Skin, Soft Tissue, and Wound Healing in the Elderly

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Case Vignette

A 78-year-old man with diabetes mellitus wanted to warm his cold feet so he placed them in hot water for 30 min. He was not sure how hot the water was but he did not have much feeling in his feet for the last 5 years. He had felt that the hot water would also be good for the 2 cm ulcer on the sole of his right foot at the second metatarsal. Several hours later his wife noted that his feet were red, were weeping, and had sloughed some skin. She convinced him to visit his local doctor who noted red, nonblanching burns that were demarcated from a line just above the ankles to the soles of his feet. He had pulses on his feet but the vessels were not compressible. He was sent to the burn center and found to have full-thickness burns. He was taken to the operating room where he underwent routine excision and grafting. The grafts looked good on postoperative day 5 and he was sent home 4 days later. He was seen in clinic a week later where he complained that his grafts were draining fluid and had turned dark. Examination of his feet revealed near total graft loss and exposed tendons on the dorsal feet. Several toes had turned black and two others developed flexion contractures. He was taken to the operating room where further debridement revealed exposed bones on the ankles. The plantar ulcer was also draining pus. He eventually required bilateral below-knee amputations.

Introduction

In the industrialized world, the birth rate is down, and with modern healthcare people are living longer so that the elderly are occupying a much larger percentage of the population. US census results reveal that in 2010 24 % of the population was greater than 55 years of age and 13 % was greater than 65 years of age. These values are projected to be 31.1 % >55 years, 20.2 % > 65 years, and 4.3 % >85 years in 2050 [1]. All practitioners are going to be exposed to more geriatric patients so familiarity with skin problems will become essential knowledge. Not only are the elderly at greater risk for skin breakdown, but they also have skin changes that alter their ability to heal. Many treatments for diseases in the elderly (steroids, chemotherapy, and radiation) impair tissue repair. Chronic wounds – diabetic, vascular, venous stasis, and pressure ulcers – are much more common in the geriatric population. Chronic wounds are a huge economic burden for today's healthcare and for the individual; they frequently accompany the person for the rest of his or her life. Pressure ulcers are considered a "never event" by governmental health agencies that, if they occur, may lead to loss of reimbursement. Since simple injuries often lead to major wounds that fail to heal, prevention efforts are essential to reduce the burden of chronic wounds in the elderly. While there are increased problems with healing in the elderly, their wounds can be treated and lead to successful outcomes. This chapter will review the factors that increase the risks for wounds in the elderly, describe the pathophysiology of chronic wounds, discuss prevention, and describe so strategies for treating those wounds.

Skin Changes with Aging

The skin changes related to aging are well documented in the dermatology literature [2–7]. Typically, skin alterations due to aging are classified into "intrinsic" and "extrinsic" changes. *Intrinsic* changes are those that occur "within the

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body" as part of the normal aging process and are independent of environmental exposure. *Extrinsic* changes are those alterations that induced by environmental forces – most notably the ultraviolet portion of sunlight. While it is difficult to differentiate which factors are totally intrinsic versus extrinsic, it is clear that extrinsic factors accelerate the degenerative changes in the skin. Everyone is aware of the changes that occur in the skin that is abused by sun exposure or just poor self-care. The skin becomes thinner, dryer, more wrinkled, sags, and has variable pigment changes. Clearly, sun exposure increases the risks of skin cancers of all types. While these changes will occur with aging, good skin care, especially protection from the sun, will slow these changes.

The structural changes of the skin that occur with aging are well documented. The epidermis tends to become thinner with aging but thickens in response to ultraviolet light damage. The dermal-epidermal junction becomes flatter. The flattening of the normal rete pegs of the dermal-epidermal junction weakens the resistance to epithelial shear. In other words, the elderly are more prone to superficial wounds from minor shear forces. There are also significant changes to the normal skin adnexa – hair follicles, oil glands, sebaceous glands, and other dermal appendages. Sebaceous glands are decreased which leads to more dryness of the skin. In addition, there is decreased replacement of lipids in the stratum corneum which interferes with the normal barrier function of the epidermis. Hair follicles clearly change in many parts of the body. They heal more slowly and change in distribution. Clearly, male and female alopecia (baldness) is the most recognizable hair change, but hair follicles increase in size and decrease in density [6].

The significance of the dermal appendage changes is that healing of superficial wounds is impaired. To heal a partial-thickness wound (such as a superficial burn or blister) the dermal appendages are required. Normally, re-epithelialization takes place in two areas of the skin: the edge of the normal skin and from dermal appendages [8]. At the edge of the wound, the basal cells of the bottom layer of the epidermis are stimulated to migrate across the wound by three factors: loss of cell-cell contact, stimulation by growth factors (epidermal growth factor, transforming growth factor-α, and keratinocyte growth factors 1 and 2), and contact with proteins of the exposed wound (fibronectins, collagen type 1). Migration from the original wound edge stops after around 1–2 cm in a full-thickness wound, and the remainder of the closure is by contraction. In a superficial wound, epithelial migration also occurs in the epithelial cells of the dermal appendages, especially hair follicles. The higher the hair follicle density in a wound, the faster it can re-epithelialize. As an example, if a hair-bearing scalp is used as a split-thickness skin graft donor site, it will heal within 4–5 days. If the skin adnexa are sparse in number, such as what occurs in a lower leg with impaired circulation, then healing may take weeks. Thus, the problem with the decreased density of dermal appendages in the elderly is that their ability to re-epithelialize a wound is impaired. I have observed very superficial wounds in a hairless, elderly patient that never re-epithelialize and thus are said to "convert" to full thickness. They did not "convert," but instead had no ability to re-epithelialize.

There are significant dermal changes in the skin due to aging. The dermis is also the main target of ultraviolet light damage [2]. With increasing age there is a decrease in dermal cells (macrophages, fibroblasts, mast cells) and a decrease in antigen-presenting cells (Langerhans cells) which results in a decrease in immune function. The dermis becomes thinner and the collagen becomes less organized. The collagen molecules actually become larger but have more fragmentation and less orientation along lines of stress. The activation of matrix metalloproteinases by ultraviolet light exposure may contribute to these collagen molecule changes. This degradation in collagen is reflected in studies which demonstrate that the tensile strength of skin is decreased with age [9]. The dermal hydration decreases, and while the amount of elastin changes little, it becomes more fragmented. Thus, skin becomes less elastic, more wrinkled, and more prone to tearing or lacerations. Everyone knows that with aging comes looser skin that sags with gravity. While looser skin is considered undesirable in our society, it does benefit the healing of the elderly with small full-thickness wounds. These wounds heal by contraction so that the loose skin tends to not interfere with this process as it would in a younger person. Tension tends to interfere with wound contraction so the process may be augmented with looser skin. Clearly, contraction can lead to contractures if it occurs over functional areas such as joints. Since looser skin allows for closure with less tension, the elderly have a lower risk for contracture. In other words, allowing a wound to contract may be an alternative to surgical repair.

