Chapter 12

Venous Leg Ulceration

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Additional information is available at the end of the chapter

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Abstract

Venous leg ulcers are among the most common leg ulcerations. Advancing age, sex, race, phlebitis, family history, obesity, prolonged standing, and number of pregnancies are risk factors. Although the main pathogenetic mechanism is venous hypertension, leading to vein wall damage and thereby a cascade of events resulting in ulceration, there is no consensus about progression from venous hypertension to ulceration.

Diagnosis is based on a thorough patient history and physical examination. A typical venous ulcer is shallow and has irregular, well-defined borders with surrounding skin alterations. However, variable vascular and laboratory tests and skin biopsy may occasionally be necessary in differential diagnosis.

Although pain reduction, closure of the ulcers, and prevention of the recurrences are the main goals of the treatment, targeted therapy should be the reversal of deep venous insufficiency. Leg elevation and long-term compression therapy are essential in this context. Additionally, appropriate wound care including infection control, debridement, dressings, and antibiotics should be performed and, if needed, adjuvant therapies should be planned according to the patient.

Keywords: venous leg ulcers, lower extremity ulcers, venous insufficiency, diagnostic testing, management

1. Introduction

Venous ulcers are the most common form of leg ulcers and important medical problem, which causes significant morbidity and economic burden. Clinical findings and history are helpful in making the diagnosis, but additional diagnostic testing is helpful in confirming the diagnosis

and excluding other causes of leg ulcerations. The main purpose of venous ulcer management includes healing of the ulcer and prevention of recurrence. This chapter highlights the epidemiology, pathophysiology, clinical presentation, diagnostic testing, differential diagnosis, and treatment of venous ulcers.

2. Epidemiology

Venous leg ulcers (VLUs) are the most common lower extremity ulceration and responsible for 70% of all leg ulcers, with overall prevalence ranging from 0.06 to 2% [1–4]. It occurs frequently between the ages of 60 and 80 years; however, most people have their first ulcer before the age of 60 years [5, 6]. VLUs have slight female predominance, with a female-to-male ratio ranging from 1.5:1 to 10:1 [7, 8].

Venous ulcers have a significant socioeconomic impact with reduced work productivity and quality of life. Long-term treatments are needed and recurrence is widely common, ranging from 54 to 78% of treated subjects [9]. The overall cost of VLU treatments was 1–2% of the healthcare budgets of European countries [10]. In the United States, approximately 2.5 billion dollars was expended for the treatment of VLUs per year [11].

Advancing age, sex, race, phlebitis, family history, obesity, occupation involving prolonged standing, and number of pregnancies are risk factors that have been described with chronic venous insufficiency and, subsequently, with venous ulcers [12, 13].

3. Pathogenesis

3.1. Normal venous anatomy and physiology

The venous system of the lower extremities includes the superficial veins, perforator veins, and the deep veins according to their relationship to the muscular fascia. The superficial veins comprises the reticular veins, the large (larger) and small (smaller) saphenous veins, and their tributaries. The great saphenous vein originates from where the dorsal vein of the first digit merges with the dorsal venous arch of the foot. After passing in front of the medial malleolus, it ascends the medial side of the leg. It joins the femoral vein just below the inguinal ligament. The small saphenous vein arises from the dorsal venous arch of the foot and ascends posterolaterally from behind the lateral malleolus. Usually, it drains into the popliteal vein near the popliteal fossa. The reticular veins, a network of veins parallel to the skin surface, communicate with either saphenous tributaries or the deep veins through perforators. The perforator veins connect the superficial and deep vein systems. The deep venous system is categorized as either intramuscular or intermuscular. Intermuscular veins are three paired tibial veins including, the posterior tibial vein, the anterior tibial vein, and the peroneal vein. These veins join to form the popliteal vein in the popliteal area. At the level of the adductor canal, the popliteal vein is renamed the superficial femoral vein. This vessel joins the deep femoral vein in the femoral

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triangle to form the common femoral vein. After passing beneath the inguinal ligament to enter the pelvis, the femoral vein is renamed the common iliac vein. The superficial veins are low-pressure systems, whereas the deep veins are high-pressure systems. All three venous systems have one-way bicuspid valves, which only open toward the deep venous system and, under normal conditions, prevent reflux of blood. Normally, ambulation and the pumping action of the calf muscles propel venous blood upward toward the heart, and the valves close when pressure rises in the deep venous system, which prevents retrograde flow [4, 14, 15].

3.2. Pathophysiology

In patients with venous disease or failure, venous pressure in deep system falls less than normal during ambulation and rises in orthostatic position, and this is termed venous hypertension. In conclusion, venous hypertension in the deep veins may be transmitted to the superficial veins [4, 16]. There is no general consensus about the transition from venous hypertension to venous ulceration. Several hypotheses have been proposed.

(a) Precapillary fibrin cuffs and fibrinolytic abnormalities hypotheses:

According to this theory of Browse and Burnand [17], venous hypertension leads to distention of capillary walls and leakage of macromolecules such as fibrinogen into the dermis and subcutaneous tissues of the calf. The leaked fibrinogen polymerizes to form precapillary fibrin cuffs in the extravascular space. These precapillary cuffs were assumed to act as a physical barrier, which impede the diffusion of oxygen and nutrients, resulting in ischemia, cell death, and ulceration [17–19]. In addition, local and systemic fibrinolytic/coagulation abnormalities such as prolonged euglobulin lysis time, elevated plasma fibrinogen levels, increased levels of protein C, fibrin-related antigens, D-dimer, D-monomer, fibrin monomer, and reduction in factor XIII activity may present in patients with venous disease [20–22]. However, it is unclear whether these abnormalities are primary or secondary to venous disease.

(b) Leukocyte trapping hypothesis:

As a result of venous hypertension, there is a decreased pressure in capillary bed perfusion and capillary flux. This gives rise to erythrocyte aggregation and leukocyte plugging in the capillaries, leading to local ischemia. Moreover, these leukocytes release cytokines, tumor necrosis factor α (TNF-α), proteolytic enzymes, and free radicals which can cause increased vascular permeability resulting in the leakage of fibrinogen into the pericapillary tissues and the decreased fibrinolytic activity [23–25].

