

NON-HEALING WOUNDS

Epidemiology/Pathophysiology

It is estimated that 1 to 2 percent of the population in developed countries will suffer from a chronic wound in their lifetime [1]. In the United States, it is reported that chronic wounds affect approximately 6.5 million patients. The incidence of chronic wounds is expected to increase as our population ages. The impact of chronic wounds on the health and quality of life of patients and their families should not be underestimated. Patients with chronic wounds may experience chronic pain, loss of function and mobility, increased social stress and isolation, depression and anxiety, prolonged hospitalization, increased financial burden, and increased morbidity and mortality. The financial burden imposed by chronic wounds on society is substantial. In the United States, more than \$25 billion is spent by the health care system on treating wound-related complications per year [1].

Chronic non-healing wounds are wounds that have failed to progress through a timely sequence of repair, or one that proceeds through the wound healing process without restoring anatomic and functional results [2]. Typically, there is a physiologic impairment that slows or prevents wound healing. Although there is no clear consensus in the duration of a wound that defines chronicity, a range of 4 weeks to 3 months has been used to define chronic wounds in the literature. The Wound Healing Society classifies chronic wounds into 4 major categories: pressure ulcers, diabetic foot ulcers, venous ulcers, and arterial insufficiency ulcers. Each of these types of wounds, and others, will be discussed in this module.

When wound healing is impaired, there is usually not a single factor, but rather multiple contributing factors at play. This is due to the fact that there are overlapping mechanisms in normal wound healing that prevent a single factor from disrupting the process. However, when the wound healing process is disrupted and wound healing is impaired, chronic non-healing wounds will develop. In general, non-healing wounds share similar characteristics: high level of proteases, elevated inflammatory markers, low growth factor activity, and reduced cellular proliferation [3]. There are several factors that affect wound healing and contribute to the pathogenesis of chronic wounds. Some the common factors are infection, ischemia, metabolic conditions, immunosuppression, and radiation. They are discussed below.

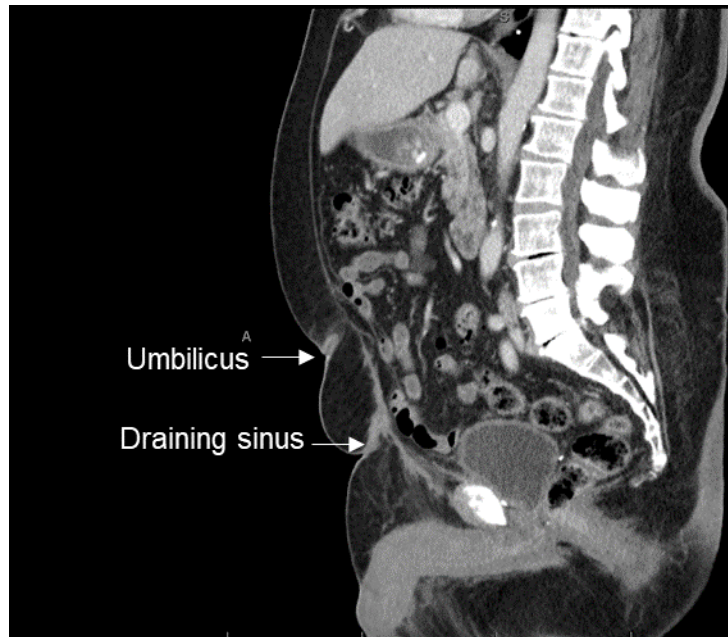
I. Infection

Wound infection can lead to the interruption of several processes along the wound healing pathway. Bacteria produce inflammatory mediators that inhibit the inflammatory phase as well as epithelialization phase of wound healing. Bacteria in an infected wound cause cell death, which will lead to an increase in local inflammation response and prolonged acute inflammatory phase. The presence of necrotic tissue prevents the ingrowth of new tissue. In addition, necrotic tissue also serves as a culture for bacterial proliferation, therefore, leading to a vicious pathologic cycle.

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Sometimes a foreign body is present in the wound that can serve as an ongoing nidus for infection. This often presents as a draining sinus (**Figure 1**). Some common examples are stitch abscess from nonabsorbable sutures, infected surgical mesh, and retained bullet. In order for the wounds to heal, the foreign bodies have to be removed.

Figure 1: CT scan demonstrates a draining sinus after prostatectomy that persisted for 2 years. The sinus was explored surgically with removal of a retained non-absorbable suture, resulting in resolution of draining sinus.



II. Ischemic conditions

Ischemia is a condition that results in chronic non-healing wounds and can be seen in arterial insufficiency, venous hypertension, and pressure injuries. These ischemic conditions are discussed below.

Ischemic condition due to arterial insufficiency: In patients with arterial insufficiency, arterial blood flow to the tissue is diminished, leading to a decrease in the delivery of oxygen and nutrients to the wound, and impairment in the removal of metabolic waste products from the wound. Limb threatening ischemia develops when blood flow to the extremity is insufficient to meet the metabolic demands of the tissue, manifesting as rest pain or non-healing wounds. Due to the chronic deficiency of oxygen and nutrients, the skin of the affected limb is not able to maintain normal tissue architectures. Clinically, this is manifested as shiny skin surface with paucity of hair. The metabolic demands to maintain intact skin is higher than the metabolic demands to heal a wound. A simple cut or abrasion on the skin caused by poor fitting shoes can alter the balance of metabolic demand, leading to a chronic wound. The most common cause of arterial insufficiency ulcers is obstruction of large and medium-size arteries caused by

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atherosclerosis. Other conditions that affect small arteries such as vasculitis, thromboangiitis obliterans, and scleroderma can also cause ischemic ulcers, but are less common.

Ischemic condition due to venous hypertension: In patients with chronic deep vein thrombosis, arteriovenous fistula or venous insufficiency, hydrostatic pressure is built up in the venous system leading to venous hypertension. This results in the loss of pressure gradient between the arterioles and the venules, leading to slowing of the movement of blood within the capillaries. This sluggish movement of blood results in sequestration of erythrocytes and leukocytes within the capillaries, and the elevation of hydrostatic pressure within the capillaries results in capillary leak. The fibrinogen leaked from the capillaries of the dermis form a fibrin cuff. This fibrin cuff, in combination with tissue edema, result in decreased oxygen permeability, leading to tissue hypoxia and impaired wound healing. The leukocytes that are trapped in the capillaries adhere to the endothelium and release inflammatory mediators and reactive oxygen metabolites. These, in turn, cause endothelial damage, obliteration of the capillaries, and subsequent tissue ischemia. Capillaries of patients with venous stasis are also occluded by microthrombi that, in turn, reduce oxygen and nutrition to the tissue, predisposing to ulcer formation [4].

Ischemic condition due to pressure injuries: The development of pressure injuries is caused by a combination of pressure and shear force. Pressure is defined as force per unit area. Therefore, smaller areas such those over bony prominences sustain higher pressure and are at higher risk for development of pressure injuries. When the pressure applied to the skin is in excess of arteriolar pressure, oxygen and nutrient delivery to the tissue is shut off, resulting in tissue hypoxia and accumulation of waste products and free radicals [5, 6]. In animal models, pressure in excess of 70 mm of Hg for two hours result in irreversible tissue damage [5]. For comparison, an average patient lying on a standard mattress can produce a pressure of 150 mm of Hg, while sitting can generate a pressure of 300 mm of Hg over the ischial tuberosities [7]. Although critical duration of ischemia can vary among individuals and clinical situations, as a rule of thumb, pressure injuries can develop within 1 to 4 hours of sustained pressure load [8].

Beside the externally applied pressure, the individual tolerance of tissue to ischemia also plays an important role. Evidence suggests that patients with peripheral arterial occlusive disease are at higher risk for developing pressure ulcers. Critically-ill patients with higher disease severity scores such as Acute Physiology and Chronic Health Evaluation (APACHE) score, are more likely to develop pressure ulcers [9]. This is probably due to global hypoperfusion of tissue in critically-ill patients, predisposing them to ischemic pressure injuries.

Tissues also vary in their susceptibility to pressure injuries. For soft tissue, muscle is the most susceptible, followed by subcutaneous fat, and then dermis. For this reason, extensive tissue damage can occur with little evidence of superficial injury. This makes clinical evaluation of pressure injury challenging.

Shear force occurs when there is lateral displacement of the tissue, usually by gravity or patients being dragged across an external surface. In these situations, deeper tissues such as bone, muscles, and subcutaneous fat are shifted laterally while the dermis remain fixed through

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contact with external surfaces. The result of this lateral displacement is injury to the tissue, blood vessels, and lymphatics.

Excessive moisture in the form of perspiration, urine, and feces can lead to maceration of the superficial tissue and changes in the cutaneous chemical environment. Although excessive moisture by itself does not directly cause pressure injuries, it can lead to impaired wound healing and promote the generation of chronic wounds.

III. Metabolic conditions

There are several metabolic conditions that contribute to the development of non-healing wounds. These are discussed below.

Diabetes mellitus: There are several factors related to diabetes that contribute to the pathogenesis of diabetic foot ulcers. In diabetic neuropathy, damage to the sensory, motor, and autonomic nerve fibers affects peripheral sensation, motor innervation of small muscles in the foot, and fine vasomotor control of the pedal circulation [3, 10]. In sensory neuropathy, the loss of protective sensation leads to lack of awareness of sustained pressure on the tissue or injury to the tissue. Motor neuropathy usually affects the innervation of the small intrinsic muscles of the feet, resulting in the unopposed action of the larger muscles in the anterior tibial compartment. This leads to subluxation of the proximal metatarsal-phalangeal joints, giving the feet the appearance of claw toes. Consequently, the pressure is redistributed abnormally to the metatarsal heads, where reactive thickening of the skin (callus) forms. Ischemic necrosis of the tissue under the callused skin eventually leads to breakdown of the skin, resulting in a neuropathic ulcer with the punched-out appearance commonly under the metatarsal heads.