Besides the actual structural changes to the skin, there is a generalized decrease in sensation, decreased vascularity, and impaired lymph flow with aging. The sensory changes occur in a distal to proximal fashion and are especially related to decreased cold/warm sensory abilities [10]. There are actual decreases in the density of thermal sensory receptors, and some suggest that there is a decrease in peripheral nerve density. Studies suggest that there is altered angiogenesis associated with decreased cutaneous vascular reactivity [2–7]. In response to sun damage, there may be an increased angiogenic response, but the new vessels are more disorganized and more prone to leaking proteins. With impaired lymph flow, there is an increase in edema – which impairs healing. In addition, impaired lymphatic function decreases the ability to fight infections or contract wounds. There are obvious pigment changes that occur in skin with aging. Melanocytes decrease in numbers, but with ultraviolet light

exposure, there are more spotty areas of hyperpigmentation. Many cells develop mutations that alter local areas leading to "age spots" such as keratoses and nevi. While not covered in this review skin cancers increase with aging. All of these changes are accelerated with sun exposure. In addition, increased bruisability from the use of antiplatelet drugs or anticoagulants will often lead to pigment changes from the retained heme products.

Finally, changes beneath the skin contribute to the risk of skin injury in the elderly. There is a tendency to lose muscle mass from either decreased exercise or activity. Fat stores are often (but not always) reduced with aging. These changes are clearly accelerated with malnutrition – a factor that impairs wound repair. The significance of these changes is that the loss of padding tends to expose bony prominences to increased pressure and chronic breakdown. Incontinence of urine or stool increases the risk for maceration which increases the risk of shear injury. As people age, they become slower in their ability to respond to a dangerous situation. Their reflexes tend be slower so that they have more difficulty escaping an injury. I have observed many elderly patients who were unable to extinguish flaming clothing or escape scalding water. This slowing of reflexes and an impaired ability to respond to injury lead to more extensive and deeper wounds. We know from burn studies that the elderly have a much lower ability to tolerate large wounds so a small injury can be fatal. Finally, people at the extremes of ages become more dependent on others for care. An unfortunate consequence of this unwanted dependency is that there is an increase in the risk for elderly abuse. One must always be wary if an injury does not fit the "story" of how it occurred. Just as for children, caregivers are obligated to report suspected abuse.

Diseases of the Elderly Affecting Wound Healing

Fortunately, healing processes remain fairly normal in healthy people until the extremes of ages. Since many elderly take good care of themselves they tolerate surgery and minor injuries quite well. It is important to recognize, however, the factors or diseases that impair tissue repair. These inhibitors of wound healing affect all age groups, but they are, unfortunately, more common in the elderly population. One must be aware of these factors that may delay or prevent healing if he or she is planning surgery or treating a wound.

Malnutrition

Studies have shown for over 100 years that malnutrition impairs wound healing [11–14]. The impairment exists with total protein/calorie (marasmus) malnutrition or with protein (kwashiorkor) malnutrition. Simply, if one holds nutritional support at the time of wounding, a marked impairment in tensile strength will result within 1–2 weeks [15]. The clinical significance of malnutrition relates to the risks of complications with surgery such that if a patient has lost weight from a malignancy or from an inability to eat, then there is a much higher risk for dehiscence. The hidden side of this healing impairment is that altered healing could lead to a bowel anastomosis leak which in turn may lead to an abscess. Since the metabolic reserve is reduced in the elderly, this complication of failing to heal often leads to sepsis, multiple organ dysfunction syndrome, and ultimately death. The clinician can reduce complications by assessing the nutritional status of the elderly and providing supplemental nutrition prior to surgery. In addition, an aggressive approach to perioperative nutrition may make the difference between normal healing without complications and a rocky course and ultimate death.

There are some vitamins and micronutrients that influence tissue repair. Vitamin C is essential for the hydroxylation of proline or lysine in the formation of normal procollagen triple helices [16]. When there is a deficiency, collagen is not properly produced, and people may suffer from scurvy. Since there is a balance between collagen formation and breakdown during the maturation phase of scar formation, recently healed wounds may break down. In addition, vitamin A has been found to augment tissue repair [17, 18]. Several minerals such as zinc [19, 20] and copper [20] are essential for normal healing, and when they are deficient, problems may result. We have noted that patients with subnormal copper levels have impaired healing of their burn wounds [21]. A deficiency in arginine may also lead to altered tissue repair [22].

Diabetes Mellitus

Diabetes mellitus is a major cause of healing problems in people of all ages [23–25]. Since the disease is seen more commonly in the elderly, it is important to know its impact on tissue repair. Some statistics are important to emphasize its impact on the development of chronic wounds. Twenty percent of hospital admissions in diabetes are related to wound healing problems. Twenty-five percent of diabetic patients will have a foot ulcer during their lifetimes, and 50 % of all nontraumatic amputations are related to diabetes mellitus. A common scenario is that a diabetic patient will not notice a pebble in their shoe due to their impaired sensation. This will create a small wound that goes unnoticed, and eventually a wound is noticed and not properly treated. When the patient finally seeks care, the wound is infected with purulence tracking up the fascial planes of the foot. This patient often presents with cellulitis or invasive infection that leads to an amputation.

Even if a wound is detected, early tissue repair is significantly impaired. As an example, Margolis reviewed several clinical trials that tested treatments for diabetic ulcers [26]. He collected the "controls" which received "standard" treatment. What he found was that only 31 % healed within 20 weeks of aggressive therapy. It is likely that the two-thirds that did not heal stayed open for the remainder of their lives. There are several reasons why tissue repair is impaired in patients with diabetes mellitus [23–25]. First of all, *peripheral vascular disease* is increased in this population. Diabetics not only suffer from *macrovascular* disease but also from *microvascular* disease where there is thickening of the capillary basement membrane. This *microvascular* disease leads to impaired delivery of oxygen and nutrients from an increase in edema and impaired diffusion. This process also impairs leukocyte migration into the wound. If the patient suffers from renal disease, healing is inhibited further by *uremia* and its resulting edema [27].

The second factor that contributes to alter healing in diabetes mellitus is its tendency to cause peripheral *neuropathy*. Loss of sensation progresses from distal to proximal so that the feet are usually involved first. As stated earlier, people with neuropathic feet do not sense injury, and thus minor injuries tend to worsen or fail to recognize that they are injured. We have recently reviewed our 10-year experience with diabetics who burn their feet [28]. It is common for them to walk outside on hot pavement or try to warm their "cold" feet with hot water or by placing them near heaters. We admitted 68 patients with burns to their feet during that period, and the incidence is increasing. As for other types of diabetic wounds, the patients admitted for burns to their feet tended to have prolonged hospital stays and frequent graft failure. Another often unrecognized consequence of neuropathy is that the foot loses its normal feedback to maintain the arch. The foot thus tends to flatten which leads to increased pressure on the first or second metatarsal head. The classic diabetic foot ulcer is a wound that is on the plantar surface on the first or second metatarsal head. The final consequence of neuropathy is that with loss of normal sympathetic innervation, the skin loses its ability to sweat and thus tends to dry and crack. These cracks may lead to a site for infection. Patients should be tested for neuropathy using a 10-g Semmes Weinstein monofilament, 128-hertz tuning fork, vibration perception threshold testing, or a good neurologic exam for sensory loss [29].