(c) The growth factor trap hypothesis:

Falanga and Eaglstein [26] recommended that macromolecules such as fibrinogen and $\alpha_2$macroglobulin, which leak into the dermis as a result of venous hypertension, bind to or trap growth factors, which then become unavailable for the maintenance of tissue integrity and repair process. The precapillary fibrin cuff of the venous ulcer contains growth factors such as

transforming growth factor β (TGF-β). Trapping of growth factors can impair activation of the cells that are needed for healing process [27].

4. Diagnosis

4.1. Clinical presentation

In general, the venous ulcer is an irregularly, well-defined border and typically non-painful [4, 8]. Nevertheless, deep ulcers or small venous ulcers surrounded by atrophie blanche are highly painful [28]. The size and site of ulcers are variable, but they usually located over the medial malleolus (**Figure 1**).

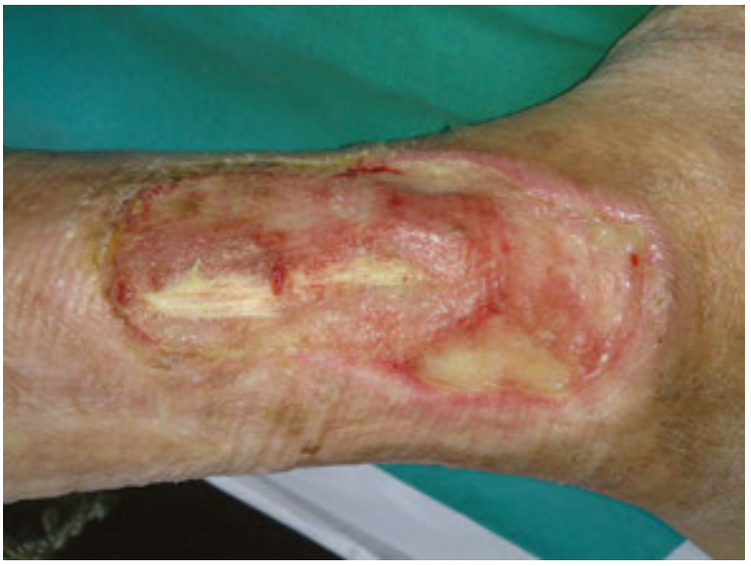

Figure 1. Typical venous ulcer over the medial malleolus.

There may be yellow fibrinous exudates on the ulcer bed. Varicose veins and ankle edema are common. The surrounding skin is erythematous or hyperpigmented with variable degrees of induration. Eczematous changes associated with venous dermatitis are commonly present. Long-standing venous disease can lead to loss of the subcutaneous fat and fibrotic changes in the skin called lipodermatosclerosis, giving the characteristic "inverted champagne-bottle" appearance of the leg [29]. The main complications of chronic venous ulcers are osteomyelitis and neoplastic transformation [4, 30]. Long-term ulcers may require biopsy at regular intervals for malignant change. If osteomyelitis is suspected, radiography, bone scanning, and bone biopsy should be considered.

4.2. Diagnostic testing

The diagnosis of venous ulcers is mainly based on patient history and clinical examination; however, there are diagnostic tests to evaluate venous anatomy and aid the diagnosis.

4.2.1. Venous duplex ultrasound

Duplex ultrasound is the first-line diagnostic test to evaluate the insufficiency in venous ulcers [31]. Continuous-wave Doppler provides information about superficial venous incompetence or obstruction; nonetheless, it can be difficult to differentiate deep from superficial venous incompetence [32, 33].

4.2.2. Venous plethysmography

Photoplethysmography and air plethysmography measure the degree of venous reflux and the calf muscle pump efficiency [8, 34, 35].

4.2.3. Venous imaging

In case of suspected venous obstruction, additional contrast imaging with computed tomography venography or magnetic resonance venography should be done; whereupon diagnosis should be confirmed by contrast venography and intravascular ultrasound [31].

4.2.4. Laboratory testing

Patients who have a history of venous thrombosis and thrombophilia should undergo a workup for inherited hypercoagulable factors including protein C and S, factor V Leiden, antiphospholipid antibodies, prothrombin gene mutation, homocysteine, cryoglobulins, and cryoagglutinins [8, 31].

4.2.5. Arterial testing—Ankle Brachial Pressure Index (ABI)

Patients with venous leg ulcers may have concomitant peripheral arterial disease component. Therefore, arterial pulse examination, Doppler ultrasound and ABI should be evaluated for the elimination of coexistent arterial disease. ABI is the ratio of the systolic blood pressure at the ankle compared with the systolic blood pressure in the arm. An ABI in the range of 0.9–1.1 is considered normal and 0.5–0.8 indicates moderate peripheral vascular disease and claudication, while less than 0.5 indicates more severe disease [4, 8, 36].

4.2.6. Wound biopsy

Most studies suggest wound biopsy for those that do not improve with standard wound and compression therapy after a period of 4–6 weeks of treatment. The biopsy specimen should be obtained from several sites, including the wound edge and central provisional matrix [31].

4.3. Classification

4.3.1. CEAP

Classification of venous ulcers, known as CEAP [clinical findings (C), etiology (E), anatomical distribution (A), and pathophysiology (P)] based on clinical findings was introduced in 1994 and revised in 2004 [37, 38] (**Table 1**).

CEAP	Definition
Clinical classification	
C0	No visible or palpable signs of venous disease
C1	Telangiectasies or reticular veins
C2	Varicose veins
C3	Edema
C4a	Pigmentation and/or eczema
C4b	Lipodermatosclerosis and/or atrophie blanche
C5	Healed venous ulcer
C6	Active venous ulcer
CS	Symptoms, including ache, pain, tightness, skin irritation, heaviness, muscle cramps, as well as other complaints attributable to venous dysfunction
CA	Asymptomatic
Etiologic classification	
Ec	Congenital
Ep	Primary
Es	Secondary (post-thrombotic)
En	No venous etiology identified
Anatomic classification	
As	Superficial veins
Ap	Perforator veins
Ad	Deep veins
An	No venous location identified
Pathophysiologic classification (basic)	
Pr	Reflux
Po	Obstruction
Pr,o	Reflux and obstruction
Pn	No venous pathophysiology identifiable

Modified from Eklöf et al. [38].

Table 1. Basic revised clinical, etiologic, anatomic, and pathophysiologic (CEAP) classification system.