Autonomic neuropathy is characterized by a lack of autonomic tone in the arteriolar and capillary circulation, causing shunting of blood from the arterioles directly to the veins, thus bypassing the tissue that needs the nutrients. Although the feet may have bounding pulses and distended veins, the tissue may lack the perfusion needed for healing and to fight infection. Additionally, the loss of autonomic innervation to the sweat glands of the feet results in dry, scaly skin that can crack easily, allowing bacteria to penetrate.

The Charcot foot is a later complication of diabetes and is characterized by collapse of the arch of the midfoot (**Figure 2**). Osteopenia due to arteriolar-venous shunting of autonomic neuropathy combined with small intrinsic muscle wasting, lead to loss of structural integrity of the bone [10]. Stress and minor trauma induces fracture of a weakened bone, putting more stress on the adjacent weakened bones, and the cycle repeats, ultimately leading to gross deformity. The resulting abnormal bony prominences that form greatly increase the risk of ulceration.

Figure 2: (A) The illustrations demonstrate normal plantar arch and Charcot foot deformity.

(A)

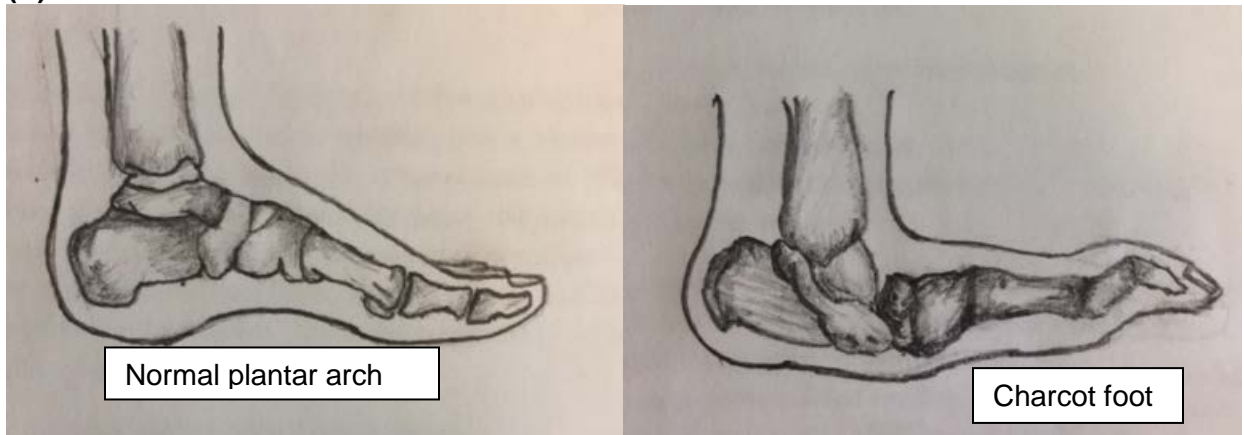


Figure 2: (B) The radiograph shows diffuse osteopenia, fusion of midfoot, and loss of plantar arch, consistent with neuropathic deformity of the foot.

(B)



Diabetes increases the risk of atherosclerotic disease. In the lower extremities, diabetes tends to affect the vessels in the calf, while sparing more proximal vessels. Diabetes also affects the microvascular beds by altering the structure of the basement membrane, the integrity of the capillary wall, the regulatory function of the endothelium, and the propensity for microvascular

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thrombosis [10]. Micro and macrovascular disease in diabetes result in tissue ischemia and impaired wound healing.

Malnutrition: Fatty acids are essential for the inflammatory phase of wound healing as they provide the arachidonic acid substrate for eicosanoid synthesis. Proteins are required for the proliferation of fibroblasts and the synthesis and deposition of collagen. Proteins are also required for important immunologic functions such as phagocytic activity of macrophages, T-cell function, and complement and antibody production [11]. Malnutrition can impair wound healing by prolonging the inflammatory phase and by reducing the proliferation of fibroblasts and deposition of collagen. Malnutrition is associated with increased risk of wound infection, which has deleterious effects on wound healing.

IV. Immunosuppression

Systemic immunosuppression can contribute to the development of non-healing wounds. Corticosteroids have been shown to interfere with all major steps of the wound healing process in both animals and human studies [12]. In the inflammatory phase, corticosteroid decreases the expression of cytokines that are responsible for the recruitment of inflammatory cells, as well as the expression of adhesion molecules responsible for adhesion and migration of granulocytes. In the proliferative phase, corticosteroids reduce the levels of transforming growth factor- β and keratinocyte growth factor, which attenuates fibroblast proliferation and wound epithelization respectively. In the remodeling phase, corticosteroids impair collagen accumulation as well as collagen turnover. Clinically, patients who are on chronic corticosteroids that undergo surgery have significantly increased infection rate as well as wound dehiscence rate.

Immunosuppressive agents can suppress the expression of several inflammatory mediators that are involved in the wound healing process. Immunosuppressive agents inhibit the proliferation of immune cells and may blunt the inflammatory phase of wound healing. Sirolimus, a immunosuppressive agent that inhibits the threonine kinase known as mammalian target of rapamycin (mTOR), is associated with a significantly higher wound complication rate compared to other common immunosuppressive agents [13].

Chemotherapeutic agents, particularly those that target vascular endothelial growth factor (VEGF) and epidermal growth factor receptor (EGFR), can have detrimental effects on wound healing. Inhibition of VEGF results in the suppression of angiogenesis, which is an important part of wound healing [14]. Epidermal growth factor receptor inhibitors can negatively impact wound healing by inhibiting epithelialization [15].

V. Radiation

Ionized radiation used in the treatment of cancer can cause delay in wound healing. Sometimes, radiation injury results in chronic non-healing wounds. Ionizing radiation causes

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cellular damage by breaking the double-stranded cellular DNA and releasing free radicals. This effect is most profound in cells undergoing DNA replication and mitosis [16]. The resulting effect is apoptosis and cellular necrosis. Radiation also causes eccentric myointimal proliferation in the small arteries and arterioles, which may cause luminal thrombosis and obstruction [17]. This results in ischemia to the tissue which may progress to tissue necrosis.

Signs and Symptoms

I. History

When evaluating a patient with non-healing wounds, a detailed history about the wound should be obtained. This information will help determine the causative factors and to help guide preventive and treatment strategies. See Table 1.

| Table 1: Wound history |
|---|
| Timing and onset |
| Perceived causal factors |
| Qualitative changes such as size and drainage |
| Current wound care regimen |
| Previous treatments |
| Severity of the pain |
| Prior wounds if any (location, characteristic, previous treatments) |

Medical history of conditions that may affect wound healing should be investigated. These include history of diabetes, peripheral arterial disease, venous insufficiency, conditions that affect mobility (such as stroke, neurological conditions, and recent trauma), recent weight loss, smoking, radiation, immunosuppressive therapy and cancer. Chronic wounds impose a significant social burden on the patients and their family, and their successful treatment requires strong family and social support. Therefore, a good history on the patient's employment and how wound care will affect their daily life should be determined. Previous surgical history, especially those related to treatment of the wounds, such as wound debridement, skin grafting, arterial revascularization, and vein ablation procedures should be detailed.

II. Physical examination

While a complete physical examination should be obtained, there are several components of the examination that warrant more detailed discussion. These include wound assessment, vascular assessment, and neurological assessment.

Wound assessment: The location, number of wounds, and characteristics of each wound should be illustrated by pictures and a diagram, and described in detail. Wound dimensions and calculated volume of the wounds should be recorded with each visit to assess healing potential

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over time. Photography should be used as it decreases interobserver variability and allows for accurate and consistent assessment of changes over time.

Virtually all wounds are colonized with bacteria and the presence of bacteria in the wound does not equal wound infection. Wound infection is a clinical diagnosis and not a microbiological one. The presence of infection can adversely affect wound healing. Therefore, it is of vital importance to assess the wound for signs of infection. Wound culture in itself is not helpful in the diagnosis of wound infection, but it could be useful in determining antibiotic coverage once the clinical diagnosis of wound infection has been made. Table 2 lists clinical signs that are suggestive of wound infection.

| Table 2: Clinical signs of wound infection |
|--|
| Increased blanching erythema in area surrounding the wound |
| Induration surround the wound |
| Lymphangitis – red streaking proximally |
| Wound drainage – especially thick, purulent, foul drainage |
| Foul odor |
| Increased tenderness |
| Increased warmth |
| Fever |

Vascular assessment: In patients with chronic extremity wounds, careful and accurate assessment of the vascular system is essential. In patients with peripheral arterial disease, diminished blood flow to the extremities leads to thinning of the skin and functional loss of skin appendages. The skin of the lower extremity appears thin, dry, shiny and hairless. The nail bed may also become brittle, hypertrophic and ridged. As the blood flow rate to the skin is diminished, the skin will feel cool to the touch. The demarcation of temperature differences can give a rough determination of the level of arterial occlusion.

Leg elevation test (Buerger's test) involves elevation of a leg with the patient in a supine position, and after the veins have completely drained, the leg is then placed in a dependent position. Elevation of the leg approximately 25 cm above the table will generate enough pressure to exceed the central venous pressure, allowing venous blood in the leg to drain centrally. The extremity is expected to remain pink and perfused in normal individuals. However, in patients with arterial insufficiency, the limb will become pale and ischemic. In fact, these patients may complain of ischemic pain with leg elevation. When the leg is subsequently placed in a dependent position, the veins should become dilated again within 20 seconds in normal individuals. If duration exceeds 20 seconds, arterial insufficiency may be present.