There is an increased risk for infection for wounds that form in the diabetic patient. It is well known that hyperglycemia leads to an impaired ability to fight local infection and that avoiding wide swings in glucose levels improve [30]. There are also studies that suggest that leukocyte migration and function is impaired. The inability to fight infections predisposes diabetics to a higher risk for amputations. In addition, there are several metabolic factors that may contribute to impair healing that are covered in other reviews [25, 31]. One interesting concept is that hyperglycemia may lead to deposition of glucose byproducts known as advanced glycosylation end-products (AGES) in the tissues. There are "receptors for advanced glycosylation end-products" (RAGES) that detect these products of hyperglycemia and stimulate an inflammatory response. One theory is that activation of RAGES may lead to the chronic inflammatory state ("metabolic syndrome") of diabetes mellitus and obesity [32]. This chronic inflammatory state may also contribute to impaired tissue repair.

Since healing is impaired in diabetic patients, it is essential that prevention efforts are made to prevent a wound from developing. The Wound Healing Society has published guidelines for the treatment and prevention of diabetic wounds, and new guidelines should be published in 2016 [33, 34]. All clinicians who treat diabetes mellitus should discuss the risks of foot ulcers with their patients. Diabetics should inspect their feet daily and be extremely careful with the care of their nails. Podiatrists are extremely helpful in these matters. Diabetics with neuropathy should always wear well-fitted shoes and be especially vigilant after the first few days of wearing new shoes. Any new wound should be treated aggressively and early. People with diabetes mellitus should always avoid walking outside while barefoot and never warm their insensate feet with any heated agent. Once a wound develops, they should be treated with something that "off-loads" the pressure point on the wound (metatarsal head). "Total contact casts" have been found to be effective [35]. Studies suggest that topical growth factors or skin substitutes may be effective, but they are extremely costly [36–38]. Vascular disease should be treated if present. Unfortunately, our success with treating these wounds is only marginal, so prevention is essential. Anyone who is fortunate to heal a diabetic foot ulcer should practice extra precautions because the recurrence rate is up to above 50 %. Those patients should wear protective footwear and have daily inspections of their feet for the rest of their lives [39–41].

Therapies That Alter Wound Healing

Wound healing involves the recruitment and rapid proliferation of many different cell types. It makes sense, then, that any drug that impairs rapid proliferation of cells alters tissue repair. Unfortunately, the strategy for dealing with many diseases includes suppressing the inflammatory response, which also requires rapid proliferation of cells. *Steroids* have been known for decades to impair tissue repair, and their use should be minimized if possible to allow for better healing [42, 43]. The treatment of cancer also involves the killing of rapidly proliferating malignant cells so it is also obvious that *chemotherapy agents* [44, 45] or *radiation* [46, 47] impairs tissue repair. In the advent of neoadjuvant therapy (chemotherapy and/or radiation) combined with surgery, it is clear that one must be

extremely careful with the healing of these patients. One must optimize their nutritional status if they are to undergo these combined treatments. There are very few agents that augment healing in these situations, but vitamin A has been shown to at least partially reverse impairments due to steroids or radiation [17, 18]. Growth factors may also play a role in improving healing, but these are based on animal studies [48–54].

Neurologic Diseases

Neurologic diseases do not impair wound healing, but they do predispose the elderly to the risk of developing wounds. Dementia leads to forgetfulness and risky behavior that may lead to injury. The person may forget to turn off stoves or fail to practice safe techniques for self-care. People with dementia have a more difficult time with cleanliness and maintaining a diet and thus may not clean wounds and tend to be more malnourished. Neuropathies have previously been mentioned as a risk for many types of wounds. Any loss of sensation clearly predisposes a person to pressure sores, since pain is the main warning sign of chronic pressure. Tremors may predispose the elderly to spills and an inability to quickly react to a dangerous situation. Incontinence may lead to maceration of the skin which in turn increases the risks for abrasions or tears with moving. Seizures are risky in people who cook or around hot items since during the seizure they will not react to an injury. People who seize while cooking or bathing frequently sustain very deep burns.

Problem Wounds of the Elderly

There are specific types of wounds that all practitioners must know about when treating the elderly. These wounds are relatively easy to prevent but are particularly difficult to treat once they are present. These chronic wounds are a significant burden to society in cost and interference with normal living. They may occur in any age group but they are more common in the elderly. Since they are a major contributor to morbidity in the elderly, one must know how to diagnose and treat these problem wounds. The Wound Healing Society has recently published consensus guidelines in the prevention and treatment of these problem wounds, which provide hundreds of references [55–60]. New and revised guidelines are scheduled to be published in 2016.

Pressure Ulcers

Pressure ulcers may develop at any age, but they are commonly manifested in the elderly as they develop reduced ability to move or after the development of neuropathy [55–61]. These wounds are found in around 10 % of inpatients. The pathophysiology is simple; any pressure on the skin and underlying tissues of greater than 30 mmHg that persists for a prolonged period of time can lead to enough ischemia to create a pressure ulcer. Normally, pressure produces pain which leads to a shift in the body to redistribute the pressure to another area. When we sleep we are constantly and subconsciously moving. Even intoxicated people will move to prevent these wounds. When people lose sensation, such as after paralysis, or when so ill that they are unable to move (such as in an intensive care unit), they are prone to pressure ulcers. Nurses play a major prevention role by rolling patients from side to side. Not uncommonly, however, pressure ulcers develop where bony prominences create pressure. The classic sites are in the presacral region and the occiput and on the heels. There are scoring systems that grade the severity of pressure ulcers that are useful for documentation. Pressure ulcers are staged as 1 when the skin is intact but just reddened for a prolonged period, 2 when the skin has been broken, 3 when the ulcer has become full thickness, and 4 when the wound tunnels into deeper tissues [61, 62]. The wound management becomes more difficult with increasing severity. The usefulness of this paradigm has been recently challenged [63]. It is unclear of the relevance of a stage 1 ulcer, and the pathophysiology varies between stage 2 and stage 3 or 4 ulcers. Stage 2 ulcers result from damage from the "outside in," and higher staged ulcers are produced from the "inside out." Irrespectively, the staging system is helpful for documentation and management strategies.