The clinical findings are divided into six categories, where C_0indicates no visible or palpable signs of venous disease; C1, the presence of telangiectasies or reticular veins; C2, varicose veins; C3, edema; C4, changes in skin and subcutaneous tissue secondary to venous disease (C4a, pigmentation or eczema; C4b, lipodermatosclerosis or atrophie blanche); C5, skin changes with healed venous ulcer; C6, active venous ulcer. Each clinical class is further supplemented by (A) for asymptomatic and (S) for symptomatic presentation. Symptoms include aching, pain,

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skin irritation, tightness, heaviness, muscle cramps, and other complaints. The etiologic classification is separated into three categories; Ec, congenital; Ep, primary; Es, secondary (post-traumatic or post-thrombotic); and En, no venous cause identified. The anatomical classification is divided into four categories: As, superficial veins; Ap, perforator veins; Ad, deep veins; and An, no venous location identified. The pathophysiologic classification is divided into four categories; Pr, reflux; Po, obstruction; Pr,o, combination of reflux and obstruction; and Pn, no venous pathophysiology identifiable.

The venous clinical severity score (VCSS) was developed because of subjective and inadequate definition of the categories in CEAP classification (**Table 2**).

	None: 0	**Mild: 1**	**Moderate: 2**	**Severe: 3**
Pain or other discomfort (i.e., aching, heaviness, fatigue, soreness, burning)		Occasional pain or other discomfort (i.e., not restricting regular daily activities)	Daily pain or other discomfort (i.e., interfering with but not preventing regular daily activities)	Daily pain or discomfort (i.e., limits most regular daily activities)
Presumes venous origin Varicose veins "Varicose" veins must be ≥3 mm in diameter to qualify in the standing position		Few: scattered (i.e., isolated branch varicosities or clusters) Also induces corona phlebectatica (ankle flare)	Confined to calf or thigh	Involves calf and thigh
Venous edema Presumes venous origin		Limited to foot and ankle area	Extends above ankle but below knee	Extends to knee and above
Skin pigmentation Presumes venous origin Does not include focal pigmentation over varicose veins or pigmentation due to other chronic diseases	None or focal	Limited to perimalleolar area	Diffuse over lower third of calf	Wider distribution above lower third of calf
Inflammation More than just recent pigmentation (i.e., erythema, cellulitis, venous eczema, dermatitis)		Limited to perimalleolar area	Diffuse over lower third of calf	Wider distribution above lower third of calf
Induration Presumes venous origin of secondary skin and subcutaneous changes (i.e., chronic edema with fibrosis,		Limited to perimalleolar area	Diffuse over lower third of calf	Wider distribution above lower third of calf

	None: 0	Mild: 1	Moderate: 2	Severe: 3
hypodermitis) Includes white atrophy and lipodermatosclerosis				
Active ulcer number	0	1	2	≥3
Active ulcer duration (longest active)	N/A	<3 months	>3 months but <1 year	Not healed for <1 year
Active ulcer size (largest active)	N/A	Diameter >2 cm	Diameter 2–6 cm	Diameter >6 cm
Use of compression therapy	0 Not used	1 Intermittent use of stockings	2 Wears stockings most days	3 Full compliance: stockings

Modified from Vasquez MA, Rabe E, McLafferty RB, Shortell CK, Marston WA, Gillespie D, et al. Revision of the venous clinical severity score: venous outcomes consensus statement: special communication of the American Venous Forum Ad Hoc Outcomes Working Group. J Vasc Surg 2010;52:1387–96.

Table 2. Revised venous clinical severity score (VCSS) system.

A VCSS may range from 0 to 30 [31, 33, 39]. A score of more than eight indicates the progression of venous problem. In addition, the VCSS has been shown to be useful to evaluate the response to treatment.

5. Differential diagnosis

5.1. Arterial ulcers

Arterial leg ulcers result from peripheral arterial occlusive disease. Arterial ulcers typically are round or punched out with a sharply demarcated border and extremely painful. A fibrous yellow base or necrotic eschar is commonly seen (**Figure 2**).

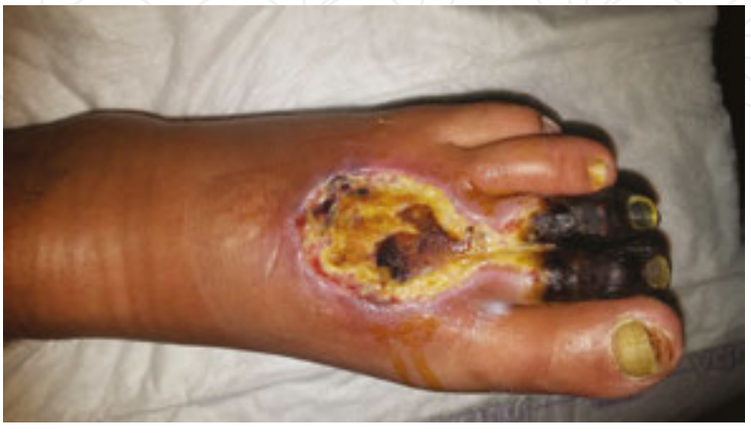

Figure 2. Arterial ulcer.

The surrounding skin is cool to the touch. These ulcers frequently occur at the tips of the toes and over the bony prominences. Associated findings are weak or nonexistent arteria dorsalis pedis pulse, hair loss, atrophic skin, dystrophic nails, the presence of claudication, or rest pain. The ABI of 0.5 or less indicates severe arterial disease [4, 40, 41].

5.2. Neuropathic ulcers

Neuropathic ulcers are more common in patients with diabetes mellitus (DM). Trauma and/or pressures can cause wounding and ulcer formation in patients with neuropathy [41–43]. These ulcers usually tend to be on the plantar surface of the foot. An abnormal, thickened callus develops at pressure areas, with ultimate disrupt of the tissue resulting in ulcer formation (**Figure 3**).

