

BMJ Best Practice

Chronic venous insufficiency

The right clinical information, right where it's needed



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Summary

- ◇ Clinical presentation includes increasing leg pain, fatigue, and heaviness with prolonged standing, associated with dilated tortuous veins.
- ◇ More severe cases exhibit progressive skin changes, venous stasis dermatitis, lipodermatosclerosis, and frank ulceration.
- ◇ Underlying venous insufficiency is most efficiently documented, localised, and graded by duplex ultrasound.
- ◇ Conservative treatment requires graded compression.
- ◇ Open surgical or endovenous treatment options may be used in highly selected cases.
- ◇ Venous ulceration and bleeding are recognised complications.

Definition

Chronic venous insufficiency (CVI) refers to functional changes that may occur in the lower extremity due to persistent elevation of venous pressures. This most commonly results from venous reflux due to faulty valve function developing as a long-term sequela of DVT and recanalisation and may also develop due to primary valvular incompetence without previous episode(s) of DVT. The term 'CVI' is usually reserved for more advanced disease involving oedema, skin changes, or frank ulcers.

Epidemiology

CVI affects about 7% of the population.[3] [4] The prevalence of venous leg ulcers, the most extreme form of CVI, has been estimated to range from 0.2% to 1%.[3] [5] [6] Following treatment, up to 7 in 10 wounds recur. The total cost of treating venous leg ulcers in the US alone was \$3 billion in 2006.[7]

Aetiology

CVI is caused by functional abnormalities in lower extremity veins. The abnormality is usually reflux, but it can also be chronic obstruction or a combination of the two. It occurs in as many as 50% of people within 5 to 10 years of an episode of DVT.[8] Congenital absence of the venous valves is a less common cause, and isolated primary varicose veins (pure superficial incompetence) uncommonly causes severe CVI.

Pathophysiology

Normal venous return from the extremities to the heart requires the presence of normal calf and foot muscle pumps, patent veins, and competent valves. Theoretically, problems with any of these systems can result in venous insufficiency.

Severe CVI usually results from chronic valvular reflux, less commonly from venous obstruction, and frequently from a combination of both. These pathophysiological changes produce ambulatory venous hypertension. While walking, people with normal venous function have a relatively low extremity venous pressure (<20 mmHg). This can more than double in people with deep system incompetence.

The typical constellation of findings that ensue include oedema, lipodermatosclerosis, and eventual ulceration. Lipodermatosclerosis characteristically results from capillary proliferation, fat necrosis, and fibrosis of the skin and subcutaneous tissues. Hyperpigmentation (usually a reddish-brown discoloration) of the ankle and lower leg is also known as brawny oedema. It results from extravasation of blood and deposition of haemosiderin in the tissues due to longstanding ambulatory venous hypertension.

The fibrin cuff hypothesis of Burnand suggests that the problem is venous hypertension with resultant extravasation of plasma proteins and fibrinogen into the soft tissue, resulting in a fibrin cuff around the capillaries and tissue hypoxia. The white cell trapping theory of Coleridge-Smith suggests that white cells are trapped in capillaries due to venous hypertension, with secondary escape of proteins into the interstitial space and resultant diminished tissue oxygenation.[7]

Classification

Revised CEAP criteria^[1]

These criteria are based on the clinical class (C), aetiology (E), anatomy (A), and pathophysiology (P) of chronic venous disease of the leg and are summarised below.

Clinical classification

- C0: no visible or palpable signs of venous disease
- C1: telangiectasias or reticular veins
- C2: varicose veins (distinguished from reticular veins by a diameter 3 mm or more)
- C3: oedema
- C4: changes in skin and subcutaneous tissue secondary to chronic venous disease (now divided into 2 subclasses to better define the differing severity of venous disease)
 - C4a: pigmentation or eczema
 - C4b: lipodermatosclerosis or atrophie blanche
- C5: healed venous ulcer
- C6: active venous ulcer
- S: symptomatic (including ache, pain, tightness, skin irritation, heaviness, muscle cramps, and other complaints attributable to venous dysfunction)
- A: asymptomatic.

Aetiological classification

- Ec: congenital
- Ep: primary
- Es: secondary (post-thrombotic)
- En: no venous cause identified.

Anatomical classification

- As: superficial veins
- Ap: perforator veins
- Ad: deep veins
- An: no venous location identified.

Pathophysiological classification (basic CEAP)

- Pr: reflux
- Po: obstruction
- Pr,o: reflux and obstruction
- Pn: no venous pathophysiology identifiable.