The factors that predispose the elderly to pressure ulcers include the loss of padding with aging, malnutrition, loss of sensation, thinner skin, and incontinence. People with more fat are slightly more protected. Like all wounds, prevention is essential with frequent shifting of the patient, frequent inspection, maintaining normal nutrition, preventing maceration, and getting people out of bed. One recommendation that may reduce presacral ulcers is to leave the head of the bed as flat as possible, but this recommendation is in conflict with recommendations to minimize ventilator-associated pneumonia (keeping the head of the bed at 30°) [64]. The use of special padding in hospital beds may also assist with the reduction of these ulcers [65]. The Braden Score is the most commonly used screening method to determine the risk for pressure ulcers [66]. The score is based on six parameters: sensory perception, moisture, activity, mobility, nutrition, and friction/shear. Pressure ulcers have become such an important issue that they have been declared a "never event" that requires documentation and monitoring in hospitals. The Centers for Medicare and Medicaid Services (CMS) has set up guidelines that result in fines of up to $10,000 per day if compliance is lacking. Once a pressure ulcer develops, it is very difficult to heal. Clearly, one must eliminate pressure from that area, but it is often difficult to prevent people from

bearing weight on bony protuberances. Studies suggest that pressure sores may have improved healing with growth factors [67, 68]. Frequently, plastic surgeons will perform various myocutaneous flaps to try to cover these wounds, but once they develop, they have a high incidence of recurrence. If there is no closure after a prolonged period, then surgical closure is recommended.

Arterial Insufficiency Ulcers

These ulcers are the result of ischemia that results from vascular insufficiency [57, 58]. In fact, pure arterial insufficiency ulcers are rare, but usually tissue hypoxia contributes to the failure to heal in wounds caused by other etiologies. It is clear that hypoxia leads to impaired tissue repair. Since peripheral vascular disease is a major problem in the elderly (around 30 % of people over 75 years), it is important to remember that if a wound lacks a blood supply (or oxygen), then it will not heal. One of the major indicators for operating on peripheral vascular disease is for a "limb at risk" from failing to heal. The elderly should have a proper assessment of their pulses if they have a wound that does not heal. Other signs of peripheral vascular disease include loss of hair, shiny and dry skin, mummified or black toes, devitalized soft tissue with a moist or dry crust, thickened toenails, purple skin color with dependency, and cool skin. As a rough rule, if the region around the wound has a transcutaneous partial pressure of oxygen ($PtcO_2$) of less than 40 mmHg, it will have difficulty healing, and if the level drops below 20 mmHg, then healing will not occur. Revascularization will often remedy this problem. All lower extremity wounds must be evaluated for an adequate blood supply in order to treat them. Simple ankle/branchial indices are helpful, but the assistance of Doppler studies is also helpful. Once an arterial ulcer has formed, there are really only two options for treatment – revascularization or amputation. Vascular surgeons are experts in the evaluation and treatment of peripheral vascular disease and should be consulted as necessary. Prevention of arterial ulcers really involves all of the standard means of reducing atherosclerosis – cessation of smoking, reducing hyperlipidemia, exercise, and others. Unfortunately, once one leg requires revascularization of an ulcer, then there is a 20 % chance of the other leg developing an arterial insufficiency ulcer [69].

Venous Stasis Disease

These wounds are not a sole problem of the elderly but are important to discuss in this chapter. Advanced venous disease, manifested by edema, pigment changes (lipodermatosclerosis), and ulceration, affects 2.5 million people per year in the United States and cost around 3 billion dollars in 1997 [59, 60, 70–73]. The predisposing problem for these ulcers is venous valvular insufficiency that usually results from deep venous thrombosis. The loss of valves leads to ambulatory venous hypertension that interferes with local blood flow to the distal lower extremities. The classic venous stasis ulcer occurs above the medial malleolus with a surrounding hyperpigmented region. As for all venous insufficiency, edema contributes to the problem. With a column of blood coursing from the heart to the feet, there is a large amount of venous pressure that tends to interfere with capillary blood flow. The resulting increase in hydrostatic pressure leads to increased capillary leak and more edema. Any edema creates a greater distance for nutrients to travel from the capillaries to the cells and an increased risk for local hypoxia. Local capillary leaks tend to deposit fibrin which may lead to further hypoxia and impaired nutrient delivery or may "trap" leukocytes leading to persistent inflammation. The actual mechanism of the creation of the wound is not clearly known. There are many theories that need to be proven or disproven [74].

The diagnosis of venous leg ulcers depends on the history of deep venous thrombosis and/or diseases suggestive of venous valvular insufficiency such as varicose veins. A history suggestive of other diseases such as arterial insufficiency, sickle cell disease, or others should make the diagnosis more difficult. Examination of the legs is essential to determine whether there are varicosities, edema, and pigment changes. Color duplex ultrasound scanning that checks for abnormal venous reflux or obstruction should be performed in the standing and supine positions [75].

Venous ulcers tend to increase with advancing age but may occur in younger age groups with venous insufficiency. Once the ulcer develops, it can be healed, but since the underlying venous hypertension persists, it tends to recur. Treatment is conceptually simple. The leg must be elevated to reduce venous pressure and edema. Compression plays a major role in healing by reducing edema [76]. "High-compression" systems such as multilayered elastic compression or inelastic compression should be used. The "Unna boot" (fine mesh gauze with calamine lotion and zinc oxide) has been used with some success for years. Intermittent pneumatic compression devices may also help. Clinical studies suggest that growth factors [77–79] and biologic skin substitutes [80, 81] may help with closure, but nothing has reduced recurrences. Skin grafts may temporize the wound but they have a high failure and recurrence rate [82].

There are several options for dealing with the etiology of venous stasis disease. Surgery that interferes with venous backflow ("subfascial endoscopic perforator surgery") may be helpful [83, 84]. Currently, noninvasive techniques are often preferred. "Pathologic perforating veins" associated with a nonhealing venous ulcer and that have an outward flow of >500 ms of duration and are >3.5 mm in diameter

may be eliminated using percutaneous methods (ultrasound-guided sclerotherapy, endovascular thermal ablation, or laser). This therapy should be combined with compression [85, 86]. If there is ilio-caval obstruction, the possibility of recanalization with a stent may be considered [87]. What is needed is some way of repairing venous valves but this has not yet been accomplished.

Principles of Wound Healing of Chronic Wounds

There are repeated themes for the treatment of all chronic wounds irrespective of the etiology. These principles should improve the healing of all types of nonhealing wounds:

- Control the underlying etiology causing the failure to heal the wound:
  - Tight glucose control for diabetes mellitus.
  - Reperfuse ischemic limbs.
  - Eliminate pressure from all wounds (especially in pressure ulcers and diabetic foot ulcers).
  - Eliminate venous hypertension by eliminating incompetent perforators, relieving venous obstruction, and potentially repairing venous valves.
- Healing in a moist environment is always preferred.
- Control infection:
  - Wounds with $>10^5$ bacteria usually fail to heal.
  - Remove biofilms – bacteria in biofilms are more resistant to treatments.
  - Treat underlying osteomyelitis with debridement of necrotic bone and 2–4 weeks of antibiotics (preferably) or prolonged antibiotics if unable to debride the bone.
- Debride the wound of any nonviable and chronic, unchanging tissue:
  - All studies show that a freshly debrided wound heals better than one that has not been debrided.
- Wounds that fail to show signs of improvement within 4–8 weeks should be reassessed for a different diagnosis:
  - Infection should be ruled out.
  - Ischemia should be ruled out (transcutaneous pO_2 should be >40 mmHg).
  - Wounds that are more painful or darker in color may have a different diagnosis:
- Pyoderma gangrenosum, IgA monoclonal gammopathies, Wegener's granulomatosis, cutaneous chronic granulomatous disease, mycobacteria or fungal infections, and malignancy
  - Biopsies for histology and culture should be obtained.
- Treatment strategies should change when chronic wounds do not improve:
  - Adjuncts to wound healing may improve the outcome:

    Growth factors, cytokines, platelet-rich plasma, cellular and acellular skin equivalents, negative pressure wound therapy, electrical stimulation, ultrasound, hyperbaric oxygen, and extracorporeal shock wave therapy have all been studied and have varying efficacy.
  - Prevention is essential to prevent initial and recurrent ulcers:

    Screening for early signs of wounds (feet, pressure areas).