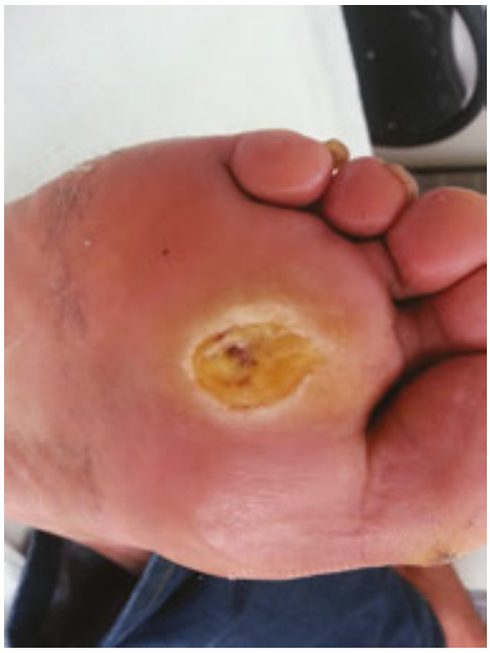

Figure 3. Diabetic neuropathic foot ulcer.

5.3. Pressure ulcers

Pressure ulcers mostly occur in patients with limited mobility. These ulcers can start to develop when soft tissue is compressed for a prolonged period of time. The main risky sites are the heel of the foot, malleoli, and sacral and trochanter areas [4, 44].

5.4. Hypertensive leg ulcer (Ulcus Cruris Hypertonicum Martorell)

Hypertensive leg ulcers are extremely painful and commonly located on the distal portion of the lower leg above the lateral malleolus. These ulcers are seen in patients with prolonged, severe, or poorly controlled hypertension [41, 42]. The ulceration is secondary to tissue ischemia caused by increased vascular resistance.

5.5. Mixed ulcer

Patients with mixed etiology ulcers have combined venous and arterial disease. Often further complicating factors such as DM, rheumatoid arthritis (RA), or lymphedema also exist [42].

5.6. Pyoderma gangrenosum

Pyoderma gangrenosum is a neutrophilic dermatosis. Clinically it starts with sterile pustules that rapidly progress and turn into painful ulcers with purplish-blue, undermined borders [42, 45]. It may be associated with inflammatory bowel disease, rheumatic, or myeloproliferative disorders [8, 12] (**Figure 4**).

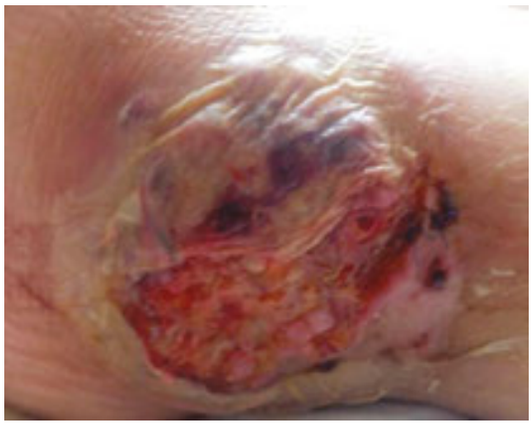

Figure 4. Pyoderma gangrenosum.

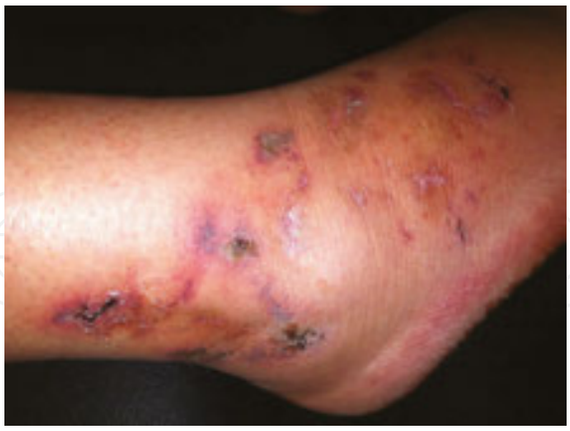

Figure 5. Livedoid vasculopathy and tiny ulcerations.

5.7. Vasculitis

Cutaneous vasculitis may present as palpable purpura, urticaria, nodule, bullae, livedo reticularis, necrotic areas, or skin ulceration. Vasculitic leg ulcers are often painful, multilocular

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and, surrounded by livid erythema and purpura (**Figure 5**). The different types of vasculitis that can cause cutaneous ulceration include small vessel vasculitis such as leukocytoclastic vasculitis, medium-sized vessel vasculitis such as polyarteritis nodosa, microscopic polyangiitis, and Wegener granulomatosis [41, 46]. Routine blood work, sedimentation, antineutrophil cytoplasmic antibody (ANCA), urinalysis, chest X-ray, and multiple skin biopsies should be done.

Livedoid vasculopathy (LV) is characterized by irregularly shaped, recurrent perimalleolar painful ulcers overlying areas of purpura. LV typically has three phases including livedo racemosa, ulcerations, and atrophie blanche [41, 42] (**Figure 5**).

5.8. Autoimmune diseases

5.8.1. Rheumatoid ulcers

Approximately 10% of individuals with RA develop leg ulcers [41] (**Figure 6**). The cause of leg ulcerations in RA is multifactorial, including vasculitis, venous insufficiency, paraproteinemias, medications, superficial ulcerating rheumatoid necrobiosis, pyoderma gangrenosum, and Felty's syndrome [45–48](**Figure 6**).

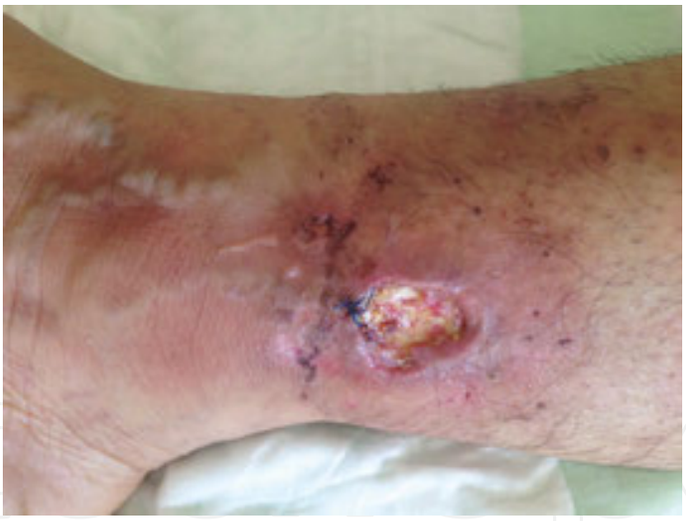

Figure 6. Rheumatoid ulcer.

