Venous leg ulcers: Pathophysiology and Classification

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INTRODUCTION

Definition, rationale and scope

Venous leg ulcers (VLUs) are defined as open lesions between the knee and ankle joint that occur in the presence of venous disease.[1] They are the most common cause of leg ulcers, accounting for 60-80% of them.[2] The prevalence of VLUs is between 0.18% and 1%.[3] Over the age of 65, the prevalence increases to 4%.[4] On an average 33-60% of these ulcers persist for more than 6 weeks and are therefore referred to as chronic VLUs.[5] These ulcers represent the most advanced form of chronic venous disorders like varicose veins and lipodermatosclerosis.[6]

Risk factors for development of VLUs include older age, female sex, obesity, trauma, immobility, congenital absence of veins, deep vein thrombosis (DVT), phlebitis, and factor V Leiden mutation.[7-9]

Poor prognostic factors[10,11]

a. Duration of more than 1 year - recurrence rate in these ulcers is more than 70%
b. Larger wounds
c. Fibrin in >50% of wound surface
d. Ankle-brachial pressure index (ABPI) <0.8
e. History of venous stripping/ligation.[10,11]

Chronic venous leg ulcer results in reduced mobility, significant financial implications, and poor quality of life. There are no uniform guidelines for assessment and management of this group of conditions, which is reaching epidemic proportions in the prevalence. There is a wide variation in healing and recurrence rates of these ulcers in the Indian population due to differing nutritional status, availability of medical facilities and trained medical staff to diagnose and manage such conditions. These guidelines are devised based on current available evidence to help all concerned in accurately assessing, correctly investigating and also providing appropriate treatment for this condition.

Pathophysiology

Venous hypertension

Deep vein thrombosis, perforator insufficiency, superficial and deep vein insufficiencies, arteriovenous fistulas and calf muscle pump insufficiencies lead to increased pressure in the distal veins of the leg and finally venous hypertension.

Fibrin cuff theory

Fibrin gets excessively deposited around capillary beds leading to elevated intravascular pressure. This causes enlargement of endothelial pores resulting in further increased fibrinogen deposition in the interstitium. The “fibrin cuff” which surrounds the capillaries in the dermis decreases oxygen permeability 20-fold. This permeability barrier inhibits diffusion of oxygen and other nutrients, leading to tissue hypoxia causing impaired wound healing.[12]

Inflammatory trap theory

Various growth factors and inflammatory cells, which get trapped in the fibrin cuff promote severe uncontrolled inflammation in surrounding tissue preventing proper regeneration of wounds.[13] Leukocytes get trapped in capillaries, releasing proteolytic enzymes and reactive oxygen metabolites, which cause endothelial damage. These injured capillaries become increasingly permeable to various macromolecules, accentuating fibrin deposition. Occlusion by leukocytes also causes local ischemia thereby increasing tissue hypoxia and reperfusion damage.

Dysregulation of various cytokines

Dysregulation of various pro-inflammatory cytokines and growth factors like tumor necrosis

factor-α (TNF-α), TGF-β and matrix metalloproteinases lead to chronicity of the ulcers.[14,15]

Miscellaneous

Thrombophilic conditions like factor V Leiden mutation, prothrombin mutations, deficiency of antithrombin, presence of antiphospholipid antibodies, protein C and S deficiencies and hyperhomocysteinemia are also implicated.[16]

CLASSIFICATION OF CHRONIC VENOUS INSUFFICIENCY

The classification and staging of chronic venous insufficiency (clinical severity) can be measured by a scoring system called clinical manifestations, etiological factors, anatomical distribution, and pathophysiological conditions[17,18] (evidence Level D) [Table 1].

Assessment and stepwise approach to diagnosis of VLU.

CLINICAL ASSESSMENT

1. Rule out arterial disease, which are indicated by:[19]
   a. History of intermittent claudication, cardiovascular disease and stroke
   b. Absence of pedal pulses
   c. Abnormal blood pressure (BP): It gives clues to the presence of any cardiovascular disease.

It is very important to rule out arterial etiology as application of compression in such cases can cause severe damage[20,21] (evidence Level D).