    Maintaining adequate nutrition.

    Maintain glucose control.

    Maintaining hygiene – cleanliness and cutting toenails.

    Maintaining health through exercise and activities (get off pressure areas, improve calf muscle activities in venous ulcers).

    Wearing proper fitting footwear.

    Continual compression for edema and venous disease.

    Avoid exposure to heat or other risky environments.

    Avoid obesity, smoking, and other high-risk behaviors.

Burns in the Elderly Population

There are several reasons why elderly patients are at increased risk for burn injuries. Many of these have been described earlier and make the geriatric population more prone to any form of injury. Many risky behaviors that were practiced when younger are carried into the later years of life. Many patients have voiced that they have done the same thing for years, but this time, they were not fast enough to escape. For instance, many people will use gasoline as an accelerant to burn leaves or trash. The patient may have avoided injury for years when performing this extremely dangerous practice; however, when he slowed down from aging, he could not avoid the flames. Slower reflexes clearly are predisposing factors for many of these injuries. In addition, any decline in decision making, especially with dementia, may cloud decision making and increase the risk for burns. Neuropathy is another factor that increases the risks for burns. As stated earlier, patients with diabetic neuropathy do not realize that they are burning their feet when walking barefoot on a hot surface [28]. In addition, it is common for their feet to "feel" cold, so many burns occur when warming them in hot water or with prolonged exposure to heaters. Forgetfulness will also increase the risk for kitchen fires as people forget to turn off stoves.

There are typical patterns of burn injury that accompany any age group. Toddlers typically explore their world with their hands and mouths. Therefore, they have many palm burns and are at risk for commissure burns when chewing on power cords. The elderly patient is at a high risk for the

massive flame burn when they use accelerants or fall asleep while smoking. With reduced ability to escape, their burns may become massive and lethal. A common burn pattern involves cooking over a flame. The typical pattern involves women with loose clothing leaning over a gas stove and catching their sleeve on fire. This burn pattern leads to third-degree burns to the chest, axilla, and arm. Another common elderly burn involves patient who smoke while using nasal oxygen. The oxygen ignites a brief flame that burns the central face. Fortunately, these burns are relatively small, and we try to avoid endotracheal intubation if at all possible. People with tremors or increased weakness are also at risk of spilling hot liquids such as tea or coffee that while being superficial can lead to prolonged healing. Finally, as elderly patients become more infirm and dependent on others for their care, there is an increase in burn-related abuse such as being "dipped" in hot water.

The approach to treating burns in the elderly has some important differences than when treating the younger population. As the skin ages, there is a greater risk for full-thickness burns – simply because the skin is thinner. Another issue is that as skin ages, there is a decrease in the skin adnexa – especially hair follicles. When there is a loss of these adnexa, even the most superficial burns will not re-epithelialize. While many people may claim that the burn "converted" to full thickness, in reality it never had a chance to heal due to the loss of skin adnexa. Both of these factors are important to remember when trying to get partial-thickness burns to heal. In addition, one must be more careful when planning skin grafting in the elderly since a split-thickness donor site would not heal if there were no hair follicles. Surgeons must select donor sites that have thicker skin such as the upper thighs or back. In addition, any vascular insufficiency or diabetes mellitus will reduce the ability of a skin graft to "take." There is one benefit of aging, however, since loose skin has greater laxity to tolerate contraction without forming contractures. Many patients with high risk for surgery will contract sizeable burns, literally over months, and still do fairly well in the end. Fortunately, most elderly patients can be treated with selective skin grafts, and the outcomes continue to improve in the elderly population.

One of the greatest concerns as one gets older is the reduced ability to tolerate the metabolic response to burns. It is well known that the older one is, the more difficult it is to tolerate major injuries. The burn community uses the LA50 to describe the ability to tolerate a burn. The LA50 provides the size of burn that leads to a 50 % survival for a specific age group. For instance, surgeons have stated that for a teenager, an 85 % total body surface area (TBSA) burn has a 50 % chance of survival. The LA50 drops as one ages so that an 80-year-old has 50 % mortality with only a 10 % TBSA burn. It is not fully known why the elderly population has such decreased tolerance to an injury, but there are some theories that make sense [88, 89]. Cells have a limited number of divisions that they can undergo before they are unable to replicate. With aging, the percentage of cells with the ability to replicate has to decrease. It has been shown that there is a cumulative damage and a decreased ability to repair DNA over time [90]. The epigenetic controls of DNA also wear out over time [91]. Therefore, there is an increase in mutations that lead to the risks for tumors and other age-related changes. It makes sense that the ability for tissues to completely repair themselves is also compromised. As one ages, especially in one who is exposed to austere conditions, there is an accumulation of injuries that lead to increased scarring. With increased scarring and fibrosis, there is impaired organ function, which also contributes to the inability to handle major stress. Another problem is that mitochondria lose the ability to repair themselves so that there is a gradual loss of energy supplies to the cells and tissues [92]. Several years ago, there was a paper that described cardiomyopathy as an "engine running out of fuel". Since the metabolic demands of burns are so great, patients with any nutritional or even metabolic compromise will have a decreased chance for survival.

A burn injury is the most profound form of stress that anyone can handle so even a younger patient is maximally stressed. Burns greater than 60 % TBSA may double the metabolic demand on a patient. I often tell patient's families that surviving a major burn is like running a marathon. The marathon, however, does not last a day but instead, several months. A younger patient can be pushed to provide the energy and endurance to survive. While an elderly person may start off fairly well, eventually the heart loses the ability to provide enough cardiac output, the liver no longer can produce the proteins, and the other organs fall behind. There is a gradual failure of organs that is known as multiple organ dysfunction syndrome. As the organs gradually fail, the patient seems to fail as a whole and eventually die. Maybe in the future, ways to improve the metabolic energy of the elderly will improve. Right now, however, geriatric patients have a much greater mortality than the younger population.

