Hindawi Publishing Corporation
Ulcers
Volume 2013, Article ID 413604, 9 pages
http://dx.doi.org/10.1155/2013/413604

Review Article

Chronic Leg Ulcers: Epidemiology, Aetiopathogenesis, and Management

Shubhangi Vinayak Agale

Department of Pathology, Grant Govt Medical College, Byculla, Mumbai 400008, India

Correspondence should be addressed to Shubhangi Vinayak Agale; shubhagale@hotmail.com

Received 18 November 2012; Revised 24 March 2013; Accepted 3 April 2013

Academic Editor: Marco A. C. Frade

Chronic leg ulcer is defined as a defect in the skin below the level of knee persisting for more than six weeks and shows no tendency to heal after three or more months. Chronic ulceration of the lower legs is a relatively common condition amongst adults, one that causes pain and social distress. The condition affects 1% of the adult population and 3.6% of people older than 65 years. Leg ulcers are debilitating and greatly reduce patients' quality of life. The common causes are venous disease, arterial disease, and neuropathy. Less common causes are metabolic disorders, hematological disorders, and infective diseases. As many factors lead to chronic lower leg ulceration, an interdisciplinary approach to the systematic assessment of the patient is required, in order to ascertain the pathogenesis, definitive diagnosis, and optimal treatment. A correct diagnosis is essential to avoid inappropriate treatment that may cause deterioration of the wound, delay wound healing, or harm the patient. The researchers are inventing newer modalities of treatments for patients with chronic leg ulceration, so that they can have better quality life and reduction in personal financial burden.

1. Introduction

Chronic leg ulcer (CLU) also known as chronic lower limb ulcer is a chronic wound of the leg that shows no tendency to heal after 3 months of appropriate treatment or is still not fully healed at 12 months [1]. The incidence of ulceration is rising as a result of the ageing population and increased risk factors for atherosclerotic occlusion such as smoking, obesity, and diabetes. Ulcers can be defined as wounds with a "full thickness depth" and a "slow healing tendency". Ulcers of skin can result in complete loss of the epidermis and often portions of the dermis and even subcutaneous fat [2]. Chronic ulceration of the lower legs is a relatively common condition amongst adults, and ulcer symptoms usually include increasing pain, friable granulation tissue, foul odor, and wound breakdown instead of healing. This results in social distress and considerable healthcare and personal costs [3, 4]. Since numerous factors lead to lower leg ulceration, it is essential that health professionals adopt an interdisciplinary approach to the systematic assessment of the individual in order to ascertain the pathogenesis, a definitive diagnosis, and optimal treatment required. A correct diagnosis is essential to avoid inappropriate treatment that may delay wound healing, cause deterioration of the wound, or harm the patient.

CLU is reported to have impact on virtually every aspect of daily life: pain is common, sleep is often impaired, mobility and work capacity tend to be restricted, and personal finances are often adversely affected. It is also known that social activities are restricted due to fear of injury and negative body image. CLU is usually associated with significant morbidity, high cost of healthcare, loss of productivity, and reduced quality of life [1–12].

2. Epidemiology

Chronic leg ulcers affect 0.6–3% of those aged over 60 years, increasing to over 5% of those aged over 80 years. CLU is a common cause of morbidity, and its prevalence in the community ranges from 1.9% to 13.1% [6]. It is thought that the incidence of ulceration is rising as a result of aging population

and increased risk factors for atherosclerotic occlusion such as smoking, obesity, and diabetes. In the course of a lifetime, almost 10% of the population will develop a chronic wound, with a wound-related mortality rate of 2.5% [4].

According to the Wound Healing Society, about 15% of older adults in the US suffer from chronic wounds, including predominantly venous stasis ulcers, pressure ulcers (bedsores), and diabetic (neuropathic) foot ulcers. Every year 2 to 3 million more Americans are diagnosed with various types of chronic wounds [7]. Estimate of annual incidence of leg ulcer in the UK and Switzerland are 3.5 and 0.2 per 1000 individuals, respectively. The prevalence of vascular ulcer in the US is estimated at 500,000 to 600,000 and increases with age [8, 9].

According to the study in Ireland the prevalence was 0.12% but it was 1.03% in the patients aged 70 years and over. Women were twice as likely to be affected. Venous disease accounted for 81% of ulcers and arterial disease for 16.3%, while ulceration due to diabetic neuropathy and rheumatoid vasculitis was unusual. Leg ulcers are an important source of morbidity in our ageing population [10].

In Brazil, a study conducted in Botucatu, São Paulo, reported a 35.5% prevalence of varicose veins and 1.5% prevalence of severe chronic venous insufficiency with an ulcer or ulcer scar [11]. The peripheral artery disease, the circulatory disease commonly associated with nonhealing wounds, affects about 8 million Americans and 12–20% of Americans of age group 65–72 years. It is estimated that there are over 7.4 million pressure ulcers in the world where estimation was possible, that is, excluding the vast number of developing countries [12].

In Western Australia (WA) in 1994, leg ulcers were found to affect 1.1 per 1000 population (0.11% point prevalence). This study demonstrated that 24% of the ulcers were present for 1 year, 35% had a problem of ulceration for 5 years, 20% had experienced 10 or more episodes of ulceration, and 45% of sufferers were housebound [13].

According to a study carried out in Germany, venous insufficiency was the dominating causative factor in 47.6% and arterial insufficiency in 14.5%, and 17.6% of ulcers were due to combined arterial and venous insufficiency. Rarer causes included vasculitis (5.1%), exogenous factors (3.8%), and pyoderma gangrenosum (3.0%) [14].