The presence or absence, as well as the quality of the peripheral pulses, need to be examined and documented carefully. Changes in pulse examination along the extremity may give an estimation of the level of occlusion of the conducting vessels. Ankle-brachial index (ABI) is a simple test that can be performed at bedside. The ABI is the ratio of systolic blood pressure measured at the ankle over the systolic blood pressure measured at the arm, using a Doppler

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probe. An ABI of <0.9 is suggestive of peripheral arterial disease. In patients with non-compressible vessels, such as patients with diabetes or advanced age, toe pressure and toe brachial index is used instead. This is usually done in the vascular lab and not at bedside. In patients with clinical findings that are suspicious for peripheral arterial disease, additional arterial studies may be indicated. These additional studies may be physiological tests such as segmental pressure measurement and pulse volume recording measurement, or vascular imaging such as arterial duplex ultrasonography, computed tomography angiography, and digital subtraction angiography.

Neurological assessment: Vibration sensation test, pressure sensation test, and superficial pain sensation test are simple examination methods validated for the screening of peripheral neuropathy. Vibration sensation test is a semiquantitative test conducted using a standard 128-Hz tuning fork. During this examination, the fork is applied to the dorsal bony prominence of the great toe and the patient is asked to report the perception of both the start of vibration and the cessation of vibration on dampening. If a patient reports both the start of vibration as well as cessation of vibration, he/she is thought to have normal vibration sensation. Pressure sensation test is performed using 10-g monofilament applied to the dorsum of the first toe. The superficial pain sensation test or simple pinprick test is conducted using a pin applied to the skin of the dorsum of the toes. The lack of sensation with these maneuvers suggests presence of neuropathy.

Clinical features of pressure ulcers: Pressure ulcers are more prevalent in hospitalized patients and patients living in nursing homes. These patients often have neurological conditions such as stroke or paralysis that prevent them from feeling the pressure and/or moving to off-load the pressure. Severely ill patients who are bedridden are also at risk. Pressure ulcers usually develop in skin and soft tissue overlying bony prominences. Some common areas are sacrum, ischial tuberosities, calcaneum, medial and lateral metatarsal heads, and fibula head. Pressure injury can present as intact skin or as an open ulcer. It is important to differentiate pressure ulcers from moisture induced skin macerations overlying bony prominences, skin tears, tape burns, perineal dermal infection or excoriation, as these later conditions are more acute and are self-limiting. There are several systems available for staging of pressure ulcers. The most commonly used staging system in the United States is the National Pressure Ulcer Advisory Panel (NPUAP) classification system. The stages of pressure ulcers are described below (**Figure 3** on next page).

Stage 1: Non-blanchable erythema of intact skin. These color changes do not include purple or maroon discoloration; these may indicate deep tissue pressure injury.

Stage 2: Partial-thickness skin loss with exposed dermis. The wound bed is viable, pink or red, moist, and may also present as an intact or ruptured serum-filled blister. Fat is not visible and deeper tissues are not visible. Granulation tissue, slough and eschar are not present. These injuries commonly result from adverse microclimate and shear in the skin over the pelvis and shear in the heel.

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Stage 3: Full-thickness skin loss. Full-thickness loss of skin, in which fat is visible in the ulcer. Fascia, muscle, tendon, ligament, cartilage and/or bone are not exposed. If slough or eschar obscures the extent of tissue loss, this is an Unstageable Pressure Injury.

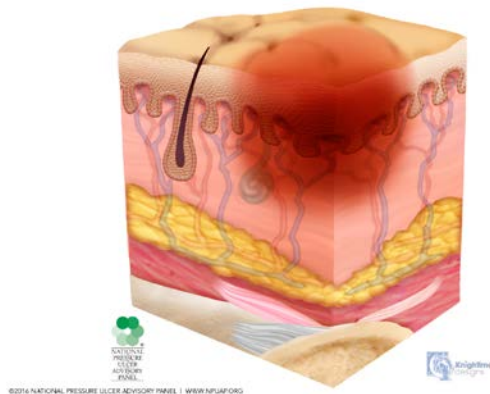
Stage 4: Full-thickness skin and tissue loss. Full-thickness skin and tissue loss with exposed or directly palpable fascia, muscle, tendon, ligament, cartilage or bone in the ulcer. If slough or eschar obscures the extent of tissue loss, this is an Unstageable Pressure Injury.

Unstageable Pressure Injury: Obscured full-thickness skin and tissue loss. Full-thickness skin and tissue loss in which the extent of tissue damage within the ulcer cannot be confirmed because it is obscured by slough or eschar. If slough or eschar is removed, a Stage 3 or Stage 4 pressure injury will be revealed. Stable non infected eschar on the heel or ischemic limb should not be softened or removed.

Deep Tissue Pressure Injury: Persistent non-blanchable deep red, maroon or purple discoloration. Intact or non-intact skin with localized area of persistent non-blanchable deep red, maroon, purple discoloration or epidermal separation revealing a dark wound bed or blood-filled blister. This injury results from intense and/or prolonged pressure and shear forces at the bone-muscle interface. The wound may evolve rapidly to reveal the actual extent of tissue injury, or may resolve without tissue loss.

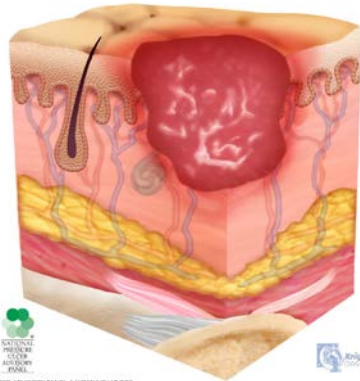
Figure 3: Staging of pressure ulcers by the National Pressure Ulcer Advisory Panel. Both the NPUAP staging system and illustrations are used with the permission of the National Pressure Ulcer Advisory Panel. (Photographs of different stages: courtesy of Pirko Maguina, MD, FACS, University of California, Davis)

Stage 1 Pressure Injury - Lightly Pigmented

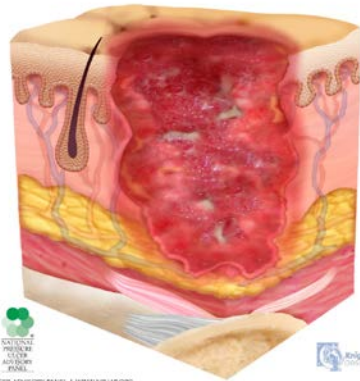


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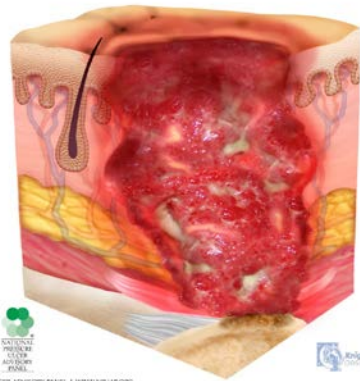
Stage 2 Pressure Injury



Stage 3 Pressure Injury

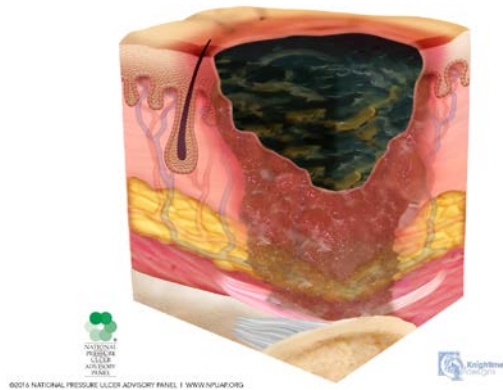


Stage 4 Pressure Injury

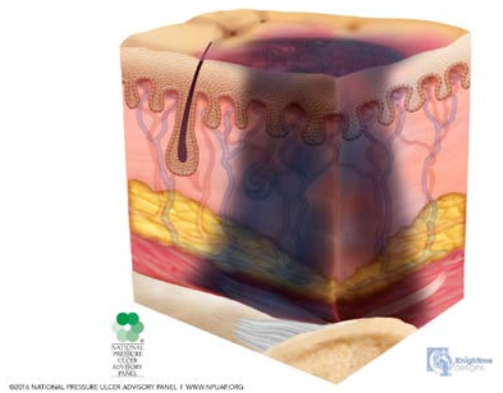


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Unstageable Pressure Injury - Dark Eschar



Deep Tissue Pressure Injury



Clinical features of diabetic foot ulcers: Chronic ulceration in diabetic patients can result from neuropathy alone or from a combination of neuropathy and ischemia. They commonly occur in locations that experience repeated trauma, such as the plantar metatarsal heads and dorsal interphalangeal joints (**Figure 4** on next page). About half of all diabetic foot ulcers occur on the plantar surface and are mainly caused by elevated pressure during ambulation. Hyperkeratotic callous formation in the area of the ulcer with associated undermining of the borders may be present (punch out appearance). The loss of vibration, pressure or pain sensations are indicative of peripheral neuropathy and further support the etiology of diabetic foot ulceration.

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Figure 4: Diabetic foot ulcer at first metatarsal head of the foot. There is a callus surrounding the ulcer. There is also loss of plantar arch and claw toes deformity noted.