Prevention

It is clear that prevention is by far better than treating a wound in the elderly. It is interesting that teaching prevention is helpful but that despite understanding prevention principles, people often do not follow those principles. People often take shortcuts or risks that lead to injury. The most effective prevention means is through regulations and legislation. Many laws have saved thousands of lives. An example is the law that requires all buildings to have smoke detectors. Voluntary efforts were only moderately successful in reducing fire-related deaths, but with the introduction of regulations requiring smoke detector use, deaths from fires have

decreased markedly. The legislative efforts to reduce chronic wounds really do not exist. The intention of making pressure sores a "never event" that is reportable should at least make hospital personnel more aware of the risks of pressure sores. I am very doubtful that they will be eliminated.

Prevention efforts for the elderly should include close monitoring for the maintenance of adequate nutrition. Education and training about dangerous behaviors will help. Their living quarters should be made as safe as possible to reduce falls, the risk for burns and other injuries. As the elderly lose the ability to manage themselves, especially with dementia, caregivers should be provided to at least monitor their care. The elderly must be made aware that their reflexes may be slower so that they are less able to respond to a dangerous situation. I have treated many aged people who have placed logs onto fires "just as they had for years" but due to a slower response time they could not react in time to prevent their clothes from catching on fire. Simple matters such as avoiding loose clothing over flames may reduce injury. Lowering water heater temperatures to 120 °F will prevent many accidental scald burns. As stated earlier, those people with neuropathies should have their feet checked on a regular basis. Simple actions such as these may prevent many lifelong wounds.

Outcomes for Wounds in the Elderly

It is known that the metabolic reserve of a person decreases with increasing age. Fortunately, people are taking better care of themselves, and more people are living to the 80s, 90s, and even over 100 years old. One must not assume that all individuals are the same at the same age. We all know relatively young people who have not treated their bodies well and appear greater than their stated age. There are just as many elderly who have done very well with managing their fitness. We have treated older patients who have tolerated moderately sized burns who have done amazingly well. The elderly who have been able to avoid many of the risk factors for impaired healing (diabetes, peripheral vascular disease, malignancy) tend to tolerate significant injuries. It is clear that with sound principles of treating wounds, the elderly can heal their wounds.

Summary

- There are *intrinsic* changes to the skin as one ages. The skin becomes thinner, looser, and loses hair follicles. These alterations due to aging can be accelerated by *extrinsic* factors such as ultraviolet light.
- Diseases common to the elderly impair wound healing:
  - Malnutrition, even short term, impairs tissue repair.
  - Diabetes mellitus leads to altered vascularity, neuropathy, and impaired ability to fight infections, all of which impair healing.
  - Treatments of malignancy and steroids impair tissue repair.
  - Neurologic changes predispose the elderly to severe wounds.
- Problem wounds are a major burden to society:
  - Pressure ulcers
  - Arterial insufficiency ulcers
  - Venous stasis ulcers
- There are principles of improving healing that apply to all chronic wounds.
- Burns in the elderly:
  - The elderly are at high risk for burns.
  - There are specific burn patterns common to the elderly.
  - Healing of burns is more difficult.
  - The elderly are less capable of handling large burns compared to younger patients.
- Prevention of all wounds is essential for the geriatric population.
- Outcomes are improving for the elderly with wounds and burns.

References

1. U.S. Census Bureau, Statistical Abstract of the United States: 2012. http://www.census.gov/compendia/statab/2012/tables/12s0009.pdf. Accessed 28 June 2012.
2. Gosain A, DiPietro LA. Aging and wound healing. World J Surg. 2004;28:321–6.
3. Zouboulis CC, Makrantonaki E. Clinical aspects and molecular diagnostics of skin aging. Clin Dermatol. 2011;29:3–14.
4. Ramos-e-Silva M, Boza JC, Cestari TF. Effects of age (neonates and elderly) on skin barrier function. Clin Dermatol. 2012;30:274–6.
5. Wulf HC, Sandby-Moller J, Kobayasi T, Gniadecki R. Skin aging and natural photoprotection. Micron. 2004;35:185–91.
6. Birch MP, Messenger JF, Messenger AG. Hair density, hair diameter and the prevalence of female pattern hair loss. Br J Dermatol. 2001;144:297–304.
7. Sharma R. Skin age testing criteria: characterization of human skin structures by 500 MHz MRI multiple contrast and image processing. Phys Med Biol. 2010;55:3959–79.
8. Greenhalgh DG. Wound healing. Chapter 46. Herndon D, Total burn care. 3rd ed. Edinburgh: Saunders Elsevier, Inc.; 2007. 578–595.
9. Sussman MD. Aging of connective tissue: physiologic properties of healing wounds in young and old rats. Am J Physiol. 1973;224:1167–71.
10. Guergova S, Dufour A. Thermal sensitivity in the elderly: a review. Ageing Res Rev. 2011;10:80–92.
11. Howes EL, Briggs H, Shea R. Effect of complete and partial starvation on the rate of fibroplasia in the healing wound. Arch Surg. 1933;26:846–58.
12. Rhoads JE, Fliegelman MT, Panzer LM. The mechanism of delayed wound healing in the presence of hypoproteinemia. JAMA. 1942;118:21–5.
13. Daly JM, Vars HM, Dudvich SJ. Effects of protein depletion on strength of colonic anastomoses. Surg Gynecol Obstet. 1972;134:15–21.