5.8.2. Scleroderma

The prevalence of lower extremity ulcers in scleroderma is 3.6% and various parts of the leg can be affected [49]. These ulcers are painful and relatively refractory to standard treatment methods. Antiphospholipid antibody, fibrotic skin, vascular compromise, coagulation abnormalities, and tissue calcium deposition may have a role in their pathogenesis [45, 46, 48].

5.8.3. Systemic lupus erythematosus (SLE)

Leg ulcers of SLE are usually painful, sharply marginated, or punched out that located over the malleolar, supramalleolar, or pretibial areas [50]. Vasculitis, antiphospholipid antibody, thrombosis of vessels, venous insufficiency, lupus profundus, and drug-induced lupus syndrome have been associated with leg ulcerations.

5.8.4. Sjögren syndrome

Leg ulcerations of Sjögren syndrome have been associated with cryoglobulinemia, anticardiolipin antibody, and vasculitis [46, 51].

5.8.5. Dermatomyositis

Leg ulcers of dermatomyositis have been reported to involve calcinosis cutis and vasculitis [46].

5.8.6. Mixed connective tissue disease (MCTD)

MCTD is an overlap syndrome combining features of SLE, RA, systemic sclerosis, and dermatomyositis together with the presence of antibodies to U1-RNP. Chronic leg ulcers are not rare in MCTD and they have been reported to be due to subcutaneous calcification, vasculitis, vasospasm (Raynoud's phenomenon), vascular thrombosis, and antiphospholipid antibodies [46, 52, 53].

5.9. Infections

Numerous infections can precipitate ulcerations on the lower legs. Ecthyma, atypical mycobacterial infections, late syphilis, cutaneous leishmaniasis, actinomycoses, nocardioses, human immunodeficiency virus (HIV) infection, herpes simplex, and cytomegalovirus infections must be considered [41, 43, 54]. In addition, all chronic wounds may be secondarily contaminated with bacteria. Tissue culture will help elucidate the cause [4].

5.10. Metabolic diseases

Various metabolic factors such as diabetes mellitus, amyloidosis, hyperhomocysteinemia, prolidase deficiency, oxalosis, calciphylaxis, and gout can play a role for the lower leg ulcerations.

Necrobiosis lipoidica is a rare, chronic granulomatous disease of the skin. Clinical presentation characterized by atrophic, indurated plaques with a yellowish center and telangiectasies [42]. The lower legs, especially the shins, are the most common sites of involvement. During the course, ulcerations may occur. Necrobiosis lipoidica frequently occurs in association with diabetes mellitus (**Figure 7**).

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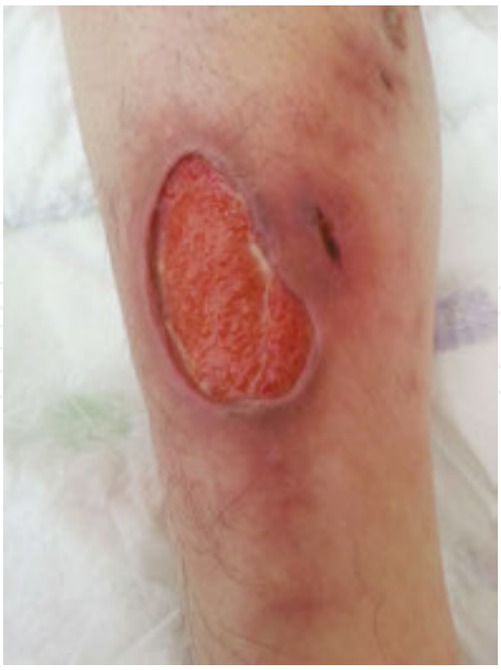

Figure 7. Necrobiosis lipoidica.

Calciphylaxis is an uncommon disorder, classically associated with renal disease and secondary parathyroidism [55]. Clinical presentation may begin as microlivedo that develop into painful ulcerations.

5.11. Hematologic diseases

Several forms of anemia (thalassemia, sickle cell anemia, hereditary spherocytosis, glucose 6 phosphate dehydrogenase deficiency), and hypercoagulable disorders (antiphospholipid antibody syndrome, antithrombin III, protein C or S deficiency, essential thrombocythemia, thrombotic thrombocytopenic purpura, polycythemia, or abnormal clotting factors such as factor V Leiden, factor II mutant) have been associated with lower leg ulceration [54].

5.12. Neoplasia

Many tumor types such as basal cell carcinoma, squamous cell carcinoma, and melanoma may present with skin ulceration. Basal cell carcinomas arising from venous ulcers appear as exuberant granulation tissue rolling onto the wound edges [4]. In addition, malignancy that presents as Marjolin's ulcers is most commonly associated with chronically inflamed, or scarred skin. Skin biopsy is necessary to identify ulcerated malignant tumors on the leg.

5.13. Medications

Hydroxyurea is a cytostatic drug used in various myeloproliferative disorders. A rare complication is the development of painful ulcers, usually localized on the malleoli or in neigh-

boring regions [42, 54]. The coumarin derivatives, nifedipine, diltiazem, barbiturates, and erythropoietin in very rare cases, may trigger ulcer development [42].

6. Management

It is essential to treat the patients with multidisciplinary approach. The complete assessment of the chronic venous insufficiency should be evaluated together with vascular surgeons. The decision of the surgical treatment in appropriate cases should be considered with plastic surgeons. Knowledge of pathogenesis of venous ulcers and avoiding from its risk factors will be provided to choose the optimal treatment for patients with venous leg ulcers, which cause both impairment of life quality and socioeconomic burden. A multidisciplinary team of specialists will be helpful in the evaluation of venous leg ulcers and providing the most appropriate treatment.

Several treatment options are available for the management of venous ulcers. Pain reduction, closure of the ulcers, and prevention of the recurrences are the main goals of the treatment [56]. Reversing the effects of venous hypertension is the primary purpose of the treatment of venous leg ulcers. The easiest method is leg elevation [57]. Although it seems to be impractical to most of the patients, elevation of the legs above the heart level for 30 minutes, 3–4 times a day, provides the dissolution of the swelling and improves the microcirculation [58]. Leg elevation can also be performed at night by raising the foot 15–20 cm high [59]. Moreover, good nutrition and assessment with each dressing change are necessary to support the therapy. Initially and at each dressing change, the depth, width, and height of the wound bed should be measured to evaluate the improvement. Appropriate therapy of the wound must be selected patient centered. Infection control, debridement, antibiotics, dressings, compression, and adjuvant therapies will be described in this section.