While there are few Indian studies on the epidemiology of chronic wounds, one study estimated the prevalence at 4.5 per 1000 population. The incidence of acute wounds was more than double at 10.5 per 1000 population [15].

According to data from epidemiological studies, the incidence of chronic ulcers in surgically hospitalized patients in China is 1.5% to 20.3%. In one study, of the 580 wound areas in 489 patients, 366 or 63% were ulcers on the lower extremities [16, 17].

The period prevalence of leg ulcers in New Zealand has been estimated at 79 per 100,000 per year, although capture-recapture analysis suggests a more accurate estimation, which is between 393 and 839 per 100,000 per year [18]. Prevalence of leg ulceration increases dramatically with age, although ulcers can occur in quite young people and there are records of people suffering with venous ulcers for up to 60 years.

Table 1: Causes of leg ulcers [21].

Vascular	Venus
	Arterial
	Mixed
Neuropathic	Diabetes
	Tabes
	Syringomyelia
Metabolic	Diabetes
	Gout
	Prolidase deficiency
Haematological	Sickle cell disease
	Cryoglobulinemia
Trauma	Pressure
	Injury
	Burns
Tumors	Basal cell carcinoma
	Squamous cell carcinoma
Infection	Bacterial
	Fungal
	Protozoal
Panniculitis	Necrobiosis lipoidica
	Fat necrosis
Pyoderma	Gangrenosum
Special	Hypertensive ulcer

3. Aetiopathogenesis

It has been reported that ulcers related to venous insufficiency constitute 70%, arterial disease 10%, and ulcers of mixed etiology 15% of leg ulcer presentations [19]. The remaining 5% of leg ulcers result from less common pathophysiological causes, and this latter group comprise considerable challenges in diagnosis, assessment, and management [20].

In the Western world, leg ulcers are mainly caused by venous insufficiency, arterial insufficiency, neuropathy, diabetes, or a combination of these factors (Table 1) [21]. Venous ulcers are the most common type of leg ulcers, accounting for approximately 70% of cases. Arterial disease accounts for another 5% to 10% of leg ulcers; most of the others are due to either neuropathy (usually diabetic) or a combination of those diseases [21, 22]. The study from India shows that etiology of chronic wounds included systemic conditions such as diabetes, atherosclerosis, tuberculosis, and leprosy. Other major causes included venous ulcers, pressure ulcers, vasculitis, and trauma. The study report stated that inappropriate treatment of acute traumatic wounds was the most common cause of the chronic wound [15]. Chinese study shows that the principle etiology (67%) of ulceration is trauma or traumatic wounds compounded by infection. Diabetic ulcers, venous ulcers, and pressure ulcers accounted for 4.9%, 6.5%, and 9.2%, respectively. The majority of these wounds were seen in farmers and other agricultural workers [16, 17].

It is useful to divide leg ulcers into those occurring in the gaiter area and those occurring in the forefoot because

the aetiologies in these two sites are different. At least two aetiological factors can be identified in one third of all lower limb ulcers. Venous ulcers most commonly occur above the medial or lateral malleoli. Arterial ulcers often affect the toes or shin or occur over pressure points. Neuropathic ulcers tend to occur on the sole of the foot or over pressure points [23, 24].

Patients with reduced mobility or obesity may develop ulceration in the gaiter area because of venous hypertension resulting from inadequate functioning of the calf muscle pump. The commonest causes of vasculitis ulcers are rheumatoid arthritis, systemic lupus, and polyarteritis nodosa. The blood dyscrasias that most commonly lead to leg ulceration are sickle-cell disease, thalassaemia, thrombocythaemia, and polycythaemia rubra vera [23]. Other hematological disorders associated with the development of leg ulcers include leukaemia, hereditary spherocytosis, thrombotic thrombocytopenic purpura, granulocytopenia, and polyclonal dysproteinaemia [6]. Leg ulcers related to hematological disorders generally result from microcirculatory occlusion [25].

Microcirculatory and vascular disorders that can result in atypical leg ulceration include Raynaud's phenomenon, Martorell's ulcers, and cutaneous vasculitis. There are numerous disorders that can result in neuropathy of the lower legs and associated ulceration due to insensate injury, burns, or pressure ulcers, for example, leprosy, alcoholic neuropathy, and tabes dorsalis [6].

According to a recent report, chronic kidney disease (CKD), hypertension, and myocardial ischemia may also be associated with increased risk of developing foot ulcers including severe ulcers that necessitate amputation. Additionally, there are reports of higher rates of malnutrition and deficiencies of vitamins and minerals such as zinc in patients with chronic venous leg ulcers compared to the general population [5].

4. Pathogenesis of Chronic Leg Ulcers

4.1. Venous Ulcers. The association between ulceration at the ankle and venous disorders of the lower limbs has been known for more than 2000 years. Venous circulation of the lower extremities progresses from the superficial to perforating to deep veins, with valves in each system to ensure unidirectional blood flow. As the calf muscles contract, the pumping action causes the blood to flow from the deep veins into the inferior vena cava. Disease of these pathways results in venous insufficiency. Venous insufficiency is the most common cause of lower-leg ulcers, accounting for nearly 80% of all cases. Of the approximately 7 million people in the United States with venous insufficiency, approximately 1 million develop venous leg ulcers [25]. Approximately 1% of the population will suffer from leg ulceration at some point in their lives. Chronic venous leg ulceration has an estimated prevalence of between 0.1% and 0.3% in the United Kingdom. Prevalence increases with age. The overall prevalence of venous ulcers in the United States is approximately one percent. Venous ulcers are more common in women and older persons. The primary risk factors are older age, obesity, previous leg injuries, deep venous thrombosis, and phlebitis. Venous ulcers are often recurrent, and open ulcers can persist from weeks to many years. Severe complications include cellulitis, osteomyelitis, and malignant change [26]. Patients who develop chronic venous ulcer before their 50th birthday appear to represent a distinct group in terms of aetiology, natural history, and prognosis.