When evaluating diabetic foot ulcers, it is important to determine the extent and depth of the wound, the presence of ischemia, and/or presence of infection, all of which will help determine the nature and intensity of diagnostic studies and treatment. Approximately half of the patients with diabetic foot ulcers have some element of ischemia associated with the ulcers. These patients should be evaluated for peripheral vascular disease and treatment plan may include revascularization. Approximately 60% of diabetic foot ulcers are complicated by infection, and the presence of infection is a strong predictor of major amputations [18]. Therefore, it is critical to identify infections early so that appropriate treatment is rendered to mitigate the risk of amputation. Signs of wound infection can be found in Table 2 on page 8.

Osteomyelitis is a common complication of patients with diabetic foot infection. It is present in approximately 15% of moderate diabetic foot infections and in 50% of severe infections [19]. Although osteomyelitis is suspected in the setting of acute diabetic foot infection, it can be present even in ulcers that do not have any outward sign of inflammation. Thus, clinicians should have a high index of suspicion when making the diagnosis osteomyelitis. There are certain clinical findings that help raise suspicion for the presence of osteomyelitis. These include grossly visible bone or probe to bone, larger ulcers ($> 2\text{cm}^2$), and deeper ulcers ($> 3\text{mm}$) [20]. Elevated erythrocyte sedimentation rate (70 mm/h) is also associated with presence of osteomyelitis [21]. These patients will require additional imaging studies or bone biopsy to help make the diagnosis of osteomyelitis.

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Clinical features of venous ulcers: Venous ulcers are typically located between the knee and the ankle, with the medial and lateral malleolus being the most common sites (**Figure 5**). The patients generally describe a dull ache and swelling that improve with elevation. A history of recurrence of an ulcer in the same area is highly suggestive of venous ulcers. Venous ulcers are generally shallow and irregular with a wound bed lined with beefy red granulation tissue. Sometimes, a layer of superficial fibrinous gelatinous layer is present, covering over a granulated wound bed underneath. The skin surrounding the ulcer is eczematous, presenting with scaling, weeping and crusting and is intensely pruritic. The leg is usually edematous, firm and warm with reddish-brown hyperpigmentation from hemosiderin deposits. Dilated tortuous superficial veins are usually visible on the surface.

Figure 5: Venous ulcers with granulated wound bed and surrounding dry, scaly, eczematous, and hyperpigmented skin.



Clinical features of arterial insufficiency ulcers: Patients with arterial insufficiency ulcers often present with other signs and symptoms of arterial insufficiency. They may have symptoms of claudication and/or rest pain depending on the severity. Rest pain of the foot may be aggravated by elevation and relieved by dangling in dependent position. The locations of the ulcers are typically in the most distal part of the toes where there is the least blood flow, or in areas where there is potential for pressure such as areas between the toes and over phalangeal heads. Sites that are subjected to repetitive trauma such as contact points with footwear are also affected. The ulcers usually have sharply demarcated punched out margins and are

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associated with minimal exudate. Due to the insufficient blood flow, the wound bed of the ulcers is usually pale, gray or yellow with very little evidence of granulation tissue growth. Chronic ischemia also makes the skin of foot appear thin, dry, shiny, and hairless, and the nail beds appear brittle, hypertrophic, and ridged. Tissue loss in patients with arterial insufficiency can present with chronic non-healing ulcers or with gangrene. Although not absolute, the ankle-brachial index of patients presented with tissue loss is generally very low (<0.4).

Other types of chronic ulcerations: There are other cutaneous ulcerations that occur in the setting of systemic autoimmune and chronic inflammatory diseases. These skin ulcerations can be excessively painful and may not respond to routine wound care treatment. Some of these conditions include pyoderma gangrenosum, IgA monoclonal gammopathies, Wegener's granulomatosis, and cutaneous chronic granulomatous disease. These are difficult to treat and are often colonized with resistance bacteria. Wound biopsy for histology will be helpful with the diagnosis. Appropriate medical treatment of the underlying condition must be addressed prior to any consideration of surgical debridement.

Relevant Diagnostic Studies

I. Laboratory tests

Serum marker of inflammation such as white blood cell count (CRP), C-reactive protein, erythrocyte sedimentary rate (ESR) and procalcitonin (PCT) may be elevated in patients with active infection. In patients with diabetic foot osteomyelitis, WBC and PCT may be normal, but ESR and C-reactive protein may be elevated [20]. Elevated ESR together with evidence of ulcer connection to bone in diabetic patients should prompt additional imaging to evaluate for osteomyelitis.

Diabetic control is a very important part of treating patients with diabetic foot ulcers. In these patients, hemoglobin A1C (HbA1C) should be used as a marker for sustained diabetic control. Renal function tests should also be measured, as the presence of renal failure in patients with diabetes is associated with increased risk of diabetic foot ulcers or lower extremity amputations. Patients with large wounds are often malnourished and are in persisted catabolic state. Nutritional assessment labs including prealbumin, albumin, and total lymphocyte counts should be considered.

II. Imaging studies for patients with suspicion for osteomyelitis

Plain radiographic evaluation of the extremity is indicated when osteomyelitis is suspected. Signs of osteomyelitis on plain radiographs are periosteal thickening, lytic lesions, endosteal scalloping, osteopenia, and loss of trabecular architecture [22] (**Figure 6** on next page). In general, osteomyelitis must extend at least 1 cm or compromise 30 to 50% of the bone mineral content to produce noticeable changes on conventional radiographs. This is about 2 to 3 weeks into the course of the infection [23]. These findings are specific for osteomyelitis, but the sensitivity is low, especially in the earlier stages. Computed tomography [19] shows changes

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earlier than conventional radiographs. However, the radiation exposure is higher with CT and it is not as sensitive as magnetic resonance imaging (MRI). Magnetic resonance imaging is not only highly sensitive for detecting osteomyelitis, it also helps determine the extent of disease involvement. When used with gadolinium, sensitivity and specificity for osteomyelitis are 90% and 85% respectively [23]. Other imaging studies such as white blood cell labeled radionuclide scan, hybrid 99mTc white blood cell labeled single-photon emission computed tomography/computed tomography (99mTc SPECT/CT), and hybrid positron emission tomography/computed tomography (PET/CT) have also been used for the diagnosis of osteomyelitis, especially when MRI is contraindicated [20].

Figure 6: Radiograph demonstrates patient with bony destruction (osteopenia and bone loss) of the distal phalanges of the first and second digits, consistent with advanced osteomyelitis. Also present are soft tissue defects at the tip of the toes at the areas of chronic ulcerations. A previous 4th toe amputation is also evidenced on the radiograph.



III. Arterial studies for patients with suspicion for arterial insufficiency

In patients with clinical findings that are suspicious for peripheral arterial disease, additional arterial studies may be indicated. In the segmental pressure study, systolic blood pressures are measured at the proximal thigh, distal thigh, below the knee, and ankle using a Doppler. A drop in systolic blood pressure from one location to the next indicates stenosis/occlusion at the intervening segment. Pulse volume recording study detects volume changes sequentially down the extremity. Similar to segmental pressure measurement, cuffs are placed in several strategic locations. Tissue volume changes beneath the cuffs cause small pressure changes within the cuffs, and these changes can be displayed as arterial waveforms. A normal pulse volume waveform is characterized by sharp systolic upstroke, peak and prominent dicrotic notch. A loss of dicrotic notch or rounded waveform suggests diminished flow due to upstream occlusion. Both

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segmental pressure measurements and pulse volume recordings are noninvasive physiologic studies and are typically performed in the vascular laboratory.

A noninvasive vascular imaging study is the arterial duplex scan. This study uses ultrasonography to visualize the arteries, and uses Doppler effect to detect relative blood flow velocities within the arteries. Areas of arterial stenosis can be visualized on B-mode ultrasound imaging and can be demonstrated by Doppler as increased flow velocities. Computed tomography angiography requires intravenous contrast timed specifically for arterial enhancement. It can provide three-dimensional imaging of the arterial system and is particularly useful for operative planning. Digital subtraction angiography is an invasive imaging study that is performed under fluoroscopy. This study requires arterial access and catheterization for contrast injection. It provides real-time imaging of the arterial systems in question. It also allows the possibility of endovascular intervention.

IV. Cultures and biopsy

For wounds that are infected, wound or tissue cultures should be obtained to help direct antimicrobial therapy. Routine culture in non-infected wounds is discouraged as it does not help make the diagnosis or guide therapy. If the etiology of the wound is not known, or if a wound fails to heal after three months despite adequate treatment, tissue biopsy should be obtained for histological diagnosis and to rule out cancer.

Non-operative Management

The most important aspect of treating patients with non-healing wounds is to address the underlying processes that contribute to the chronicity of the wounds. If the causal factors are not alleviated, wounds will have little chance of healing. In this section, we will discuss the general treatment strategies for each of the common types of chronic wounds (pressure ulcers, diabetic foot ulcers, venous ulcers, and arterial insufficiency ulcers). We will also discuss some basic principles of wound management, including wound debridement, wound dressings, nutritional supports, glycemic control, and adjuvant therapies.

I. General treatment strategy for pressure ulcers

The underlying contributing factors for pressure ulcers must be reduced by providing pressure redistribution and specialized support surfaces. A repositioning schedule to avoid pressure on the wound should be established. Typically, the patients should be repositioned every two hours. Supporting surfaces such as foam mattresses, overlays or air-fluidized bed should be used depending on available resources. The patient's underlying medical conditions that may contribute to the delay in wound healing should be addressed. Patients should undergo intense physical therapy to help alleviate their immobility status. Systemic infections should be treated and nutritional status optimized. For stage 1 and stage 2 ulcers, treatment should focus on prevention and local wound protection. For stages 3 and 4, treatment usually consists of local

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wound debridement followed by meticulous local wound care. While most patients can be managed successfully without surgery, some patients will require delayed closure, skin grafts and/or flaps for coverage. Fecal or urinary diversion procedures are rarely required and may be associated with higher surgical risks as these patients are already debilitated and malnourished. Appropriate psychosocial support should also be provided to patients and their families.

