mid axillary line bilaterally to perform component separation and myofascial transfer of the internal oblique to be able to close the defect primarily. With the prior MRSA we elected not to implant a mesh of any type.

The Wound

The wound with which this patient presented is ischemic necrosis at the midline of his abdominal flaps. This necrosis was evident 5 days after the repair of the hernia. This wound was 4 cm wide and extended for a distance of 20 cm along the midline incision.

The management of this wound is a classic problem in geriatric surgery.

Management Strategies

Surgical Debridement

When it became clear that the wound was necrosing, surgical debridement was carried out. Full thickness skin and subcutaneous tissue were excised. The necrotic tissue was excised back to bleeding tissue and a VAC drain was placed (Fig. 8.8).

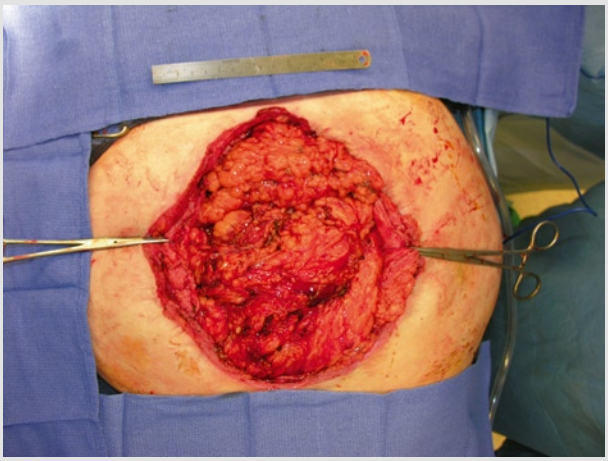

Figure 8.8 Case report: The wound after debridement of the necrotic skin flaps. Skin and full thickness subcutaneous tissue were debrided to the fascial level to remove the tissue that had suffered ischemic necrosis.

Diabetes

This patient has insulin dependent diabetes. Blood sugars was greater than 200 mg% in the face of the sepsis from the wound. Tight glucose control was instituted with continuous IV glucose drip to bring the blood sugar under 150 mg%.

Infectious Disease

The necrosis of the wound appeared to be ischemic, secondary to the raising of the lateral flaps, coupled with his overall debilitated condition. Nonetheless infection was a potential problem. He was covered with intravenous clindamycin to which his prior MRSA had been sensitive. This coverage was maintained for his initial hernia repair for 24 h and likewise at the time of his debridement.

Nutritional Support

During the post operative period after his hernia repair his nutrition was maintained with a Dobhoff feeding tube. The tube was carefully placed in the duodenum using fluoroscopic guidance. Initially a nasogastric tube was placed in the stomach to check gastric residuals. When residuals were greater than 200 cc with feeding at the rate of 60 cc per hour the feedings were discontinued. After 24 h they were reinstituted at 30 cc per hour. They were gradually returned to 60 cc per hour over 4 days.

Ascites

His ascites from alcoholic cirrhosis was managed initially with an intra-peritoneal JP drain following the primary hernia repair. This was to protect the closure from the pressure of intra-abdominal ascitic fluid. The ascities was also controlled medically with Lasix and Aldactone. When drainage from the JP drain was less than 100 cc per day, 72 h after surgery the JP drains were removed. Fortunately the re-accumulation of ascites was less of a problem than expected for this patient.

COPD

This patient developed ARDS with typical patchy infiltrate on chest X-ray and desaturation of O_2 accompanied by CO_2 retention. He required intubation and mechanical ventilation. After 10 days he was converted to a tracheostomy tube. He had gradual remission of his ARDS with this approach.

Coronary Artery Disease

After both surgeries the patient was ruled out for myocardial infarction. Serial troponins and EKG's confirmed that he did not sustain a myocardial infarction

Delirium

The patient developed florid delirium with agitation within 24 h of the initial surgery. The family asserts that he had discontinued alcohol intake; however, he appeared to be suffering from Delirium tremens. He was treated with Atavan and Haldol, and he also required four point restraints briefly. This delirium gradually cleared over 3 weeks of hospitalization.

Outcome

With this multi-pronged approach this patient survived a high risk scenario of ulcerated ventral hernia with ascites leak. After the debrided wound was treated with the VAC it granulated, and after 12 days was closed in the operating room (Fig. 8.9). It healed in a satisfactory manner, and the patient was discharged to a rehabilitation unit after 4 weeks of hospitalization.

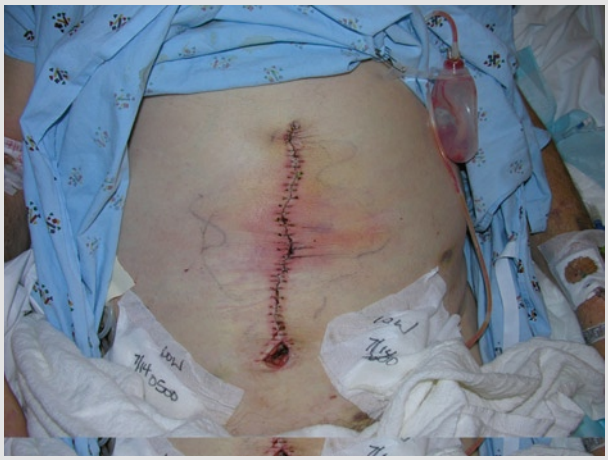

Figure 8.9 Case report: Closure of the wound after it had granulated. Open wound was treated with VAC* dressing. After it had granulated the wound was closed as shown.

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