In venous disease, ulcers are usually located in the gaiter area between the ankle and the calf, often on the medial aspect of the leg. Venous ulcers arise from venous valve incompetence. Valvular incompetence in the deep veins causes the vessels to become distended and stretch to accommodate the additional blood flow. The valves are not able to effectively close, which results in retrograde blood flow and venous hypertension [27]. The venous hypertension, leads to leakage of fluid out of the stretched veins into the tissues, causing deposition of a brownish/red pigment in the gaiter area of the leg. Venous ulceration occurs in the gaiter area in 95% of cases especially around the malleolar (the rounded protuberances on the ankle) region [28]. Veins can be damaged by surgery, trauma, or DVT, which causes a backflow of blood in the venous system at the point of damage. Other causative factors include multiple pregnancies, obesity, congenital vein abnormalities, and varicose veins.

Another factor that influences the development of venous leg ulcers is calf muscle pump failure. Calf pump failure arises from paralysis, immobility, sleeping in a chair with legs dependant for long periods of time, and fixed ankle joints. The calf muscle, through contraction and relaxation, aids in the flow of blood back to the heart through the veins. Failure of this mechanism causes stasis of blood and increased venous pressure [29].

There are three major theories of how ulceration develops. (1) Fibrin cuff theory: fibrinogen leaks from dilated capillaries of the epidermis forming a pericapillary fibrin cuff. This is then responsible for a reduced diffusion of oxygenated blood to the tissues resulting in ulceration. (2) Leukocyte entrapment theory: venous hypertension reduces the pressure gradient between the arteriolar and venular end of the capillaries. This results in sluggish movement of the blood within these capillaries and increases the adherence of blood cells to the endothelium. Inflammatory mediators (ICAM-1, VCAM-1) and reactive oxygen species are then released resulting in the obliteration of functioning capillary loops aggravating ischemia and result in ulceration. (3) Microangiopathy theory: it has been demonstrated that some of the capillaries in patients with venous leg ulcers are occluded by microthrombi or exhibit long intracapillary stasis. This in turn can reduce nutrition and oxygenation of the skin, predisposing to ulceration [30].

Venous ulceration is a chronic disease, which is characterized by periods of exacerbation and remission. Venous ulcers often take a long time to heal, which results in physical and psychological discomfort and negatively affects a patient's functional status [11].

4.2. Arterial Ulcers. Arterial leg ulcers occur as a result of reduced arterial blood flow and subsequent tissue perfusion [31]. Arterial or arteriolar occlusion due to any cause can

result in ischemia of the skin and subcutaneous tissues which might lead to ulceration. Peripheral vascular disease due to atherosclerosis, diabetes with microvascular or macrovascular disease, and/or vasculitis could lead to ischemic leg resulting in ulceration [30, 31]. A reduction in blood supply causes death of tissue in the area being fed by the affected artery. Ulcer development is often rapid with deep destruction of tissue. The limb looks pale, and there is a noticeable lack of hair.

There are three mechanisms involved in the pathophysiology of ischemic leg ulcer: (1) extramural strangulation (2) mural thickening or accretion, and (3) intramural restriction of blood flow. There is often considerable overlap, and the exact pathogenesis cannot be always well defined. Most acute forms of vasculitis and some subacute and chronic forms are likely to cause leg ulceration due to tissue hypoxia and exudation of fibrin-like substances [17].

Arterial ulceration typically occurs over the toes, heels, and bony prominences of the foot. The ulcer appears "punched out" with well-demarcated edges and a pale, nongranulating, and necrotic base [31].

4.3. Diabetic Foot Ulcer. Diabetic foot ulcers are common and estimated to affect 15% of all diabetic individuals during their lifetime. For instance, an estimated 18% of diabetic patients over the age of 65 in the US have nonhealing foot ulcers [7]. It is now appreciated that 15–20% of patients with such foot ulcers go on to need an amputation. Almost 85% of the amputations are preceded by diabetic foot ulcers [32]. Worldwide, it is estimated that a lower limb is lost every 30 seconds as a result of diabetic wound infection [7].

Diabetic patients are at higher risk for arterial diseases and neuropathy, therefore, can develop ulcers due to both entities. In addition, hyperglycemia poses the risk of ulcers secondary to neuropathic impairment of sensory, motor, and autonomic function, typically in the hand and foot, or "stocking and glove" distributions [24]. The etiology of diabetic foot ulcers usually has many components [33]. The major underlying causes are noted to be peripheral neuropathy and ischemia from peripheral vascular disease. Other factors in ulceration are trauma, deformity, callus formation, and edema [32, 33].