6.1. Wound cleansers

Cleansers are the first and main step in preparing the wound bed. Wound cleansing with a neutral, nonirritating solution with a minimum chemical and mechanical trauma should be performed at each dressing change. Wound exudate and other debris around the wound area in venous leg ulcers must be cleansed with an appropriate solution. Although several cleansing solutions are in the market, the choice of the cleanser should have the purpose of avoiding toxicity to the viable tissue in the wound bed [31].

6.2. Debridement

Debridement during the initial evaluation is recommended to remove the necrotic tissue, excessive bacterial burden, and nonviable cells [31]. Although debridement of the wound is commonly performed to allow the formation of good granulation tissue and proper epithelialization by creating an appropriate environment to keratinocyte migration, there is a lack of evidence that routine wound debridement accelerates wound healing [31]. There are several ways of wound debridement, including autolytic, chemical, and mechanical [60].

6.2.1. Autolytic debridement

In venous ulcers, it is possible that wound occlusion itself promotes re-epithelialization, reduces associated pain, enhances autolytic debridement, and provides an additional barrier to bacteria [61, 62]. Hydrogels, alginates, hydrocolloids, foams, and films are the basic occlusive dressings. Wound features, exudate amount and cost of the material, and patient and physician preference affect the choice of dressing [63].

6.2.2. Chemical debridement

Several enzyme-debriding agents have been developed to promote the removal of the necrotic tissue and the formation of proper granulation tissue [64, 65]. Specific proteolytic enzyme therapies to the venous ulcers may accelerate the removal of fibrin cuffs [66]. Various enzyme-debriding agents are available, including collagenase, papain, trypsin, and tissue plasminogen activator [60, 67, 68]. Frequency of the application of the dressing may vary up to the manufacturer's recommendations. Enzymatic debridement, which does not require a trained clinician for application, has been found in several studies to remove nonviable tissue from the wound beds of venous leg ulcers, but there is no evidence that this method provides a benefit over surgical debridement [69, 70].

6.2.3. Mechanical debridement

Application of wet-to-dry dressings, hydrotherapy, irrigation, and dextranomers are some of the methods of mechanical debridement [71]. The removal of the viable tissue along with the necrotic material is the major disadvantage of mechanical debridement [72]. Hydrosurgical debridement was showed to have a shorter procedure time but requires additional cost and a trained clinician [73, 74]. Furthermore, it may be associated with a significant periprocedural pain [69]. Dextranomer's hydrophilic structure that provides a high absorptive capacity makes it useful for wounds with heavy exudate. The possibility of dehydration of the wound bed demands caution [4]. Surgical debridement, which may be performed with a curette, forceps, scalpel, or sharp scissors, is another way to remove necrotic tissue. As venous ulcers do not comprise frank necrosis or eschar tissue, this method is rarely used in venous ulcers [75]. During surgical debridement, local infiltrative, regional block, or general anesthesia may be required according to the extensity of the wound [31].

6.3. Antibiotics

Antimicrobial therapy is suggested in venous ulcers with $>1 \times 10^6$colony-forming unit (CFU)/g of bacteria on quantitative culture and clinical evidence of infection. Systemic antibiotic therapy, guided by sensitivities performed on wound culture, is recommended. Oral antibiotics are preferred in the beginning of the therapy duration and should be limited to 2 weeks [31]. Combination of mechanical debridement and antibiotic therapy is thought to be successful in eradicating infection in venous leg ulcer. In case of cellulitis, beta-lactam and non beta-lactam antibiotics may be treatment options. Trimethoprim-sulfamethoxazole and clindamycin are recommended as initial empiric therapy if methicillin-resistant Staphylococ-

cus aureus is the suspected reason of cellulitis [76]. The use of topical silver for infected venous ulcers is controversial [31]. Recently, cadexomer iodine is reported to shorten the healing time of venous ulcers [77].

It is likely to be an increased risk of contact dermatitis in patients with chronic venous insufficiency, so in these patients any topical preparation must be used carefully [4]. There is a lack of evidence of the positive effects of topical antimicrobials in the healing of venous ulcers [31].

6.4. Periulcer skin management

It is important to keep the periulcer skin healthy to provide improvement in venous ulcers. Management of dermatitis and other abnormalities in periulcer skin accomplishes other therapy strategies in venous ulcers [31]. As mentioned above, contact dermatitis related to topical agents and dressings used in the treatment of venous ulcers are very common. In severe contact dermatitis, a short term of systemic steroids may be needed [4, 31]. Skin lubricants will be helpful in the terms of dermatitis in the calf and ankle due to venous hypertension [31]. Care of the periulcer skin will improve the venous wound healing; therefore, it is necessary to recognize the abnormalities in this area and start the appropriate treatment.

6.5. Dressing

Several types of wound dressings including gauzes, films, gels, foams, hydrocolloids, alginates, hydrogels, and other polymers are being used beneath compression bandages. Some of the dressings show biological activity on its own, while some provide the release of bioactive constituents. Different types of wound dressings such as hydrogels, hydrocolloids, foams, films, and wafers may comprise of antimicrobials, anti-inflammatory agents, analgesics, growth factors, and proteins, which would be useful in different problems of wound healing [78, 79]. During the choice of the wound dressing type, features of the ulcer should be considered and the mostly desired function of the dressing (such as cleaning, absorbing, regulating, creating a moist environment, and the possibility of adding medication, protecting the periulcer skin) should be decided [80]. Of course, the patient's needs and cost-effectiveness are other factors affecting the dressing choice [81]. The optimal wound dressing should absorb the exudate and also maintain a moist, warm wound bed and protect the periulcer skin [31, 76]. Routine use of topical antimicrobial dressings is not recommended [31]. While using wound dressings, risk of allergy should be kept in mind in venous ulcers. In conclusion, topical wound dressings are recommended as a part of the standard therapy in venous ulcers [31].