Revised clinical classification of chronic venous disease of the leg^{[1] [2]}

Many clinicians solely use the clinical classification (C) part of the CEAP criteria:

- C0: no visible or palpable signs of venous disease
- C1: telangiectasias (dilated intradermal venules less than 1 mm in diameter), reticular veins (dilated, non-palpable, subdermal veins 3 mm in diameter or less), malleolar flare

- C2: varicose veins (dilated, palpable, subcutaneous veins over 3 mm in diameter)
- C3: oedema without skin changes
- C4: skin changes ascribed to venous disease
 - C4a: pigmentation, venous eczema, or both
 - C4b: lipodermatosclerosis, atrophie blanche, or both
- C5: skin changes with healed ulceration
- C6: skin changes with active ulceration.

Primary prevention

No specific measures have been shown to prevent CVI. However, avoiding prolonged sitting or standing, controlling weight, abstaining from tobacco, exercising, and intermittently elevating the leg may all be helpful. Theoretically, aggressive prophylaxis against DVT, particularly for patients admitted to the hospital, may reduce the incidence of CVI, as it occurs in as many as 50% of people within 5 to 10 years of an episode of DVT.^[10] Long-term treatment with low molecular weight heparin, rather than oral anticoagulation after DVT, may reduce or prevent development of post-thrombotic CVI.^[11] Patients at high risk of CVI, such as those with a family history of varicose veins, those with a previous history of DVT, and those with an orthostatic occupation, should consider wearing graduated compression stockings.

Secondary prevention

Prolonged standing, especially in one place, should be avoided. If this is not possible, compression stockings should be worn. If obese, patients should be advised to lose weight.

Patients with severe CVI or previous ulcers generally require lifelong graded compression stockings of at least 30 to 40 mmHg. Compliance with compression therapy markedly reduces, but does not eliminate, long-term sequelae.

Case history

Case history #1

A 55-year-old man presents with a 6-month history of a large wound on his right lower leg. He has had chronically swollen legs for over 10 years. He notes that his brother (deceased, myocardial infarction) and mother (deceased, pulmonary embolism) had similar problems in their legs. He had 2 documented DVT in the affected leg 5 years earlier.

Case history #2

A 70-year-old woman presents with gradual, progressive leg swelling. She also has itching, occasional skin flaking, and darkness of the leg. The swelling gets worse as the day progresses. Various topical agents have provided little relief.

Other presentations

Patients with CVI may also present with superficial thrombophlebitis, which presents as localised pain, tenderness, and erythema in the involved area. Skin changes may be advanced in CVI patients with more severe disease (e.g., pigmentation, eczema, frank ulceration). The skin and subcutaneous tissues may also be fibrotic with brawny induration, a condition known as lipodermatosclerosis.

Step-by-step diagnostic approach

The diagnosis of CVI is based on a careful clinical history, a thorough physical examination, and targeted investigations.

Clinical history

Patients may present with symptoms of heavy legs, leg fatigue, aching, and/or discomfort that develop and worsen towards the end of the day and on prolonged standing, and improve on elevation. Burning and itching of the skin and leg cramps may be present and are often associated with venous stasis and eczema. Initially, periodic elevation may reduce the swelling, but more severe cases almost always require additional control through compression.^{[3] [9] [12] [13] [14] [15]}

Physical examination

The lower extremities should be examined with the patient standing:^[3]

- Early signs of CVI include telangiectasias (dilated intradermal venules <1 mm in diameter), reticular veins (dilated, non-palpable, subdermal veins ≤3 mm in diameter), and corona phlebectatica (also known as malleolar flare or ankle flare). It consists of a fan-shaped pattern of small intradermal veins on the ankle or foot and is thought to be a common early physical sign of advanced venous disease.
- Palpation for bulges consistent with varicose veins (dilated, palpable, subcutaneous veins >3 mm in diameter) is undertaken. The extent, size, and location of the tortuous dilated veins are noted.

Primary varicose veins are not commonly associated with significant oedema or skin changes, but occasionally pure superficial venous system incompetence can be associated with oedema, skin changes, and even frank ulceration.

- Ankle swelling (usually unilateral but may be bilateral) due to oedema is also common. It characteristically indents with pressure and initially occurs in the ankle region but may extend to the leg and foot.