4.4. Pressure Ulcer. Pressure ulcers are, as their name implies, caused primarily by unrelieved pressure. They usually occur over bony prominences such as the sacrum or the heel but can occur on any part of the body subjected to pressure. Approximately 70% of all pressure ulcers occur in the geriatric population. Pressure ulcers can be a major source of infection and lead to complications such as septicemia, osteomyelitis, and even death. Prevention of pressure damage to the skin and the underlying tissue is an essential part of treatment in at-risk patients [1].

5. Management of Chronic Leg Ulcers

An ideal management plan for patients with chronic leg ulcers should involve an early strategic and coordinated approach to delivering the correct treatment option for each individual patient, based on accurate assessment of the underlying pathophysiology [34].

Table 2: Assessment of lower limb ulcers [24, 34].

Patient	History of ulcer development
	Past and current medical problems
	General health status
	Nutrition
	Social, occupation
	Mobility problem
	Limitations to self care
	Obesity
Skin changes	Arterial
	Malignant
	Autoimmune
Vascular assessment	Pedal pulses
	Ankle Brachial Pressure Index
Limb factors	Oedema
	Circumferences
	Lymphoedema
	Orthopaedic problems
	Sensation and pain
Ulcer	Site-venous, arterial, pressure
	Appearance
	Size-measure
	Wound base
	Exudate level
	Surrounding skin

The management of leg ulcers should include a detailed history of the onset of the problem, examination of the legs and skin, investigations, and modalities of treatments. Successful management of leg ulcers requires a clear diagnosis, establishment of a treatment plan, accurate monitoring, and adherence to the plan as the ulcer decreases in size. Education and training is vital for all those involved in caring for patients with chronic ulceration.

5.1. Clinical Assessment

5.1.1. History. The first step toward diagnosis of any leg ulcer is to compile a comprehensive history and assessment of the patient (Table 2) [35]. This should include general health status, social and occupational situation, past and current medical history of relevant diseases (such as deep vein thrombosis, diabetes, autoimmune disorders, inflammatory bowel disease, and connective tissue disease), condition of the skin, current vascular status, limb size and shape, and history and status of the ulcer [35]. The patient should be asked about lower extremity pain, paresthesia, anesthesia, and claudication [24]. It is important to determine the duration of ulceration and whether it is a first episode or recurrent. Pain is a major problem for patients with leg ulcers unless there is

Table 3: Assessment of leg ulcers: The difference between venous and arterial disease [29].

Assessment criteria	Venous disease	Arterial disease
Presenting history, physical and social risk factors	Previous history of DVT Varicose veins Reduced mobility Traumatic injury to the lower leg Obesity Pregnancy Nonhealing ulceration Recurrent phlebitis Previous vein surgery	Diabetes Hypertension Smoking Previous history of vascular disease Obesity Inability to elevate limb
Position of ulceration	Gaiter area of the leg Common site is medial aspect	Lateral malleolus and tibial area are common sites as well as toes and feet Over pressure points
Pain	Throbbing, aching, and heavy feeling in legs Improves with elevation and rest	Intermittent claudication Can be worse at night and at rest Improves with dependency
Ulcer characteristics	Shallow with flat margins Often presents with slough at the base with granulation tissue Moderate to heavy exudate	Punched out, occasionally deep Irregular in shape Unhealthy appearance of wound bed Presence of necrotic tissue or fixed slough Low exudate unless ulcers infected
Condition of the lower leg	Haemosiderin staining Thickening and fibrosis Dilated veins at the ankle Crusty, dry, and hyperkeratotic skin Eczematous, itchy skin Pedal pulses present Normal capillary refill (less than three seconds) Limb edema is common	Thin, shiny, and dry skin Reduced or no hair on lower leg Skin feels cooler to touch Pallor on leg elevation Absence or weak pedal pulses Delayed capillary refill (greater than three seconds) Development of gangrene

a neuropathic component. Lack of pain, therefore, suggests a neuropathic aetiology. Patients should also be asked about their mobility [23].

Clinical course of the ulcer can suggest its etiology. Possible considerations to rule out include diabetes; hypertension; hyperlipidemia; coronary artery disease; alcohol and tobacco use; thyroid, pulmonary, renal, neurologic, and rheumatic diseases; peripheral vascular disease; deep vein thrombosis; specifically cutaneous factors including cellulitis, trauma, and recent surgery [24].

5.1.2. Examination. The examination of the leg should include palpation of pulses and a search for the signs of venous hypertension, including varicose veins, haemosiderin pigmentation, varicose eczema, atrophie blanche, and lipodermatosclerosis. The range of hip, knee, and ankle movement should be determined, and sensation should be tested to exclude a peripheral neuropathy [23].

The ulcer examination should include site, size, appearance, wound base, exudates level, and surrounding skin (Table 2) [35]. The surrounding region should be examined for pain, edema, erythema, warmth, induration, discoloration, maceration, dryness, scarring from previous wounds, hair pattern, gangrenous digits, clubbing, cyanosis, capillary refill, and varicose veins. It is important to bear in mind that venous and arterial disease may coexist in the same patient [24].

The venous ulcers considerably differ from arterial ulcers (Table 3) [29] and other ulcers of lower extremity (Table 4) [26]. An irregular ulcer border, black necrosis, erythema, or bluish or purple discolorations of adjacent skin are suggestive for ulcer due to vasculitis [2]. A painful leg ulcer with violaceous borders suggests pyoderma gangrenosum.

Investigations. (1) The Ankle Brachial Pressure Index (ABPI) using a handheld Doppler ultrasound and sphygmomanometer can be carried out for more accurate assessment of arterial perfusion. The results are used to determine the likelihood of arterial insufficiency and can be used to guide the management plan (Table 5) [28].