6.6. Compression

Compression therapy remains the mainstay treatment of venous leg ulcers [76]. Compression is a kind of mechanical therapy, which is simply based on applying pressure to the limb [31]. There is a significant improvement in ulcer healing and reduction in recurrence rates with an appropriate compression therapy [4, 82]. Compression therapy corrects the venous hypertension by improving venous pumping function and lymphatic drainage [83]. And as a result of

compression, local hydrostatic pressure increases and superficial venous pressure decreases; thus, the edema dissolves resulting in cutaneous blood flow increase [83]. Other effects of compression therapy are clinical improvement in lipodermatosclerotic skin through lymph propulsion along with the increase in lymph transport and fibrinolysis [4]. Besides the mechanical effect, compression reduces the release of macromolecules into the extravascular space, some of which play role in wound healing [84].

Various types of devices have been used for compression therapy, such as different types of bandages, bandage systems, ready-to-use garments, and several pneumatic devices [31]. It is thought that an external pressure of 35–40 mm Hg at the ankle is necessary to overcome venous hypertension [85]. For acute disease, reducing edema and improving the healing process, inelastic or rigid bandages as well as elastic and multilayered bandages are suggested. The bandage system should have high pressures when the patient walks (working pressure) and low pressure when the patient is on rest (resting pressure). Traditional Unna boot, a moist zinc-impregnated paste bandage, is a prototype of this system [83, 86]. Modified Unna boots (short-stretch bandages) have the same properties. Their stable shape despite the volume changes in leg secondary to edema reduction, unpleasant odor due to wound exudate, and potential development of contact dermatitis are the limiting factors of Unna boots' use [76, 77]. After edema reduces, long-stretch bandages are beneficial as they provide appropriate working pressure and higher resting pressure. Its easy use and providing of frequent dressing changes make the elastic compression bandages practical. Covering the leg by overlapping the bandage between turns will produce a multilayer bandage. Different components of bandages may be applied at each layer. While this application increases the pressure and also makes the final multilayer bandage less elastic and more stiff due to the friction between the surfaces of each bandage [31], intermittent pneumatic compression (IPC) pumps are also used. These devices consist of plastic air chambers, encircling the lower leg. As the air chamber fills to a preset pressure then deflated. With this system, compression of the leg is provided periodically [87].

Although compression therapy is known to be effective in both healing of venous ulcers and prevention of recurrent ulcers, there is still no optimized compression method [31, 88].

6.7. Adjuvant therapies

Systemic pharmacotherapy may be useful as an adjuvant therapy in venous ulcers. Most of the systemic agents used as adjuvant therapy acts in mechanism of one or more points in the pathophysiology of venous leg ulceration.

6.7.1. Pentoxifylline

Pentoxifylline, an antifibrinolytic agent, is thought to promote wound healing as an adjunctive therapy. Pentoxifylline has been shown to play role in microcirculation by promoting leukocyte migration, reducing platelet aggregation and fibrinogen levels, decreasing plasma viscosity, stimulating collagenase production, and blocking the effects of tumor necrosis factor-alpha on fibroblasts [89, 90]. Pentoxifylline may act in venous ulcer healing through the effects of cytokine production [91]. The conventional dose of pentoxifylline in venous leg ulcers is 400

mg three times a day. But recently, it has been proposed that the use of pentoxifylline 800 mg three times a day is more effective in venous ulcer healing. The main side effects reported were gastrointestinal disturbances such as nausea, indigestion, and diarrhea [89, 92, 93]. In studies, pentoxifylline has shown to be an effective adjuvant to compression therapy in venous leg ulcers. According to a Cochrane review, pentoxifylline plus bandaging is more effective than compression plus placebo and pentoxifylline may even be effective in the absence of compression [93].

6.7.2. Aspirin

There is currently insufficient evidence for the effectiveness of aspirin in venous leg ulcers [94]. The use of acetylsalicylic acid as an adjunct for the treatment of venous ulcers has been evaluated in one pilot study and one randomized controlled trial to date. The effect of aspirin in venous ulcers is through its irreversible inhibition of cyclooxygenase, resulting in reduction in thromboxane A2 implicated in platelet aggregation [95].

6.7.3. Split-thickness skin grafting

There are no specific indications for skin grafting of the ulcers of lower extremities [4]. Surgical treatment should only be considered in patients with venous ulcers that do not heal with conservative therapies [96]. Autografts, allografts, or human skin equivalents can be used, with a resulting healing rate of 73% [97]. In venous ulcers, skin grafting can also be followed by additional treatment to accelerate healing. The outcomes of the split-thickness skin grafting in venous ulcers vary in different studies [31]. There is still lack of evidence in the routine use of split-skin thickness skin grafting.

6.7.4. Negative pressure therapy

Negative pressure wound therapy (NPWT) is currently used widely in wound care and is promoted for use on wounds. In this system, a wound dressing is applied to the wound, to which a machine is attached. The negative pressure (or vacuum) that the machine applies sucks any wound and tissue fluid away from the treated area into a canister.

The evidence is insufficient in clinical effectiveness of NPWT in the treatment of leg ulcers. It is thought to be effective in wound healing through providing excess drainage, promoting angiogenesis, and decreasing the bacterial load of the wound [98]. There is some positive evidence that the treatment may reduce time to healing as part of a treatment, tissue granulation, area and volume reduction have also been reported. NPWT is not suggested as a primary treatment for venous leg ulcers [31, 99].

6.7.5. Cellular therapy

In recent years, cellular and/or tissue-derived products (CTPs) such as extracellular matrix (ECM; OASIS®) [100], human skin equivalent (HSE; Apligraf®) [101–103], and living skin equivalent (LSE; Dermagraft®) [104–107] have been explored as alternative therapeutic options.

Studies investigating the effects of CTPs are applied to the wounds that have been stuck in the inflammatory phase. CTPs provide the healing by supplying various biological factors, reducing levels of unnecessary cytokines or enzymes (such as matrix metalloproteinases), and/or forming a temporary ECM (which results in granulation) [108].

Recently, Apligraf, an allogeneic bilayer cellular therapy, has been approved by FDA for use in venous ulcers [31]. Before the application of cellular therapy, appropriate wound bed preparation, including the removal of debris and any necrotic tissue, should be done. The application of the graft is recommended to be done with a period of 1–3 weeks with observations of effectiveness before reapplication is considered. And reapplication is recommended as long as the venous ulcer continues to respond to the therapy [31]. In patients with venous leg ulcers who have failed with standard therapy for 4–6 weeks, cultured allogeneic bilayer skin replacements should be used [31].

Even though cellular treatments are initially more expensive, it may be more effective and less costly in the long term in chronic venous ulcers [109].