II. General treatment strategy for diabetic foot ulcers

Factors contributing to chronicity of diabetic foot ulcers, such as infection, neuropathy, ischemia, and bony foot deformities should be systematically addressed. Infected wounds should be treated with sharp surgical debridement together with systemic antibiotics. Patients with signs of arterial insufficiency should undergo noninvasive vascular evaluation and/or angiography, and if indicated, revascularization procedures. Mechanical off-loading with total contact cast or cast walkers should be considered to reduce pressure on the ulcers. In patients with foot deformities, referral to foot and ankle specialist is appropriate as surgical corrections may be required. The recurrence rate for diabetic foot ulcers is extremely high. Therefore, close follow-up and recurrence prevention strategies should be employed. Preventive strategies, such as protective footwear, good foot care, and daily foot inspection have been shown to reduce recurrence in patients with diabetic foot ulcers [24, 25].

III. General treatment strategy for venous ulcers

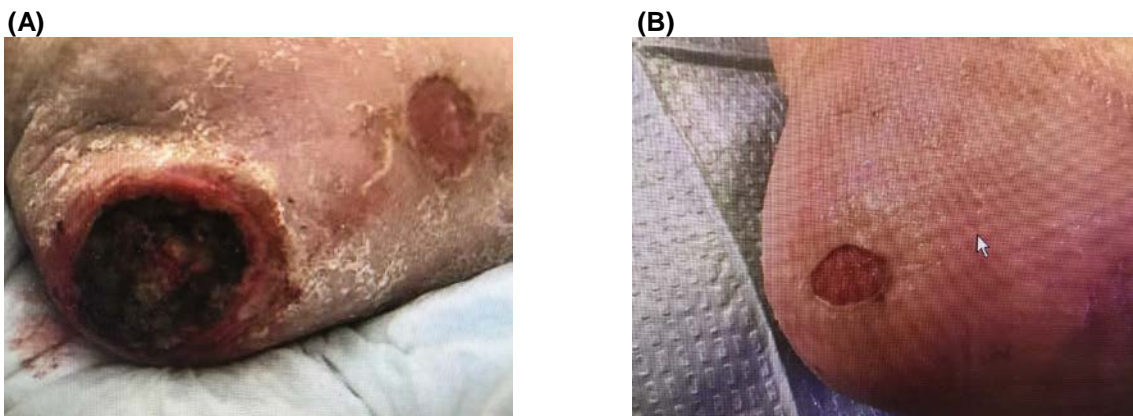
The primary objective in the treatment of venous ulcers is enhancing venous blood flow. This can be achieved mechanically and pharmacologically. Leg elevation above the heart can improve cutaneous microcirculation, reduce edema, and promote wound healing [26]. Plantar flexion exercise has been shown to improve venous circulation, but its impact on ulcer healing is not known. Nevertheless, this exercise should be recommended to the patients. Static compression therapy with hosiery or bandages is essential in the treatment for patients with venous insufficiency and venous ulcers. Randomized controlled trials have repeatedly demonstrated benefits of long term compression therapy in patients with venous insufficiency associated with edema or venous ulcers. These studies demonstrated that venous ulcers heal more quickly with compression therapy than without. Elastic compression therapy (stockings or bandages) is more effective than inelastic compression (Unna boot), based on a meta-analysis [27]. Systemic treatment with aspirin or pentoxifylline (phosphodiesterase inhibitor) has also been shown to improve healing of venous ulcers, and should be part of the treatment plan [28, 29]. The selection of wound dressing depends on the level of exudate of the wound and should be individualized. There is no data to support the use of one dressing type over another. Dry, itching, and eczematous skin is common in patients with venous disease, and treatment with skin moisturizer should be adequate. If needed, a low to mid potency topical corticosteroid can be used. Although most patients with venous ulcers can be managed without surgery, in selected patients with large wounds or wounds refractory to medical treatment, split thickness skin graft for coverage may be considered. The role of venous insufficiency surgeries (saphenous veins ablation, interruption of perforator veins, veins stripping, sclerotherapy) in the

treatment of venous ulcers has not been clearly elucidated. To date, there is no evidence demonstrating the superiority of surgical management over medical management [30].

IV. General treatment strategy for arterial insufficiency ulcers

Arterial insufficiency ulcers often begin as minor traumatic wounds that fail to heal as a result of insufficient blood supply to meet the increased demands of the healing tissue. The main strategy in treating arterial insufficiency ulcers is to restore blood flow to the tissue to support wound healing (**Figure 7**). This can be accomplished by endovascular interventions and/or open vascular reconstructions. Prior to revascularization, an anatomical roadmap of the arterial system should be obtained by computed tomography angiography or digital subtraction angiography. If revascularization is not an option or if revascularization fails, amputation may be the only remaining option. For patients with dry gangrene or with non-infected ulcers, the extremity should be revascularized first. Restoration of blood flow is crucial to infection control and must be addressed first prior to any attempt at debridement. In patients with wet gangrene or abscess, the wound should be immediately debrided regardless of any need for revascularization. Once infection is controlled, revascularization procedure should follow. Once blood flow has been restored, the focus can then be shifted to local wound care to allow healing, delayed wound closure, and/or coverage. Long term maintenance of patient with arterial insufficiency ulcers primarily involves risk factor reduction strategies such as smoking cessation and control of diabetes, hypertension, and hyperlipidemia.

Figure 7: Arterial insufficiency ulcer located at weight bearing surface. This patient has diabetes as well as arterial insufficiency. (A) Heal ulcer prior to revascularization. (B) Heal ulcer after anterior tibial artery angioplasty, debridement, local wound care, and non-weight bearing status. (Courtesy of Nasim Hedayati, MD, University of California, Davis)



V. Basic principles of wound care management

For proper wound healing, the wounds need to be clear of infections, free of necrotic tissue, adequately perfused, and moist. Meticulous local wound care with debridement and proper wound dressings will help maintain a healthy environment that will promote granulation tissue

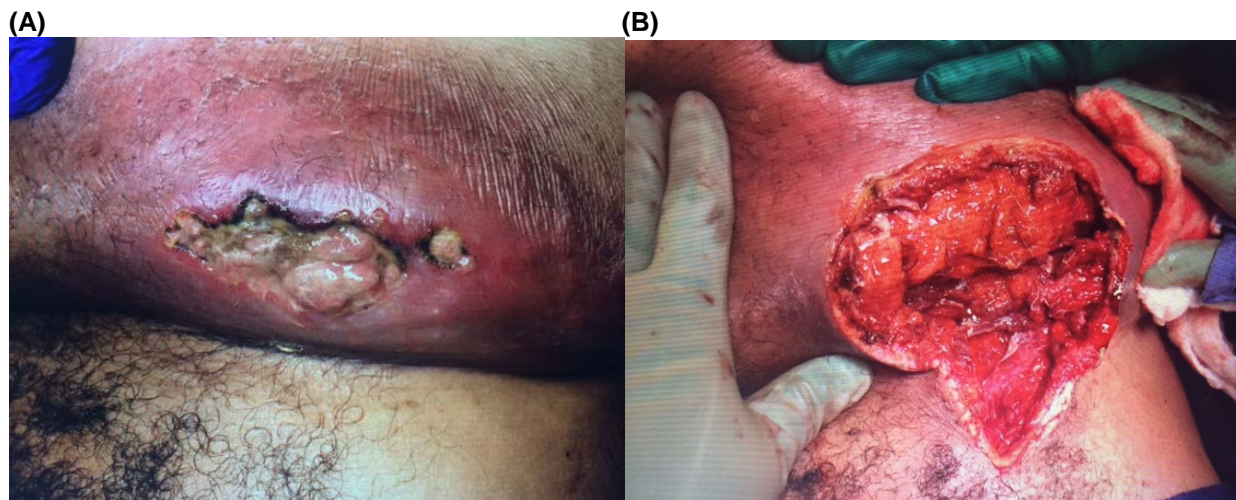
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formation, tissue ingrowth and epithelization. When a wound demonstrates healing potential as evidenced by the presence of granulation tissue and epithelization, it is ready for primary closure or coverage.

Wound Debridement: Wound debridement can be accomplished by sharp debridement, wound irrigation, autolytic debridement, enzymatic debridement and/or maggot debridement. The goal of debridement is to remove infected or devitalized tissue, pathogens, contaminants, and foreign materials, in order to prepare the wound bed for optimal healing and closure.

For infected wounds or wounds with large amount of nonviable tissue, sharp debridement is the most appropriate choice (**Figure 8**). Sharp excisional debridement reduces the bacterial load and stimulates granulation, contraction, and epithelization. It is the most rapid and effective way to achieve a clean wound. A disadvantage of sharp debridement is that it causes pain. In cases when significant debridement or pain is expected, it is best to do the debridement in the operating room under anesthesia.

Figure 8: (A) Infected chronic pressure-injury wound over the left pannus. (B) The infected wound has been debrided to remove infected and necrotic materials, leaving a health wound base. (Courtesy of Francois A. Trappey, MD, University of California, Davis)



Wound irrigation can be used to remove loose necrotic materials from the wound bed and to reduce bacterial load. It should be a routine part of wound management. For most wounds, low pressure irrigation using a bulb syringe should be adequate. For highly contaminated wounds, high pressure pulse irrigation should be considered. Sterile saline is the most common solution used for irrigation, but clean tap water can be just as effective. Several studies reported no significant difference in the rate of infection or wound healing rate between clean tap water and sterile saline, when used for wound irrigation [31]. It is not necessary to add antiseptics, such as iodine, chlorohexidine or hydrogen peroxide to the irrigation fluid as they can cause irritation to the tissue and they do not add any benefit.