When Doppler tests indicate arterial insufficiency, arterial duplex ultrasonography will (noninvasively) provide accurate anatomic and haemodynamic information on the site and extent of the arterial disease [34]. When indicated, further detailed anatomic information for treatment planning can be obtained from magnetic resonance angiography, computer tomographic angiography, or digital subtraction angiography [34].

(2) Accurate and regular measurement of the wound is important to give an objective assessment of the effectiveness of the current management plan. The Leg Ulcer Measurement Tool (LUMT) is a validated tool that has been developed to quantify leg ulcer assessment and can be used to track change in wound status over time [36].

Table 4: Common lower extremity ulcers [25, 26].

Ulcer type	General characteristics	Pathophysiology	Clinical features
Venous	Most common type; women affected more than men; often occurs in older persons	Venous hypertension	Shallow, painful ulcer located over bony prominences, particularly the gaiter area (over medial malleolus); granulation tissue and fibrin present Associated findings include edema, venous dermatitis, varicosities, and lipodermatosclerosis
Arterial	Associated with cardiac or cerebrovascular disease; patients may present with claudication, impotence, and pain in distal foot; concomitant with venous disease in up to 25 percent of cases	Tissue ischemia	Ulcers are commonly deep, located over bony prominences, and round or punched out with sharply demarcated borders; yellow base or necrosis; exposure of tendons Associated findings include abnormal pedal pulses, cool limbs, femoral bruit, and prolonged venous filling time
Neuropathic	Most common cause of foot ulcers, usually from diabetes mellitus	Trauma, prolonged pressure	Usually occurs on plantar aspect of feet in patients with diabetes, neurologic disorders, or Hansen disease
Pressure	Usually occurs in patients with limited mobility	Tissue ischemia and necrosis secondary to prolonged pressure	Located over bony prominences; risk factors include excessive moisture and altered mental status

Table 5: ABPI symptoms: management correlation guide [28].

Index	Symptoms	Severity of disease	Management
>0.8–0.95	None/mild intermittent claudication	Mild arterial disease	Modify risk factors, stop smoking, regular exercise, and consider antiplatelet therapy
>0.5–0.8	Intermittent claudication	Moderate arterial disease	As for patients with ABPI between 0.8 and 0.95, together with routine referral to a vascular surgeon. Possible arterial duplex scan/angiogram
>0.3–0.5	Severe intermittent claudication and rest pain	Severe arterial disease	As for patients with ABPI between 0.8 and 0.95, together with urgent referral to a vascular surgeon. Possible arterial duplex scan/angiogram
0.3 or below or ankle systolic pressure of less than 50 mmHg	Critical ischaemia (rest pain for greater than 2 weeks duration) with or without tissue loss (ulcer, gangrene)	Severe arterial disease; risk of losing limb	Urgent referral to the vascular emergency on-call team and possible surgicalor radiological intervention
Abnormally high ABPI (greater than 1.3)	Variable	Vessel calcification	As for patients with ABPI between 0.8 and 0.95, together with referral to avascular surgeon

(3) Blood investigations such as complete blood count, erythrocyte sedimentation rate, blood sugar, lipid profile, renal function tests, and liver function tests are essential in patients with chronic leg ulcers. The plain radiography of the foot along with CT and MRI should be done to rule out osteomyelitis and malignancy.

(4) Laboratory screening tests for vasculitis: urine analysis for proteinuria, hematuria, cylindruria, routine and immunohistopathology of skin biopsies, antinuclear antibodies, rheumatoid factor, complement C4, circulating immune complexes, paraproteins, immunoglobulin fractions, antineutrophil cytoplasmic antibodies, serological tests, and cultures for underlying infections [9].

(5) Laboratory screening tests for clotting disorders: activated partial thromboplastin time, prothrombin time, thrombin time, factor V (Leiden) mutation (506R fi 506Q), factor II (prothrombin) mutation (20210G fi 20210A), antithrombin III, protein C and protein S, and lupus anticoagulant anticardiolipin [9].

(6) Venography may be performed as an investigational procedure prior to valvular surgery. Lower extremities arteriography is indicated in patients with ischemic rest pain, intolerable claudication, impending gangrene, or the presence of nonhealing ulcers of suspected arterial origin [23].

(7) Color duplex ultrasound scanning which is becoming the *de facto* standard for evaluation of venous obstruction is also used to assess the location and extent of reflux in venous ulcers [37].

(8) Plethysmography and venous pressure data are important in determining the need for surgical bypass or valve replacement. Quantitative data on venous obstruction, calf muscle pump ejection fraction, and reflux are provided by air plethysmography, whereas venous pressure studies assess the physiological importance of anatomic obstruction because the collaterals may or may not provide adequate compensation for an obstructed pathway [4].

(9) A quantitative bacterial culture is more specific and should be performed once wound infection is suspected [37]. This is performed by curetting or biopsying the bed of the ulcer. The quantitative biopsy is the current gold standard for assessing the quality and quantity of microbial pathogens within wound [37, 38]. Quantitative biopsies containing greater than 10^5 organisms per gram of tissue are considered significant, and systemic antibiotic therapy should be considered. If osteomyelitis is suspected, representative cultures need to be obtained from the bone or deepest tissue layers [6].