6.7.6. Tissue matrices, growth factors, human tissues, or other skin substitutes

In chronic wounds, human tissue (amniotic membrane, cryopreserved skin) or animal tissue (bladder, fetal bovine skin, others) constructs are being used. Growth factors or some other molecules, the tissues contain, may support healing process [110].

Granulocyte macrophage-colony stimulating factor (GMCSF) is a growth factor that has stimulatory effects on keratinocyte proliferation and endothelial cell and fibroblast differentiation [111]. In some studies, both intradermal injections of GM-CSF and topical application of GM-CSF have been shown to be effective in healing rates of venous ulcers [98]. But, injection site and bone pain can limit the intradermal use of GM-CSF [98].

Small intestine submucosa (SIS, Oasis®) is a biomaterial derived from porcine SIS that acts as an extracellular matrix. It is composed of Type I, III, IV, and V collagen, glycosaminogylcans, proteoglycans, proteoglycans, fibronectin, and growth factors [98, 112]. Successful results have only been reported in studies of using porcine small intestinal submucosa in venous leg ulcers [100]. It has been approved by FDA for use in wounds including venous leg ulcers. Use of porcine small intestinal submucosa tissue construct in addition to compression therapy for the treatment of venous leg ulcers is only suggested in patients who did not respond to the standard therapy for 4–6 weeks [31]. It was shown to be well tolerated and nontoxic and did not induce an adverse immunological reaction even in patients given repeated applications.

6.7.7. Therapeutic ultrasound

Ultrasound has been used as a therapeutic tool for nearly 50 years [113]. Recently, ultrasound therapy has been applied for the treatment of chronic wounds in some centers [114]. Although high-frequency ultrasound (HFU) (1–3 MHz) has been shown to promote healing of some injuries [115, 116], it has some disadvantages such as, burns or endothelial injury. However, in some studies low-dose application of ultrasound has been reported to be more successful than

high-dose ultrasound in the treatment of skin wounds [117]. Thus, noncontact ultrasound therapy is among the newer modalities. Use of lower frequency (40 kHz) ultrasound in wound management was approved by the FDA in 2004 [118]. Low-frequency ultrasound therapy provides wound healing via the production, vibration, and movement of micron-sized bubbles in the coupling medium and tissue. The healing process improves by the reduced bioburden, increased angiogenesis, stimulated cellular activity, and the removal of necrotic tissues [119]. Additional studies are necessary to determine standardized protocols of therapeutic ultrasound in venous ulcers treatment. Routine use of ultrasound therapy in venous ulcer management is not suggested [31].

6.8. Surgical management

Surgical procedures are often applied when dressings and compression therapies fail in the venous ulcer treatment [76]. There are two approaches in surgical treatment of venous ulcers: ameliorating the cause of the ulcer and treating the ulcer itself by surgical procedures [4].

Superficial venous insufficiency is present in about forty to fifty percent of patients with venous ulcer [2]. Superficial vein surgery, simply comprised of ligation or sclerosis of the long and short saphenous systems, with or without communicating vein ligation or sclerosis, may be useful in patients with superficial venous insufficiency but only when deep veins are competent [120]. Although superficial vein surgery does not affect the success of improvement in venous ulcers, ulcer recurrence has shown to be reduced by the procedure [120]. Subfascial endoscopic perforating vein surgery, a new surgical technique, has proven to be effective in patients with perforator vein insufficiency [8]. In this technique, perforator veins are ligated by an endoscopic camera system through a small incision. This procedure has low complication rates and morbidity [121]. As mentioned above, it has been shown that venous surgery does not seem to improve the healing but delays or reduces the recurrences [76].

Radical excision of the diseased area including the whole ulcer bed, the fibrotic suprafascial tissues, and the abnormal superficial and perforating veins, and flapping this large soft tissue defect have been shown to be successful in a few cases. However, highly invasive character of this procedure limits its application [122].

Skin grafting has proven beneficial to heal large-size recalcitrant ulcers [120]. Contamination with microorganisms and risk of trauma are the main factors that should be kept in mind when grafting for ulcer [123]. Split-thickness skin grafts, punch grafting, and meshed grafts are some of the grafting methods used in venous leg ulcers. While pinched grafts are suitable for small ulcers, meshed grafts are useful for large highly exudative ulcers [4].

6.9. Prevention

In the period that patient has no venous ulcers, it is important to keep in cooperation with and offer some simple lifestyle changes to the patient. Leg elevation is thought to provide venous return, reduce edema, and improve cutaneous circulation [98]. Elevation of the legs above heart level for 30 minutes three or four times a day is a simple and effective method in reducing edema and improving the cutaneous microcirculation in patients with chronic venous

insufficiency [87]. Calf muscle pump dysfunction is usually present in venous insufficiency and venous ulcers. Appropriate calf exercise regimes have shown to be useful to improve muscular endurance and may even provide proper functioning of the muscle pump [124]. Even in the first stages of chronic venous disease, starting the effective treatment of symptoms will help for preventing progression to ulcer. The most important step is to persuade the patient, with risk factors or early signs of venous insufficiency, to apply the appropriate compression. It is important to make the patients understand that compression therapy will be a lifelong therapy. The elastic bandages with the appropriate length and strength of compression must be worn daily. Moreover, weight management of obesity, regular exercise programs (with the aim of improving the efficiency of calf muscle pump), and treatment of varicosities (endovenous laser ablation, radiofrequency ablation, and other approaches to repair veins and valves) should be planned. Thrombophilia is increasingly recognized as a major risk factor for DVT, which is the most common identifiable risk factor for the development of chronic venous ulcer. More than 40% of patients with CVU have at least one thrombophilia and chronic venous ulcer patients with post-thrombotic disease are shown to have lower response rates to medical and surgical therapy. Thrombophilia screening is suggested to be performed in patients who have venous ulcer before the age of 50 to stratify the thrombotic risk and start the appropriate prophylactic and therapeutic management. Good nutrition is important in venous ulcer patients as protein deficiency is associated with impaired wound healing. Also smoking affects healing via decreasing the fibroblast proliferation [76]. All these factors together will help to prevent the progression of chronic venous disease to ulceration. Commitment to lifelong exercise programs, weight control, and protection against skin injury is necessary for the prevention of venous leg ulcers [31, 125].

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