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Autolytic debridement is a process in which the body's own proteolytic enzymes within the wound fluid help breakdown the devitalized tissue over time. This process facilitates the separation of necrotic tissue from the healthy wound bed to promote wound healing. Autolytic debridement can be augmented by the use of semi-occlusive dressings such as transparent films, hydrogels, and/or hydrocolloids, to keep the wound fluid in constant contact with the wound (*see Wound dressings below*). A disadvantage of autolytic debridement is that it takes time. Additionally, anaerobic growth may occur with the use of occlusive dressings, requiring frequent wound monitoring for infection. This technique should only be used in non-infected wounds with minimal amount of devitalized tissue.

Enzymatic debridement involves application of commercially available enzymatic agents such as collagenase or papain to the wound. Collagenase is an enzyme isolated from the bacterium *Clostridium histolyticum*. It possesses the ability to selectively digest collagen in necrotic tissue but not in healthy tissue. Papain is a proteolytic enzyme that is found naturally in the papaya fruit. Its proteolytic function must be activated by urea which is also included in the commercially available papain formulation. Another papain ointment formulation contains papain, urea and chlorophyllin. Similar to collagenase, papain selectively digests proteins in nonviable tissue and spares the healthy granulation tissue. Papain should not be used in the presence of hydrogen peroxide, which may inactivate the enzyme. It is the general consensus that enzymatic debridement and autolytic debridement are slow and are only effective in wounds with minimal necrosis. They can be used as an adjunct to surgical debridement [31].

Medical maggot therapy has been used in the treatment of chronic wounds [32, 33]. Maggots secrete proteolytic enzymes that break down necrotic tissues which are then ingested by the larvae leaving behind healthy tissue. There is data to suggest that maggot therapy in addition of conventional wound care results in more complete debridement compared to conventional wound care alone [31]. However, this has not translated into reduction in time to complete wound healing in randomized controlled trials [34-36]. Pain can be associated with maggot therapy, but the main disadvantage of maggot therapy is the negative perception about its use by patients and staff.

Wound dressings: Local wound care with the help of wound dressings is an important element in the preparation of the wound bed for healing, wound closure, skin graft, and/or flap closure. The choice of wound dressings can have an impact on the speed of wound healing and potentially the cosmetic appearance of healed scar. There are several different types of wound dressings to choose from; each has its unique characteristics. Unfortunately, there is no single type of dressings that can be used in all situations. The type of wound dressings used has to be individualized, based on the characteristics of the wound and the stage of healing.

Moisture level on the wound bed is very important for wound healing. The wound fluid is rich in platelet derived growth factor, fibroblast growth factor, and metalloproteases that are important in wound healing [37, 38]. The moist environment is also thought to promote migration of epithelial cells required for re-epithelization. Studies in both animal models and human models have shown that moist wounds heal faster than dry wounds [39-41].

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The primary purpose of wound dressings is to control the moisture level on and around the wound. The wound should be moist enough to promote wound healing, but excess exudate must be controlled to prevent maceration of healthy tissue. Thus, this moisture/exudate balance is the basis for the individualized choice of wound dressings. For example, high absorbent dressing, such as alginates and foams, should be used in high exuding wounds, while hydrogels, with the ability to donate water, should be used in dry/low exuding wounds.

The stage of the wound is also a consideration for dressing selection. During the debridement stage, a dressing that can perform mechanical debridement or promote autolytic debridement is preferred. During the granulation stage, low adherent moisture-retaining dressing will help protect the delicate granulation tissue, while maintaining a moist environment for epithelial migration. Common types of wound dressing materials are discussed below. Table 3 summarizes the characteristics of some of the common dressing materials.

1. Gauze dressing is the most common dressing used in open surgical wounds. The gauze is moistened with saline prior to placing it into the wound. Typically, more absorbent gauze or pads are placed over the moist gauze and secured by tape or bandage. As the moistened gauze dries, it adheres to the surface of the wound, so when the dressing is removed during dressing change, some of the devitalized tissues comes with it. This method of wound care is commonly known as wet to dry dressing. This is typically used on infected wounds, freshly debrided wounds, or wounds that still have a lot of devitalized tissues. Dressing is usually changed twice daily. If the wound develops pseudomonas colonization as evidenced by the presence of blue-green necrotic debris or if bacterial colonization increased as evidenced by the presence of odor, the dressing solution can be changed to Dakin's solution (0.25% to 0.5% sodium hypochlorite or bleach). Advantages of gauze dressings are that they are inexpensive, readily available, and they can be used virtually on any type of wound. Disadvantages of gauze dressings are that they can debride developing granulation tissue, and that they do not foster a moist wound healing environment. For these reasons, wet to dry gauze dressings should be discontinued when necrotic tissue is gone and granulation tissue is present.
2. Impregnated gauze dressing is another commonly used dressing. It is fine mesh gauze impregnated with petroleum, paraffin wax or antibiotic ointment. The primary mesh dressing is applied directly to the wound, which is then covered with another layer of absorbent pads. These dressings are non-adhering so that they can be easily removed during dressing changes with little pain or trauma to the regenerating tissue. On the other hand, these dressings do not maintain a moisture rich environment or provide good exudate control. Fluid can easily go through the mesh gauze and can collect in the overlying pads, causing desiccation of the wound bed and maceration of the surrounding skin.
3. Transparent films are sheets of self-adhesive occlusive dressings that are permeable to water vapor and oxygen, but impermeable to larger molecules such as proteins and bacteria. This property allows oxygen to enter into the wound, and at the same time,

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allows moisture vapor to escape. These films trap wound fluid within the dressing and maintain a moist wound healing environment, while simultaneously preventing bacteria invasion. These films can stay in place for up to one week. Because they are transparent, they do not have to be removed for wound inspection. These dressings are typically used on partial thickness wounds such as donor sites and superficial wounds such as minor burns. These films do not have any absorptive capacity and therefore should not be used on moderately or heavily exudative wounds. The leakage of wound fluid to the surrounding skin can cause maceration. Sometimes the adhesive sticks to the wound bed and removal can be painful.

4. Foam dressings are composed of a hydrophilic foam inner layer that conforms to the wound bed and a hydrophobic gas permeable outer layer to prevent leakage and bacteria contamination. Some foam dressings are self-adhesive, while others require a secondary adhesive dressing. They are commonly used on pressure ulcers, minor burns, skin grafts, diabetic ulcers, donor site, and venous ulcers. The foam layer is soft and does not adhere to the wound bed, making it more comfortable for the patients. They are highly absorbent and should be used in moderate to highly exuding wounds. They should not be used in dry or low exuding wounds as desiccation can occur.
5. Alginate dressings are made from calcium alginate, a polysaccharide salt derived from algae. When it comes in contact with sodium rich wound fluid, the exchange of calcium for sodium ions results in the formation of a strong hydrophilic, highly absorbent gel that conforms to the wounds. Alginate dressings come in various forms, including ribbons, beads, and pads. Their highly absorbent characteristic allows effective control of exudates while maintaining a moist wound bed. Because the dressing can conform to the shape of the wounds, they can be used for packing deeper wounds or wounds with tunneling. Alginates are nonadherent and can easily be washed away with saline, causing minimal pain to the patients. They should not be used in dry or low exuding wounds, or wounds with tendon or bone exposed, as they can cause desiccation. Alginate dressings usually require secondary dressings.
6. Hydrocolloids dressings are made up of colloid particles such as gelatin, pectin and carboxy-methylcellulose that are carried on self-adhesive polyurethane films, forming flexible wafers. When the colloid material comes in contact with exudate, they can swell into a gel-like mass. The colloid material is moderately absorbent, so it can be used in moderate exuding wounds, but not in highly exuding wounds. The colloid is impermeable to water, traps wound fluid, and promotes moist wound healing. It is also impermeable to bacteria, and potentially can be used in areas of high risk for stool contamination (near ostomy site). These dressings are commonly used on burns, pressure ulcers, and venous ulcers. On the other hand, the colloid can also trap bacteria inside the wound, so it should not be used on infected wounds. The dressings are usually changed daily and they can leave a residue on the wound bed.
7. Hydrogels consist of a matrix of synthetic polymers that is capable of holding a large amount of water. In the gel-base form, hydrogels are composed of more than 90%

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water. Hydrogel dressings come in either free-flowing gels or hydrogels impregnated into gauze pads, sponge ropes, strips or fine mesh sheets. Hydrogel matrices can absorb or donate water depending on the hydration state of the surrounding tissue. Hydrogels are most useful in dry or dehydrated wounds. The cooling sensation provided by the hydrogels can offer some pain relief in some patients. Hydrogels have been found to selectively permit gram-negative bacteria to proliferate, but no increased risk of infection has been observed. They should be avoided in infected wounds or wounds with high risk of bacterial infection.

8. Topical antimicrobial agents: There are some topical antimicrobial agents that have been used for chronic wounds. These include iodine-based agent (cadexomer iodine), silver-based agents, and medical grade honey. Both iodine and silver are toxic to bacteria and, theoretically, can reduce bacteria load within the wound and promote wound healing. Interestingly, iodine-induced hyperthyroidism has been reported in patients treated with cadexomer iodine. Honey is toxic to bacteria due to its high osmolarity and high hydrogen peroxide concentration.