(10) Ulcer biopsy is important in making a correct diagnosis and to rule out malignancy as these ulcers are prone to malignant transformation [39]. This requires taking a deep wedge of tissue from the ulcer edge and can usually be performed under local anesthesia [34]. Chronic ulcers are sometimes biopsied for experimental protocols: (A) to obtain information regarding the wound bed or the wound edge. (B) to grow cells in vitro from nonhealing wound [40].

(11) The clinical application of gene variant analysis and evaluation in patients with venous leg ulcers implies that the high risk minority of patients could be identified in advance by means of a simple blood test that would act as a genetic screening device [41].

Table 6: Treatment options for common leg ulcers [25, 26].

Ulcer type	Treatment options
Venous	Leg elevation, compression therapy, aspirin, pentoxifylline (Trental), surgical management
Arterial	Revascularization, antiplatelet medications, management of risk factors
Neuropathic	Off-loading of pressure, topical growth factors; tissue-engineered skin
Pressure	Off-loading of pressure; reduction of excessive moisture, sheer, and friction; adequate nutrition

5.2. Treatments. The treatment of chronic ulcers of the lower extremities presents a therapeutic challenge. There is clear evidence suggesting that causal treatment should have priority. A comprehensive diagnostic evaluation including vascular, metabolic, and physical aspects as mentioned above is essential at the start of treatment.

The basic principles of treatment are to remove or treat precipitating cause, for example, surgical intervention, to promote circulation and improve venous return, for example, compression therapy, to promote healing, for example, wound care, lifestyle changes, symptom management, and to promote preventative care, for example, health education, current treatments for CLU include surgery, sclerotherapy, compressive therapy (conventional therapy), and adjuvant pharmacotherapy [26]. Vowden [42] has outlined four basic therapeutic strategies that can be employed singularly or in combination to enhance healing and improve outcomes when surgical intervention is not an option. He has also discussed neurovascular interventions such as lumbar sympathectomy or spinal cord stimulation; systemic therapy with hyperbaric oxygen or intervenous therapy with agents such as prostaglandins; local mechanical therapy such as negative pressure wound therapy (NPWT), electromagnetic stimulation or enhanced local oxygen therapy; finally, topical therapy with vaso-active growth factors or tissue-engineered skin products. The various treatment options for different types of ulcers are as shown in Table 6 [25, 26].

5.2.1. Recent Advances in Management. Several researchers are still discovering other modalities of treatment.

(1) The discovery of miRNAs has opened up vast therapeutic opportunities. The knowledge of miRNA function in the regulation of wound healing and developing improved miRNA modulation techniques in the skin will help in translating this knowledge into more effective therapies [43, 44].

(2) The clinical practices could be strongly influenced by the results of the HFE genetic test. The presence of C282Y mutation would strengthen the indications and priorities for surgical correction of superficial venous insufficiency [41].

(3) Chronic wounds are characterized by changes in cell receptors (integrins). The activation or inhibition of integrin receptors by various agents may provide an excellent means of influencing wound healing [45].

(4) Venous leg ulcers can be healed with a spray formulation of allogeneic neonatal keratinocytes and fibroblasts without the need for tissue engineering, at an optimum dose of 0.5×10^6 cells per mL every 14 days [46].

(5) The regenerative medicine is utilizing therapeutic potential of the stem cells to promote skin regeneration. The promise of regenerative medicine lies in the ability to understand and regulate these stem cell populations to promote skin regeneration, and biomaterials will continue to play a central role in regenerative medicine by providing the framework upon which to reconstruct functional niches [47]. Stem cell-based therapies offer tremendous potential for skin regeneration following injury and disease. Functional stem cell units have been described throughout all layers of human skin, and the collective physical and chemical microenvironmental cues that enable this regenerative potential are known as the stem cell niche. Stem cells in the hair follicle bulge, interfollicular epidermis, dermal papillae, and perivascular space have been closely investigated as model systems for niche-driven regeneration. These studies suggest that stem cell strategies for skin engineering must consider the intricate molecular and biologic features of these niches. Innovative biomaterial systems that successfully recapitulate these microenvironments will facilitate progenitor-cell-mediated skin repair and regeneration [47].

(6) According to Frade et al., the natural biomembrane of latex extracted from Hevea brasiliensis proved to be safe as a dressing, for it did not induce hypersensitivity reactions among the volunteers who underwent the patch test or among users of the natural biomembrane, as it was clinically and immunologically demonstrated by IgE levels [48].

The vegetal biomembrane was important for the induction of the healing, especially on the inflammatory stage, confirmed by the abundant exudation and debridement of the ulcers in relation of the control treatment of chronic venous ulcers, which seems to be directly related to the intense vascular formation followed by reepithelialization [49].

(7) Authors report that a 115-aa fragment of secreted Hsp90α (F-5) acts as an unconventional wound healing agent in mice. Topical application of F-5 peptide promoted acute and diabetic wound closure in mice far more effectively than did PDGF-BB [7].

6. Conclusions

An ulcer which is present for more than three months is considered as chronic ulcer. The majority of chronic leg ulcers are caused by venous insufficiency followed by arterial ulcers. A comprehensive assessment of the patient, limb, and ulcer is required to determine etiology and to formulate an appropriate management plan. Management of patients with chronic ulcers has to be multidisciplinary and should include detail history, physical examination, investigations, basic and newer treatment modalities, and educating patients on issues of correct foot care and the importance of seeking early medical advice.

Conflict of Interests

The author declares that there is no conflict of interests.