14. Irvin TT. Effects of malnutrition and hyperalimentation on wound healing. Surg Gynecol Obstet. 1978;146:33–7.
15. Greenhalgh DG, Gamelli RL. Immunomodulators and wound healing. J Trauma. 1987;27:510–4.
16. Bartlett MK, Jones CM, Ryan AE. Vitamin C and wound healing. I. Experimental wounds in guinea pigs. N Engl J Med. 1942;226:469–73.
17. Ehrlich HP, Hunt TK. Effects of cortisone and vitamin A on wound healing. Ann Surg. 1968;167:324–8.
18. Levenson SM, Gruber CA, Rettura G, Gruber DK, Demetriou AA, Seifter E. Supplemental vitamin A prevents the acute radiation-induced defect in wound healing. Ann Surg. 1984;200:494–512.
19. Pories WJ. Acceleration of healing with zinc oxide. Ann Surg. 1967;165:432–6.
20. Pinnell SR, Martin GR. The cross linking of collagen and elastin. Proc Natl Acad Sci U S A. 1968;61:708–14.
21. Liusuwan RA, Palmieri T, Warden N, Greenhalgh DG. Impaired healing due to copper deficiency in a pediatric burn: a case report. J Trauma. 2006;51:464–6.
22. Seifter E, Rettura G, Barbul A, Levenson SM. Arginine: an essential amino acid for injured rats. Surgery. 1978;84:224–30.
23. McMurry Jr JF. Wound healing with diabetes mellitus. Surg Clin North Am. 1984;64:769–78.
24. Goodson III WH, Hunt TK. Wound healing and the diabetic patient. Surg Gynecol Obstet. 1979;149:600–8.
25. Greenhalgh DG. Wound healing and diabetes mellitus. Clin Plast Surg. 2003;30:37–45.
26. Margolis DJ, Kantor J, Berlin JA. Healing of diabetic neuropathic foot ulcers receiving standard treatment. A meta-analysis. Diabetes Care. 1999;22:692–5.
27. Yue DK, McLennan S, Marsh M, Mai YW, Spaliviero J, Delbridge L, et al. Effects of experimental diabetes, uremia, and malnutrition on wound healing. Diabetes. 1987;36:295–9.
28. Barsun A, Sen S, Palmieri TL, Greenhalgh DG. A ten year review of lower extremity burns in diabetics: small burns that lead to major problems. J Burn Care Res. 2013;34:255–60.
29. Mythili A, Kumar KD, Subrahmanyam KA, Venkateswarlu K, Butchi RG. A comparative study of examination scores and quantitative sensory testing in diagnosis of diabetic polyneuropathy. Int J Diabetes Dev Ctries. 2010;30:43–8.
30. Christman AL, Selvin E, Margolis DJ, Lazarus GS, Garza LA. Hemoglobin A1c predicts healing rate in diabetic wounds. J Invest Dermatol. 2011;131:2121–7.
31. Kamal K, Powell RJ, Sumpio BE. The pathobiology of diabetes mellitus: Implications for surgeons. J Am Coll Surg. 1996;183:271–89.
32. Medzhitov R. Origin and physiological roles of inflammation. Nature. 2008;454:428–35.
33. Steed DL, Attinger C, Colaizzi T, Crossland M, Franz M, Harkless L, et al. Guidelines for the treatment of diabetic ulcers. Wound Rep Reg. 2006;14:680–92.
34. Steed DL, Attinger C, Brem H, Colaizzi T, Crossland M, Franz M, et al. Guidelines for the prevention of diabetic ulcers. Wound Repair Regen. 2008;16:169–74.
35. Armstrong DG, Nguyen HC, Lavery LA, van Schie CH, Boulton AJ, Harkless LB. Off-loading the diabetic foot: a randomized clinical trial. Diabetes Care. 2001;24:1019–22.
36. Steed DL. Clinical evaluation of recombinant human platelet-derived growth factor for the treatment of lower extremity diabetic ulcers. The Diabetic Ulcer Study Group. J Vasc Surg. 1995;21:71–81.
37. Embil JM, Papp K, Sibbald G, Tousignant J, Smiell JM, Wong B, Lau CY. Recombinant human platelet-derived growth factor-BB (becaplermin) for helaing chronic lower extremity diabetic ulcers: an open-label clinical evaluation of efficacy. Wound Repair Regen. 2000;8:162–8.
38. Veves A, Falanga V, Armstrong DG, Sabolinski ML. Graftskin, a human skin equivalent, is effective in the management of noninfected neuropathic diabetic foot ulcers: a prospective, randomized multicenter clinical trial. Diabetes Care. 2001;24:290–5.
39. Bus SA, Waaijman R, Arts M, de Haart M, Busch-Westbroek T, van Baal J, Nollet F. Effect of custom-made footwear on foot ulcer recurrence in diabetes: a multicenter randomized controlled trial. Diabetes Care. 2013;36:4109–16.
40. Healy A, Naemi R, Chockalingam N. The effectiveness of footwear and other removable off-loading devices in the treatment of diabetic foot ulcers: a systematic review. Curr Diabetes Rev. 2014;10:215–30.
41. Dorresteijn JA, Kriegsman DM, Assendelft WJ, Valk GD. Patient education for preventing diabetic foot ulceration. Cochrane Database Syst Rev. 2012;10:CD001488.
42. Howes EL, Plotz CM, Blunt JW, Ragan C. Retardation of wound healing by cortisone. Surgery. 1950;28:177–81.
43. Sandberg N. Time relationship between administration of cortisone and wound healing in rats. Acta Chir Scand. 1964;127:446–55.
44. Ferguson MK. The effects of antineoplastic agents on wound healing. Surg Gynecol Obstet. 1982;154:421–9.
45. Falcone RE, Napp JF. Chemotherapy and wound healing. Surg Clin North Am. 1984;64:779–95.
46. Reinisch JF, Puckett CL. Management of radiation wounds. Surg Clin North Am. 1984;64:795–802.
47. Luce EA. The irradiated wound. Surg Clin North Am. 1984;64:821–9.
48. Laato M, Heino J, Kahari VM, Niinikoski J, Gerdin B. Epidermal growth factor (EGF) prevents methylprednisolone-induced inhibition of wound healing. J Surg Res. 1989;47:354–9.
49. Pierce GF, Mustoe TA, Lingelbach J, Masakowski VR, Gramates P, Deuel TF. Transforming growth factor β reverses the glucocorticoid-induced wound healing deficit in rats: Possible regulation in macrophages by platelet-derived growth factor. Proc Natl Acad Sci U S A. 1989;86:2229–33.
50. Beck LS, DeGuzman L, Lee WP, Xu Y, McFatridge LA, Amento EP. TGF-β1 accelerates wound healing: reversal of steroid-impaired healing in rats and rabbits. Growth Factors. 1991;5:295–300.
51. Lawrence WT, Sporn MB, Gorschboth C, Gorschboth C, Grotendorst GR. The reversal of an Adriamycin induced healing impairment with chemoattractants and growth factors. Ann Surg. 1986;203:142–7.
52. Mustoe TA, Purdy J, Gramates P, Deuel TF, Thomason A, Pierce GF. Reversal of impaired wound healing in irradiated rats by platelet-derived growth factor-BB. Am J Surg. 1989;158:345–50.
53. Bernstein EF, Harisiadis L, Saloman G, Norton J, Sollberg S, Uitto J, et al. Transforming growth factor beta improves healing of radiation-impaired wounds. J Invest Dermatol. 1991;97:430–4.
54. Tattini C, Manchio J, Zaporojan V, Carderelli G, Bonassar L, Spangenberger A, Weinzbweig J. The role of TGF-β and FGF in the treatment of radiation-induced wounds using a novel drug delivery system. Plast Reconstr Surg. 2008;122:1036–45.
55. Whitney J, Phillips L, Aslam R, Barbul A, Gottrup F, Gould L, et al. Guidelines for the treatment of pressure ulcers. Wound Repair Regen. 2006;14:663–79.
56. Stechmiller JK, Cowan L, Whitney J, Phillips L, Aslam R, Barbul A, et al. Guidelines for the prevention of pressure ulcers. Wound Repair Regen. 2008;16:151–68.
57. Hopf HW, Ueno C, Aslam R, Burnard K, Fife C, Grant L, et al. Guidelines for the treatment of arterial insufficiency ulcers. Wound Repair Regen. 2006;14:693–710.
58. Hopf HW, Ueno C, Aslam R, Dardik A, Fife C, Grant L, et al. Guidelines for the prevention of arterial insufficiency ulcers. Wound Repair Regen. 2008;16:175–88.
59. Robson MC, Cooper DM, Aslam R, Gould LJ, Harding KG, Margolis DJ, et al. Guidelines for the treatment of venous ulcers. Wound Repair Regen. 2006;14:649–62.