Table 3: Properties of common wound dressings

| Type | Actions | Indications | Advantages | Disadvantages |
|------------------------------------|---|--|--|--|
| Gauze | -Debridement | -All wounds -Infected wounds -Wound packing | -Inexpensive -Widely available | -Frequent change -Nonselective debridement -No moist wound healing |
| Petroleum impregnated gauze | -Non-adherent gauze | -Superficial wounds -Granulated wounds | -Non-adherent -Inexpensive -Widely available | -No exudate control -No moist wound healing |
| Transparent films | -Trap wound fluid -Allow gas exchange | -Superficial wounds -Dry or low exuding wounds | - Moist wound healing -Seal from bacteria -Infrequent change | -No absorptive capacity |
| Foams | -Absorb fluid -Moisture control -Conform to wound bed | -Moderate to high exuding wounds -Strips or ribbons for packing | -Conformability -Soft, comfortable -Non-adherent | -Can desiccate dry/low exuding wounds |
| Alginates | -Absorb fluid -Moisture control -Conform to wound bed -Promote autolytic debridement | -Moderate to high exuding wounds -Ropes or ribbons for packing | -Conformability -Non-adherent | -Can desiccate dry/low exuding wounds |
| Hydrocolloids | -Absorb fluid -Promote autolytic debridement | -Low to moderate exuding wounds -Clean wounds | -Impermeable to water, urine, stool | -Can trap bacteria - Avoid infected wounds -Leave residues |

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| Type | Actions | Indications | Advantages | Disadvantages |
|------------------|--|----------------------------|--|--|
| Hydrogels | -Rehydrate wound bed -Promote autolytic debridement | -Dry to low exuding wounds | -Donate water -Cooling; pain relief | -Permits gram negative bacterial growth -Less exudate control – avoid high exuding wounds |

VI. Nutritional support

Patients with large chronic wounds, in particular, patients with pressure ulcers are in a chronic catabolic state. These patients often have multiple medical co-morbidities that predispose them to chronic malnutrition. Their large wounds constantly weep protein rich fluid, contributing the chronic state of hypoalbuminemia. It is imperative to provide these patients with protein rich high calorie nutritional support to help promote wound healing. If oral intake is inadequate, supplementation with enteral feeding may be required. Caloric intake should be 30-35 cal/kg/day and protein intake should be 1.5 g/kg/day. Some data support the use of multi-nutrient supplementations containing zinc, arginine and vitamin C to facilitate faster wound size reduction [31, 42].

VII. Glycemic control

Glycemic controlled is widely recommended to optimize wound healing and to minimize infection risk in patients with chronic wounds. There are some observational data suggesting that sustained glycemic controls by lowering hemoglobin A1C level is positively correlated with faster wound healing [43, 44].

VIII. Adjunctive therapies

Negative pressure wound therapy (NPWT) refers to wound dressing systems that apply sub-atmospheric pressure to the surface of the wound. The application usually involves placement of the sponge materials into the wound followed by an occlusive dressing, which seals the wound from the atmosphere. The sponge dressing is then connected to an external device that collects exudates and regulates suctioning pressure through plastic tubing. Negative pressure wound therapy can accelerate the development of granulation tissue to cover deep exposed wounds. It is excellent for preparation of wound beds for skin grafting. Compared to conventional wound care, NPWT improves healing time in patients with diabetic foot ulcers [45, 46]. In these patients, the use of NPWT is also associated with decreased complication rates, shorter length of hospitalization, and reduced overall costs. In patients with pressure ulcers, the use of NPWT does not appear to make any difference with respect to wound surface area reduction [47, 48]. However, NPWT significantly improves patient comfort, as the dressing does not have to be changed frequently (usually every 2-3 days).

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Hyperbaric oxygen therapy (HBOT) has been shown, *in vitro*, to have positive effects on wound healing [49]. The increase in oxygen tension in the tissue induced by HBOT can improve endothelial progenitor cell mobilization, theoretically leading to neovascularization that can support wound healing [50]. Some observational series and clinical trials have evaluated the utility of HBOT in patients with chronic ulcers. The results have been mixed; earlier studies suggested some benefits, while later studies did not. Systemic reviews of the literature concluded that there is insufficient data to support the routine use of HBOT in the treatment of chronic wounds [51, 52].

Topical growth factors: Growth factors that are important for wound healing include platelet derived growth factor (PDGF), fibroblast growth factor (FGF) and granulocyte-macrophages colony stimulating factor (GM-CSF). To date, PDGF is the only pharmacologic agent that is approved as an adjuvant therapy for the treatment of diabetic foot ulcers. The efficacy for PDGF has not been established for use in pressure ulcers or venous stasis ulcers. There is an FDA black box warning for one gel for increased mortality rate secondary to malignancy in patients treated with 3 or more tubes. The use of FGF, GM-CSF, and epidermal growth factor in the treatment of chronic wounds is still in the experimental phase.

Operative Management

I. Delayed wound closure

It is important to stress that the underlying etiology of chronic wounds should be addressed prior to performing the definitive closure. The wounds also have to be clear of infections, free of necrotic tissue, and adequately perfused before any attempt at delayed closure. The wounds have to be small enough to allow closure with minimal tension. The wound edges are sharply debrided to allow better tissue approximation. Vertical mattress with monofilament nonabsorbable sutures are usually used to bring the deep and superficial edges together.

II. Split thickness skin grafts

Split thickness skin grafts (STSGs) are autologous dermal grafts that consist of the epidermis and a part of the dermis (**Figure 9** on next page). Split thickness skin grafts are harvested by a dermatome at a thickness that can be pre-adjusted on the instrument by the surgeon. The thickness of the grafts can range from 0.008 to 0.012 inches. Split thickness skin grafts can be harvested pretty much anywhere, but the most ideal places for harvest are large surfaces of thick skin such as the thighs and torso. Once the graft is harvested, the wound at the donor site is left to heal by reepithelization, taking advantage of the remaining hair follicles and sebaceous glands to serve as a source of epidermal progenitor cells.

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Figure 9: (A) Split thickness skin graft of the left upper extremity. The graft was meshed with a ratio of 1:2. The photograph was taken one day after surgery. (B) A healed split thickness skin graft of the left lower extremity 6 months after surgery.

(A)



(B)



The graft is usually meshed to allow expansion over a larger area. Meshing of the graft involves using a meshing device to make rows of short interrupted cuts of few millimeters long. This allows the mesh to stretch over an area that is larger than the area of the original harvested

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graft. Mesh ratios can range from 1:1 to 1:6 depending on the need of the recipient site. Meshing also allows fluid to drain through and not collect under the graft. The underside of the graft (shiny side) is placed directly onto the wound surface of the recipient site and the graft secured to the surrounding intact skin with sutures or staples. A bolster dressing or a NPWT dressing can be used to make sure the graft is firmly opposed to the wound surface. It is important to have good contact between the graft and the wound surface as the nourishment for the graft comes directly from the underlying wound surface. This process is called imbibition. At about 3 days after grafting, new blood vessels will start to form to provide permanent nutrients to the graft.

Split thickness skin grafts can tolerate a less than ideal wound bed and they can be used to cover a wider area. Additionally, the morbidity of the donor site is very low. For these reasons, STSG is by far the most common issue type used for wound coverage. A disadvantage of STSGs is that it is thin and is less ideal for areas that are exposed to repeated trauma such as the palm of the hand or the sole of the foot. Split thickness grafts contract during healing and are more prone to secondary contracture.

III. Full thickness skin grafts

Full thickness skin grafts (FTSGs) contain the epidermis and the entire dermis. Because FTSGs are thicker, they are more durable and provide better cosmetic result. For the same reason, the recipient sites have to be rich in granulation tissue to adequately nourish the grafts. Full thickness grafts are usually harvested from areas that have a lot of redundant skin like the groins, lateral thighs, lower abdomen and chest. In general, the grafts have to be small; otherwise it would be difficult to manage the donor sites, which are typically done with primary closure. Once a FTSG is harvested, the fat underlying the graft has to be removed. This is to ensure that nothing will get in between the dermis of the graft and the granulated wound bed, which would interfere with imbibition. As in STSG application, a bolster dressing is placed to guarantee opposition of the graft to the wound bed.

IV. Tissue flap reconstructions

Tissue flap reconstruction refers to the movement of tissue with its intact blood supply from a donor site to a recipient site in order to cover a defect. The difference between a flap and a graft is that a flap still has its own blood supply, while the graft does not. A graft relies on local wound environment for nourishment. Most chronic wounds will heal by secondary intention or can be closed with delayed closure. If closure is not possible, skin grafts should be sufficient to provide coverage. However, in rare instances when the defects are very large and require bulk for better strength or cosmesis, or when the defects are not well vascularized such as those with exposed bones, hardware, or tendons, flap reconstruction may be a better option.

Flaps can be classified based on blood supply, location of the flap, and tissue types. Random flaps are tissues that do not have named blood supply. These flaps rely on subdermal vascular

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plexuses to maintain their blood supply. Random flaps typically contain skin and subcutaneous tissues only and are in close proximity to the recipient site. Examples of random flaps are advancement, rotation, transposition, and interpolation flaps. Axial flaps are flaps that are supplied by named artery(s) and vein(s). Axial flaps may consist of skin, subcutaneous tissue, fascia, muscles, and/or bones. Axial flaps can be pedicle flaps or free flaps. Pedicle flaps are tissue transferred while still attached to its original vascular pedicle. Free flaps are completely detached from their native blood supply and reattached to the vessels at the recipient site.

V. Revascularization

Revascularization of a wound can be accomplished by endovascular techniques or open vascular reconstruction or both.