References

[1] B. Kahle, H. J. Hermanns, and G. Gallenkemper, "Evidence-based treatment of chronic leg ulcers," *Deutsches Ärzteblatt International*, vol. 108, no. 14, pp. 231–237, 2011.

[2] W. B. van Gent, E. D. Wilschut, and C. Wittens, "Management of venous ulcer disease," *The British Medical Journal*, vol. 341, no. 7782, pp. 1092–1096, 2010.

[3] R. V. González-Consuegra and J. Verdú, "Quality of life in people with venous leg ulcers: an integrative review," *Journal of Advanced Nursing*, vol. 67, no. 5, pp. 926–944, 2011.

[4] C. S. Sasanka, "Venous ulcers of the lower limb: where do we stand?" *Indian Journal of Plastic Surgery*, vol. 45, no. 2, pp. 266–274, 2012.

[5] O. Amir, A. Liu, and A. L. S. Chang, "Stratification of highest-risk patients with chronic skin ulcers in a Stanford retrospective cohort includes diabetes, need for systemic antibiotics, and albumin levels," *Ulcers*, vol. 2012, Article ID 767861, 7 pages, 2012.

[6] R. Rayner, K. Carville, J. Keaton, J. Prentice, and X. N. Santamaria, "Leg ulcers: atypical presentations and associated comorbidities," *Wound Practice and Research*, vol. 17, no. 4, pp. 168–185, 2009.

[7] C. F. Cheng, D. Sahu, F. Tsen et al., "A fragment of secreted Hsp90α carries properties that enable it to accelerate effectively both acute and diabetic wound healing in mice," *The Journal of Clinical Investigation*, vol. 121, no. 11, pp. 4348–4361, 2011.

[8] G. A. Rahman, I. A. Adigun, and A. Fadeyi, "Epidemiology, etiology, and treatment of chronic leg ulcer: experience with sixty patients," *Annals of African Medicine*, vol. 9, no. 1, pp. 1–4, 2010.

[9] J. R. Mekkes, M. A. M. Loots, A. C. van der Wal, and J. D. Bos, "Causes, investigation and treatment of leg ulceration," *The British Journal of Dermatology*, vol. 148, no. 3, pp. 388–401, 2003.

[10] J. F. O'Brien, P. A. Grace, I. J. Perry, and P. E. Burke, "Prevalence and aetiology of leg ulcers in Ireland," *Irish Journal of Medical Science*, vol. 169, no. 2, pp. 110–112, 2000.

[11] E. Faria, L. Blanes, B. Hochman, M. M. Filho, and L. Ferreira, "Health-related quality of life, self-esteem, and functional status of patients with Leg ulcers," *Wounds*, vol. 23, no. 1, pp. 4–10, 2011.

[12] C. K. Sen, G. M. Gordillo, S. Roy et al., "Human skin wounds: a major and snowballing threat to public health and the economy," *Wound Repair and Regeneration*, vol. 17, no. 6, pp. 763–771, 2009.

[13] S. R. Baker and M. C. Stacey, "Epidemiology of chronic leg ulcers in Australia," *Australian and New Zealand Journal of Surgery*, vol. 64, no. 4, pp. 258–261, 1994.

[14] A. Körber, J. Klode, S. Al-Benna et al., "Etiology of chronic leg ulcers in 31, 619 patients in Germany analyzed by an expert survey University Clinic," *Journal der Deutschen Dermatologischen Gesellschaft*, vol. 9, no. 2, pp. 116–121, 2011.

[15] V. K. Shukla, M. A. Ansari, and S. K. Gupta, "Wound healing research: a perspective from India," *International Journal of Lower Extremity Wounds*, vol. 4, no. 1, pp. 7–8, 2005.

[16] X. Fu, Z. Sheng, G. W. Cherry, and Q. Li, "Epidemiological study of chronic dermal ulcers in China," *Wound Repair and Regeneration*, vol. 6, no. 1, pp. 21–27, 1998.

[17] X. Fu, "Skin ulcers in lower extremities: the epidemiology and management in China," *International Journal of Lower Extremity Wounds*, vol. 4, no. 1, pp. 4–6, 2005.

[18] A. Jull, N. Walker, V. Parag, P. Molan, and A. Rodgers, "Venous ulcer management in New Zealand: usual care versus guideline recommendations," *New Zealand Medical Journal*, vol. 122, no. 1295, pp. 9–18, 2009.

[19] G. Casey, "Causes and management of leg and foot ulcers," *Nursing Standard*, vol. 18, no. 45, pp. 57–58, 2004.

[20] F. Gottrup and T. Karlsmark, "Leg ulcers: uncommon presentations," *Clinics in Dermatology*, vol. 23, no. 6, pp. 601–611, 2005.

[21] P. K. Sarkar and S. Ballantyne, "Management of leg ulcers," *Postgraduate Medical Journal*, vol. 76, no. 901, pp. 674–682, 2000.

[22] M. C. Moloney and P. Grace, "Understanding the underlying causes of chronic leg ulceration," *Journal of wound care*, vol. 13, no. 6, pp. 215–218, 2004.

[23] N. J. M. London and R. Donnelly, "ABC of arterial and venous disease. Ulcerated lower limb," *The British Medical Journal*, vol. 320, no. 7249, pp. 1589–1591, 2000.

[24] A. Adeyi, S. Muzerengi, and I. Gupta, "Leg ulcers in older people: a review of management," *The British Journal of Medical Practitioners*, vol. 2, no. 3, pp. 21–28.