Table 1: Classification of venous ulcers

Classification	Description
C0	No visible or palpable signs of venous disease
C1	Telangiectasias or reticular veins
C2	Varicose veins
C3	Edema
C4a	Milder skin changes due to venous disorders (pigmentation, eczema)
C4b	Severe skin changes due to venous disorders (dermatosclerosis, atrophie blanche)
C5	C4 along with healed ulcers
C6	Skin changes with active ulcers

Etiological classification

Classification	Description
Ec	Congenital (from birth)
Ep	Primary (cause not identifiable)
Ec	Secondary (e.g., postthrombotic, posttraumatic)

2. Obtain clues from history suggesting venous etiology[22] (evidence Level D)
   a. History of previous or current DVT
   b. Family history of leg ulcers
   c. Varicose veins or its treatment
   d. History of phlebitis
   e. Surgery, trauma or fractures of the affected leg, which can damage the valves
   f. Chest pain, hemoptysis or pulmonary embolism
   g. Occupations of prolonged standing or sitting
   h. Obesity
   i. Multiple pregnancies
   j. Aching pain in the lower limbs.

3. Clinical examination to confirm the diagnosis of venous ulcer

Examination of ulcer

   a. Location: Anterior to medial malleolus, pretibial area, lower third of leg (gaiter region)[23] (evidence Level C)
   b. Measurement of size: Serial measurement of surface area of ulcer is a reliable index of prognosis and healing. Measurements of length, width and depth of ulcer with two maximum perpendicular axes are important. Disposable ruler, photography, acetate tracings and computerized calculation (planimetry) following digital photography are the methods which are used in measurement. Measuring the ulcers help in identifying patients not responding to conventional therapy and those requiring alternative therapy[24] (evidence Level C)
   c. Characteristics of the ulcer: Shallow depth, irregular shaped edges with well-defined margins
   d. Amount and type of exudates: Yellow-white in color
   e. Appearance of ulcer bed: Presence of ruddy viable granulation tissue. Thick slough or eschar indicates arterial insufficiency
   f. Signs of infection: Cellulitis, delayed healing despite appropriate compression therapy, increase in local skin temperature, increase in ulcer pain or change in nature of pain, newly formed ulcers within inflamed margins of preexisting ulcers, wound bed extension within inflamed margins, discoloration (esp. dull, dark brick-red), friable granulation tissue that bleeds easily, increase in exudate viscosity, increase in exudate volume, malodor, new-onset dusky wound hue, sudden appearance or increase in an amount of slough, sudden appearance of necrotic black spots and ulcer enlargement[25] (evidence Level D). Take a swab only if these signs are present
   g. Ulcer odor
   h. Pain associated with ulcer: Pain may be absent, mild or extreme. Pain is more at the end of the day and usually relieved by elevation of the leg.

Anatomical classification

Type of venous system	Superficial venous system (As)	Deep venous system (Ad)	Perforator veins (Ap)
	Telangectasias, reticular veins, LSV	Inferior vena cava, iliac vein	In the thigh
	LSV, above the knee	Common iliac vein	In the leg
	LSV, below the knee	Internal iliac vein	
	Short saphenous vein	External iliac vein	
	Nonsaphenous districts	Pelvic veins: genital, large ligament, others femoral vein	
		Common femoral vein	
		Deep femoral vein	
		Superficial femoral vein	
		Popliteal vein	
		Veins of the leg: posterior tibial, anterior tibial, peroneal	
		Muscular veins: gastrocnemius, soleal, others	

LSV: Long saphenous vein

Pathophysiologic classification

Classification	Description
Pr	Reflux
Po	Obstruction
Pr+o	Both

Periulcer area

Capillary leaking causing edema leading to maceration, pruritus and scaling. Associated warmth and pruritus.

Associated changes in the leg

a. Firm ("brawny") edema
b. Hemosiderin deposit (reddish brown pigmentation)
c. Lipodermatosclerosis
d. Evidence of healed ulcers
e. Dilated and tortuous superficial veins
f. Limb may be warm
g. Atrophie blanche
h. Eczema
i. Altered shape – inverted "champagne bottle"
j. Ankle flare.

4. Regular documentation to compare results before and after treatment and progression with time
5. Assess comorbidities like obesity, malnutrition, intravenous drug use and coexisting medical conditions prior to surgery. Reduced calorie and protein intake hampers ulcer healing[26] (evidence Level D)
6. Rule out complications including severe infections, osteomyelitis and malignant changes[7] (evidence Level D).
7. If no improvement after 12 weeks or in case of recurrence or no response to treatment after 6 weeks: Reassess
   a. Risk factors for nonhealing - Increased wound size and duration, history of venous stripping or ligation, history of hip or knee replacement, ankle-brachial index < 0.8, >50% of wound covered in fibrin and undermined wound margin
   b. Accuracy of etiology
   c. Rule out allergic contact dermatitis to medications and differentiate from venous eczema. Do a patch test in all cases of venous ulcers with eczema. The common sensitizers are lanolin, topical antibiotics (gentamycin, neomycin, bacitracin), antiseptics, preservatives, emulsifiers, resins and latex.[27-31] (evidence level C). Positive patch tests in these ulcers range from 40% to 82.5%.[27,32-34] (evidence Level B)
   d. Any new comorbidities?
   e. Think of biopsy (in case of atypical and nonhealing ulcers) - to rule out malignancy, systemic disorders, collagen vascular disorders and vasculitis[35] (evidence Level D)
   f. Take bacterial, mycobacterial and fungal cultures
   g. Is the treatment appropriate?
   h. Is patient compliant with treatment?