Basic Postoperative Care

After delayed closure, grafting or flap reconstruction for coverage chronic wounds, the extremity involved should be placed on non-weight bearing status. Pressure should be kept off the grafts or flaps at all times. Skin grafts are usually inspected on post op day 5 to determine if the grafts have taken. A graft is considered taken when it is adhered to the wound bed and is vascularized. Percentage and location of take should be documented clearly by both descriptions and photographs. Once the grafts take, non-adherent dressing can be used for wound care until all of the meshed areas are completely epithelized. When the wound is completely covered, moisturizing ointment should be used to protect the graft. In areas that fail to take, the dead graft should be excised and local wound care over open areas should be resumed. It is crucial to have good exudate control to prevent maceration of the remaining graft. The donor sites should also be monitored for signs of healing or infection.

In patients who underwent flap coverage, the flaps should be closely monitoring for viability, dehiscence, venous congestion, hematoma, seroma, and infections. The most common reason for flap failure is vascular compromise. Poor flap design can lead to partial flap loss if the flaps contain tissue that extends beyond the boundary of the flap's blood supply. Vascular compromise can happen due to twisting of the vascular pedicles during transfer of the flap or compression of the pedicle by hematoma. For free flaps, vascular compromise can occur due to thrombosis at the arterial or venous anastomosis.

Questions

1. A 75-year-old man with a history of diabetes mellitus presented to surgery clinic with a 2 cm ulcer on the sole of the right foot at the level of the metatarsal heads. The wound is round with very little granulation tissue on the wound bed. The surrounding skin is thickened with callus. He has strong femoral pulses and palpable popliteal pulses bilaterally, but no palpable dorsalis pedis or posterior tibial pulses. Which of the following is NOT true about the pathogenesis of his ulcer?
 - A. This condition is associated with loss of innervation to the intrinsic muscles of the foot.
 - B. It is associated with the loss of autonomic innervation and arterioles-venules shunting.
 - C. Because of peripheral neuropathy, pain should not be expected even in the setting of acute infection.
 - D. Protective foot orthotic could have prevented this condition.
 - E. Fifty percent of patients with this condition also have peripheral arterial disease.

2. The above patient undergoes ankle brachial index (ABI) measurement. His ABI on the affected foot is 0.4. His segmental pressure measurement suggested no significant disease of the femoral vessels, but there was severe arterial disease below the knee. What is the most appropriate next step in the management of this condition?
 - A. Proceed with surgical debridement of the ulcer to achieve clean wound bed to facilitate wound healing.
 - B. Referral to Vascular Surgery for digital subtraction angiography and possible endovascular intervention.
 - C. Prescribe lower extremity elevation and compression stocking for compressive therapy.
 - D. Perform full thickness skin graft to cover the ulcer.
 - E. Referral to Plastic Surgery for local advancement flap for coverage of the ulcer.

3. A 40-year-old man with paraplegia at T8 presented with a 5 cm sacral wound, covered with eschar. The wound is draining persistently. The wound has been present for 3 months and it does not appear to be getting any smaller. Which of the following is NOT true regarding the assessment and management of this condition?
 - A. His ulcer is currently unstageable on clinical examination.
 - B. Off-loading by frequent turning and use of supporting surfaces is an important preventive measure.

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- C. Nutritional supplementation with zinc, arginine, and vitamin C has been shown to facilitate faster wound healing with regard to wound size reduction.
 - D. Care for these patients often requires multidisciplinary approach.
 - E. Most of the patients with this condition will require skin graft or flap surgery.
4. A 70-year old woman was referred to surgery clinic with a wound on her right leg. She has a history of varicose veins, and when she was in her fifties, she underwent vein stripping procedures in both lower extremities. Her wound is currently located just above the medial malleolus and is slowly enlarging, but not painful. The skin surrounding the wound is itchy, dry and brawny in appearance. What is TRUE about the treatment strategy for this condition?
- A. Calf muscle exercise by plantar flexion has been proven to speed up the healing of these wounds.
 - B. Compression therapy has been shown to enhance healing of these wounds.
 - C. Static compression therapy is superior to elastic compression therapy.
 - D. Aspirin has been shown to facilitate healing of arterial insufficiency ulcers but not venous ulcers.
 - E. Most patients with these wounds will require split thickness skin grafts.

Answers

1. A 75-year-old man with a history of diabetes mellitus presented to surgery clinic with a 2 cm ulcer on the sole of the right foot at the level of the metatarsal heads. The wound is round with very little granulation tissue on the wound bed. The surrounding skin is thickened with callus. He has strong femoral pulses and palpable popliteal pulses bilaterally, but no palpable dorsalis pedis or posterior tibial pulses. Which of the following is NOT true about the pathogenesis of his ulcer?
 - A. This condition is associated with loss of innervation to the intrinsic muscles of the foot.
 - B. It is associated with the loss of autonomic innervation and arterioles-venules shunting.
 - C. Because of peripheral neuropathy, pain should not be expected even in the setting of acute infection.**
 - D. Protective foot orthotic could have prevented this condition.
 - E. Fifty percent of patients with this condition also have peripheral arterial disease.

The correct answer is C. In patients with diabetic neuropathy, the motor innervation to the intrinsic muscles of the feet is lost, leading to unopposed action of the muscles of the anterior tibial compartment. The result is a claw toe deformity and risk of ulcer formation on the plantar surface of the metatarsal heads. Loss of autonomic innervation also leads to arteriole-venous shunting, depriving tissues of oxygen and nutrients. Patient with sensory neuropathy may experience numbness in the feet; however, in the setting of infection, patients will experience an increase in pain. Increased pain is a potential sign of infection even in patients with diabetes. Orthotic footwear is a preventive measure in patients with diabetes. Approximately 50% of patients with diabetic foot ulcers have some degree of peripheral arterial disease.

2. The above patient undergoes ankle brachial index (ABI) measurement. His ABI on the affected foot is 0.4. His segmental pressure measurement suggested no significant disease of the femoral vessels, but there was severe arterial disease below the knee. What is the most appropriate next step in the management of this condition?
 - A. Proceed with surgical debridement of the ulcer to achieve clean wound bed to facilitate wound healing.
 - B. Referral to Vascular Surgery for digital subtraction angiography and possible endovascular intervention.**
 - C. Prescribe lower extremity elevation and compression stocking for compressive therapy.
 - D. Perform full thickness skin graft to cover the ulcer.
 - E. Referral to Plastic Surgery for local advancement flap for coverage of the ulcer.

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The correct answer is B. In patients with arterial insufficiency, revascularization of the ulcer is the key to getting the ulcer to heal. When there is no clear evidence of wet gangrene or acute infection, revascularization should be done first, prior to debridement. Without revascularization to bring nutrients and oxygen to the wound, debridement will just lead to a larger wound that will not heal. Prior to revascularization, angiographic study should be done to create a road map for possible intervention. Compressive therapy is a treatment for venous ulcers and can potentially make arterial insufficiency ulcer worse. Skin graft or flaps are rarely indicated in diabetic foot ulcers or arterial insufficiency ulcers, and should not be performed without first addressing the underlying problem, which is arterial insufficiency.

3. A 40-year-old man with paraplegia at T8 presented with a 5 cm sacral wound, covered with eschar. The wound is draining persistently. The wound has been present for 3 months and it does not appear to be getting any smaller. Which of the following is NOT true regarding the assessment and management of this condition?
- A. His ulcer is currently unstageable on clinical examination.
 - B. Off-loading by frequent turning and use of supporting surfaces is an important preventive measure.
 - C. Nutritional supplementation with zinc, arginine, and vitamin C has been shown to facilitate faster wound healing with regard to wound size reduction.
 - D. Care for these patients often requires multidisciplinary approach.
 - E. Most of the patients with this condition will require skin graft or flap surgery.**

The correct answer is E. In this patient with pressure ulcer, the wound has an eschar covering that is obscuring view necessary to determine the actual stage of the ulcer. This makes this ulcer unstageable. If this ulcer is to be correctly staged, the eschar has to be debrided in order to determine the true extent of the ulcer. It is important to note that the extent of injury is typically more than what can be seen from the surface. Off-loading is an important preventive measure when treating patients at risk for pressure ulcers. Multi-nutritional supplementation with zinc, arginine, and vitamin C has been shown to improve faster healing rate. Patients with pressure ulcers often have significant medical comorbidities and are debilitated, and care for these patients requires multidisciplinary approach. Most patients with pressure ulcers will heal with meticulous medical and wound care, without skin graft or flap coverage.

4. A 70-year old woman was referred to surgery clinic with a wound on her right leg. She has a history of varicose veins, and when she was in her fifties, she underwent vein stripping procedures in both lower extremities. Her wound is currently located just above the medial malleolus and is slowly enlarging, but not painful. The skin surrounding the wound is itchy, dry and brawny in appearance. What is TRUE about the treatment strategy for this condition?

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- A. Calf muscle exercise by plantar flexion has been proven to speed up the healing of these wounds.
- B. Compression therapy has been shown to enhance healing of these wounds.**
- C. Static compression therapy is superior to elastic compression therapy.
- D. Aspirin has been shown to facilitate healing of arterial insufficiency ulcers but not venous ulcers.
- E. Most patients with these wounds will require split thickness skin grafts.

The correct answer is B. The most important treatment for patients with venous ulcers is compression therapy. Compression therapy has been shown in multiple randomized controlled trials to facilitate venous ulcer healing. Elastic compression therapy with stockings and bandages has been shown to be better than static compression (Unna boot), in a Cochrane review of the literature. Both aspirin and pentoxifylline have been shown to improve healing of venous ulcers. Most patients with venous ulcers will heal without the need for skin grafting.

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