[25] A. Aydin, S. Shenbagamurthi, and H. Brem, "Lower extremity ulcers: venous, arterial, or diabetic?" *Emergency Medicine*, vol. 41, no. 8, pp. 18–24, 2009.

[26] L. Collins and S. Seraj, "Diagnosis and treatment of venous ulcers," *The American Family Physician*, vol. 81, no. 8, pp. 989–996, 2010.

[27] M. H. Meissner, G. Moneta, K. Burnand et al., "The haemodynamics and diagnosis of venous disease," *Journal of Vascular Surgery*, vol. 46, no. 6, supplement, pp. S4–S24, 2007.

[28] J. E. Grey, K. G. Harding, and S. Enoch, "Venous and arterial leg ulcers," *The British Medical Journal*, vol. 332, no. 7537, pp. 347–350, 2006.

[29] H. Newton, "Leg ulcers: differences between venous and arterial," *Wounds Essentials*, vol. 6, no. 1, pp. 20–28, 2011.

[30] G. Irving and S. Hargreaves, "Venous and arterial leg ulceration," *InnovAiT*, vol. 2, pp. 415–422, 2009.

[31] C. Moffatt, "Leg ulcers," in *Vascular Disease*, S. Murray, Ed., pp. 200–237, Whurr Publishers, London, UK, 2001.

[32] S. P. Pendse, "Understanding diabetic foot," *International Journal of Diabetes in Developing Countries*, vol. 28, no. 5, pp. 519–526, 2010.

[33] W. Clayton and T. A. Elasy, "A review of the pathophysiology, classification, and treatment of foot ulcers in diabetic patients," *Clinical Diabetes*, vol. 27, no. 2, pp. 52–58, 2009.

[34] A. S. K. Ghauri and I. K. Nyamekye, "Leg ulceration: the importance of treating the underlying pathophysiology," *Phlebology*, vol. 25, supplement 1, pp. 42–51, 2010.

[35] S. Dean, "Leg ulcers and management," *Australian Family Physicisian*, vol. 35, no. 7, pp. 480–485, 2006.

[36] C. Burrows, "Leg ulcers," *Wound Care Canada*, vol. 8, no. 2, pp. 16–18, 2008.

[37] A. R. Siddiqui and J. M. Bernstein, "Chronic wound infection: facts and controversies," *Clinics in Dermatology*, vol. 28, no. 5, pp. 519–526, 2010.

[38] A. Han, J. M. Zenilman, J. H. Melendez et al., "The importance of a multi-faceted approach to characterizing the microbial flora of chronic wounds," *Wound Repair Regeneration*, vol. 19, no. 5, pp. 532–541, 2011.

[39] S. V. Agale, D. R. Kulkarni, A. G. Valand, R. R. Zode, and S. Grover, "Marjolin's ulcer—a diagnostic dilemma," *Journal of Association of Physicians of India*, vol. 57, no. 8, pp. 593–594, 2009.

[40] J. Panuncialman, S. Hammerman, P. Carson, and V. Falanga, "Wound edge biopsy sites in chronic wounds heal rapidly and do not result in delayed overall healing of the wounds," *Wound Repair and Regeneration*, vol. 18, no. 1, pp. 21–25, 2010.

[41] A. V. Singh, L. Subhashree, P. Milani, D. Gemmati, and P. Zamboni, "Interplay of iron metallobiology, metalloproteinases, and FXIII, and role of their gene variants in venous leg ulcer," *International Journal of Lower Extremity Wounds*, vol. 9, no. 4, pp. 166–179, 2010.

[42] P. Vowden, "Arterial disease: medical and future perspectives," in *Proceedings of the WUWHS Congress*, 2008.

[43] J. Banerjee, Y. C. Chan, and C. K. Sen, "MicroRNAs in skin and wound healing," *Physiological Genomics*, vol. 43, no. 10, pp. 543–556, 2011.

[44] M. R. Schneider, "MicroRNAs as novel players in skin development, homeostasis and disease," *The British Journal of Dermatology*, vol. 166, no. 1, pp. 22–28, 2012.

[45] A. D. Widgerow, "Chronic wounds—is cellular "reception" at fault? Examining integrins and intracellular signalling," *International Wound Journal*, vol. 10, no. 2, pp. 185–192, 2013.

[46] R. S. Kirsner, W. A. Marston, R. J. Snyder, T. D. Lee, and D. I. Cargill, "Spray-applied cell therapy with human allogeneic fibroblasts and keratinocytes for the treatment of chronic venous leg ulcers: a phase 2, multicentre, double-blind, randomized, placebo controlled trial," *The Lancet*, vol. 380, no. 9846, pp. 977–985, 2012.

[47] V. W. Wong, B. Levi, J. Rajadas, M. T. Longaker, and G. C. Gurtner, "Stem cell niches for skin regeneration," *International Journal of Biomaterial*, vol. 2012, Article ID 926059, 8 pages, 2012.

[48] M. A. C. Frade, J. C. Netto, F. G. Gomes, E. L. Mazzucato, and T. A. M. de Andrade, "Natual membrane dressing and hypersensitivity," *Anais Brasileiros de Dermatologia*, vol. 86, no. 5, pp. 885–891, 2011.

[49] M. A. C. Frade, R. V. C. de Assis, J. C. Netto, T. A. M. de Andrade, and N. T. Foss, "The vegetal biomembrane in the healing of chronic venous ulcers," *Anais Brasileiros de Dermatologia*, vol. 87, no. 1, pp. 45–51, 2012.