INVESTIGATIONS

Noninvasive

1. ABPI: This is a noninvasive test using the handheld Doppler ultrasound which identifies peripheral arterial disease in the leg. Systolic BP is measured at the brachial artery and at the ankle level.
   ABPI = highest systolic foot pressure (dorsalis pedis/posterior tibial artery)/highest systolic brachial BP
   a. ABPI: 0.8-1.2: Indicative of good arterial flow. Suggestive of venous etiology if an ulcer is present
   b. ABPI: <0.8 with the clinical picture of arterial disease-arterial insufficiency
   c. ABPI: >1.2: Suggestive of possible arterial calcification[36-41] (evidence Level B).
2. Nylon monofilament can be used as a simple screening test to rule out sensory neuropathy[42] (evidence Level C)
3. Duplex ultrasound: It is a noninvasive test which combines ultrasound with Doppler ultrasonography. Blood flow

through arteries and veins can be investigated to reveal any obstructions. It allows direct visualization of veins, identifies flow through valves and can map both superficial and deep veins[43] (evidence Level C)

4. Photoplethysmography: This is a noninvasive test which measures venous refill time. A probe placed on the skin surface just above the ankle is used for the detection. The patient is instructed to perform calf muscle pump exercises for brief periods followed by the rest. The probe actually measures the reduction in skin blood flow following exercise. This determines the efficiency of the calf muscle pump and the presence of any abnormal venous reflux. Patients with problems in superficial or deep veins usually have poor emptying of the veins and abnormally rapid refilling (<25 s)[44] (evidence Level C)
5. Pulse oximetry: This is another noninvasive test which measures the red and infrared light absorption of oxygenated and deoxygenated hemoglobin in a digit. Oxygenated hemoglobin absorbs more infrared light and allows more red light to pass through a digit. Deoxygenated hemoglobin absorbs more red light and allows more infrared light to pass through the digit. However, there is insufficient evidence to recommend this investigation as a primary diagnostic tool[45,46] (evidence Level C)
6. Toe brachial pressure index (TBPI): Noninvasive test that measures arterial perfusion in toes and feet. A toe cuff is applied to hallux and pressure is divided by the highest brachial systolic pressure, which is the best estimate of central systolic BP. TBPI identifies incompressible calcified arteries in diabetics and renal disease patients[47]
7. Transcutaneous oxygen: Measures amount of oxygen reaching the skin through blood circulation. Presently, insufficient evidence to recommend as primary diagnostic test.

Invasive

1. Biochemical tests
   a. Blood glucose - To rule out diabetes
   b. Hemoglobin - To rule out hematological disorders
   c. Urea and electrolytes
   d. Serum albumin, transferrin - To rule out nutritional deficiencies
   e. Lipids
   f. Rheumatoid factor
   g. Auto antibodies
   h. White blood cell count
   i. Erythrocyte sedimentation rate
   j. C-reactive protein.

Liver function testsk

l. Activated protein C: Detected in 25% venous ulcers and 50% of recurrent venous thromboses patients[48] (evidence level D)
2. Microbiology: Bacterial wound swab when ulcer shows clinical signs of infection like cellulitis, pyrexia, increased pain, rapid extension of the area of ulceration, malodor and increased exudates[49] (evidence Level C)
3. Histopathology: Wound biopsy only if malignancy or other etiology is suspected.

SUMMARY [EVIDENCE LEVEL C]

The prevalence of VLUs is on the increase with chronic venous insufficiency being the main culprit. A detailed accurate assessment of leg ulcer in patients is essential to ensure starting of timely and appropriate treatment. It should be an ongoing continuous assessment as signs and symptoms can rapidly change thereby requiring progressive evaluation. Good and accurate quality patient assessment will save time and cost by an enforcement of appropriate treatment regimens.

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