60. Robson MC, Cooper DM, Aslam R, Gould LJ, Harding KG, Margolis DJ, et al. Guidelines for the prevention of venous ulcers. Wound Repair Regen. 2008;16:147–50.
61. Lyder CH. Pressure ulcer prevention and management. JAMA. 2003;289:223–6.
62. Bluestein D, Javaheri A. Pressure ulcers: prevention, evaluation, and management. Am Fam Physician. 2008;78:1186–94.
63. Sibbald RG, Krasner DL, Woo KY. Pressure ulcer staging revisited: superficial skin changes & deep pressure ulcer framework. Adv Skin Wound Care. 2011;24:571–80.
64. Mimura M, Ohura T, Takahashi M, Kajiwara R, Ohura Jr N. Mechanism leading to the development of pressure ulcers based on shear force and pressures during a bed operation: influence of body types, body positions, and knee positions. Wound Repair Regen. 2009;17:789–96.
65. McInnes E, Dumville JC, Jammali-Blasi A, Bell-Syer SE. Support surfaces for treating pressure ulcers. Cochrane Databases Syst Rev (Online). 2011;12:CD009490.
66. Braden BJ, Bergstrom NA. Clinical utility of the Braden Scale for predicting pressure sore risk. Decubitus. 1989;2:44–51.
67. Mustoe TA, Cutler NR, Allman RM, Goode PS, Deuel TF, Prause JA, et al. A phase II study to evaluate recombinant platelet-derived growth factor-BB in the treatment of stage 3 and 4 pressure ulcers. Arch Surg. 1994;129:213–9.
68. Rees RS, Robson MC, Smiell JM, Perry BH. Becaplermin gel in the treatment of pressure ulcers: a phase II randomized double-blind, placebo-controlled study. Wound Repair Regen. 1999;7:141–7.
69. Tarry WC, Walsh DB, Birkmeyer NJO, Fillinger MF, Zwolak RM, Cronenwett JL. Fate of contralateral leg after infrainguinal bypass. J Vasc Surg. 1998;27:1039–48.
70. Gillespie DL. Venous ulcer diagnosis, treatment, and prevention of recurrences. J Vasc Surg. 2010;52:8S–14S.
71. Robertson LEC, Fowkes F. Epidemiology of chronic venous disease. Phlebology. 2008;23:103–11.
72. Ruckley CV. Socioeconomic impact of chronic venous insufficiency and leg ulcers. Angiology. 1997;48:67–9.
73. Van den Oever RHB, Debbaut B, Simon I. Socio-economic impact of chronic venous insufficiency: an underestimated public health problem. Int Angiol. 1998;17:161–7.
74. Liu YC, Margolis DJ, Isseroff RR. Does inflammation have a role in the pathogenesis of venous ulcers?: a critical review of the evidence. J Invest Dermatol. 2011;131:818–27.
75. Coleridge-Smith P, Labropoulos N, Partsch H, Myers K, Nicolaides A, Cavezzi A, et al. Duplex ultrasound investigation of the veins in chronic venous disease of the lower limbs: UIP consensus document: part I. Basic principles. Eur J Vasc Endovasc Surg. 2006; 31:83–92.
76. O'Meara S, Cullum N, Nelson EA, Dumville JC. Compression for venous leg ulcers. Cochrane Database Syst Rev. 2013;12:CD003557.
77. DaCosta RM, Ribeiro J, Aniceto MM. Randomized, double-blind, placebo-controlled, dose-ranging study of granulocyte-macrophage colony-stimulating factor in patients with chronic venous ulcers. Wound Repair Regen. 1999;7:17–25.
78. Falanga V, Eaglstein WH, Bucalo B, Katz MH, Harris B, Carson P. Topical use of human recombinant epidermal growth factor (h-EGF) in venous ulcers. J Dermatol Surg Oncol. 1992;18:604–6.
79. Robson MC, Phillips LG, Cooper DM, Odenheimer DJ, Parish LC, Jensen JL, Steed DL. The safety and effect of transforming growth factor-B2 for treatment of venous stasis ulcers. Wound Repair Regen. 1995;3:157–67.
80. Falanga V, Margolis D, Alvarez O, Auletta M, Maggiacomo F, Altman M. Rapid healing of venous ulcers and the lack of clinical rejection with an allogeneic cultured human skin equivalent. Human Skin Equivalent Investigators Group. Arch Dermatol. 1998;134:293–300.
81. Atillasoy E. The safety and efficacy of Graftskin (Apligraf) in the treatment of venous leg ulcers: a multicenter, randomized, controlled clinical trial. Wounds. 2000;12(Suppl A):20A–6A.
82. Jones JE, Nelson EA, Al-Hity A. Skin grafting for venous leg ulcers. Cochrane Database Syst Rev. 2013;1:CD001737.
83. Pierik EG, vanUrk H, Hop WC, Wittens CH. Endoscopic versus open subfascial division of incompetent perforating veins in the treatment of venous leg ulceration: a randomized trial. J Vasc Surg. 1997;26:1049–54.
84. Sybrandy JE, vanGent WB, Pierik EG, Wittens CH. Endoscopic versus open subfascial division of incompetent perforating veins in the treatment of venous leg ulceration: long-term follow-up. J Vasc Surg. 2001;33:1028–32.
85. Lawrence PF, Alktaifi A, Rigberg D, DeRubertis B, Gelabert H, Jimenez JC. Endovenous ablation of incompetent perforating veins is effective treatment for recalcitrant venous ulcers. J Vasc Surg. 2011;54:737–42.
86. Gloviczki P, Comerota AJ, Dalsing MC, Eklof BG, Gillespie DL, Gloviczki ML, et al. The care of patients with varicose veins and associated chronic venous diseases: clinical practice guidelines of the Society of Vascular Surgery and the American Venous Forum. J Vasc Surg. 2011;53:2S–48S.
87. Ma Y, Li J. Metabolic shifts during aging and pathology. Compr Physiol. 2015;5:667–86.
88. De Gaudio AR, Rinaldi S, Chelazzi C, Borracci T. Pathophysiology of sepsis in the elderly: clinical impact and therapeutic considerations. Curr Drug Targets. 2009;10:60–70.
89. Kammeyer A, Luiten RM. Oxidation events and skin aging. Ageing Res Rev. 2015;21:16–29.
90. Pluquet O, Pourtier A, Abbadie C. The unfolded protein response and cellular senescence. A review in the theme: cellular mechanisms of endoplasmic reticulum stress signaling in health and disease. Am J Physiol Cell Physiol. 2015;308:C415–25.
91. Zang QS, Wolf SE, Minei JP. Sepsis-induced cardiac mitochondrial damage and potential therapeutic interventions in the elderly. Aging Dis. 2014;5:137–49.
92. Neubauer S. The failing heart–an engine out of fuel. N Engl J Med. 2007;356:1140–51.