[Fig-1]

- Severe CVI is associated with characteristic skin changes such as atrophie blanche, lipodermatosclerosis, and hyperpigmentation. Atrophie blanche is characterised by localised, frequently round areas of white, shiny, atrophic skin surrounded by small dilated capillaries and sometimes areas of hyperpigmentation. Lipodermatosclerosis is a localised chronic inflammatory and fibrotic condition affecting the skin and subcutaneous tissues of the lower leg, especially in the supramalleolar region. When severe it may even lead to contracture of the Achilles tendon. Hyperpigmentation (usually a reddish-brown discoloration) of the ankle and lower leg is also known as brawny oedema. It results from extravasation of blood and deposition of haemosiderin in the tissues due to longstanding ambulatory venous hypertension.

[Fig-2]

[Fig-3]

- Dry, scaling, eczematous skin changes are typical of venous stasis dermatitis.
- Venous ulcers are located in the gaiter area (between the malleolus and mid-calf) of the calf, proximal and posterior to the medial malleolus, and occasionally superior to the lateral malleolus. Ulceration may be healed or active.

[Fig-4]

An important subset of patients with CVI have iliac vein obstruction, more commonly on the left than the right. Such patients usually present predominantly with swelling and lack other features of CVI.

Investigations

A variety of techniques may be employed to investigate patients with CVI:[3] [7] [14] [15]

- Duplex ultrasound imaging combines brightness-mode imaging and Doppler interrogation. It is the initial and most important primary diagnostic study. It can localise sites of obstruction and valvular reflux in both the deep and superficial venous systems. It should be noted that duplex ultrasound is operator dependent and that it is a reflux study and not an examination for acute DVT. Venous reflux is characterised by retrograde or reversed flow and a valve closure time of more than 0.5 seconds.
- Ascending phlebography identifies the site and level of obstruction, as well as the presence and location of collaterals, but it has been supplanted by duplex imaging, except when used by a specialist to evaluate treatment options for complex CVI.
- Computed tomography (CT) and magnetic resonance venography provide excellent anatomical detail, so are useful in evaluating congenital and complex or advanced cases of CVI.
- Patients with unilateral leg oedema suggesting iliac vein obstruction should be evaluated with a CT scan to rule out a pelvic or abdominal mass. If no evidence of extrinsic compression is found, the patient should be referred to a vascular specialist for further investigations, including an ascending phlebography. Intravenous ultrasound is also used in specialised centres as a secondary test to evaluate the significance of iliac vein obstruction in complex cases of CVI. It is extremely useful in the diagnosis and therapy of iliac vein disease.

- Air plethysmography is a non-invasive investigation that assesses venous function (identifying reflux and obstruction). It is primarily used for research and is not frequently used in the US outside of highly specialised centres or research settings.

Risk factors

Strong

increasing age

- Prevalence of venous disease increases with age.[\[9\]](#)

family history

- Strong risk factor for acute and chronic venous disease.[\[9\]](#)

smoking

- Cigarette smoking is an independent risk factor for severe CVI in men.[\[9\]](#)

DVT

- As many as 50% of people develop CVI within 5 to 10 years of an episode of DVT due to increased dilation of the venous system leading to axial system reflux.

orthostatic occupation

- Occupations (e.g., builder) that require prolonged standing are thought to predispose to venous insufficiency.[\[9\]](#)

Weak

female sex

- Leg injury, prolonged standing, increasing parity, and cardiovascular disease are all strongly associated with venous insufficiency in women.[\[9\]](#)

obesity (waist circumference)

- Increased body mass index and waist circumference increase the risk of chronic venous disease.[\[9\]](#)

ligamentous laxity

- Risk of CVI is increased in those with ligamentous laxity, suggested by, among other clinical features, the presence of flat feet and hx of hernia surgery.[\[9\]](#)

History & examination factors

Key diagnostic factors

presence of risk factors (common)

- Risk factors include increasing age, FHx of acute or chronic venous disease, an orthostatic occupation, smoking in men, DVT, female sex, and increasing parity.[\[3\]](#) [\[7\]](#)

corona phlebectatica (malleolar flare or ankle flare) (common)

- Fan-shaped pattern of small intradermal veins on the ankle or foot, thought to be a common early physical sign of advanced venous disease.[3] [7]

ankle swelling (common)

- Usually unilateral but may be bilateral. Swelling due to oedema is also common. It characteristically indents with pressure and initially occurs in the ankle region but may extend to the leg and foot.[3] [7]
[Fig-1]

hyperpigmentation (brawny oedema) (common)

- Reddish-brown discoloration affecting the ankle and lower leg. Common in advanced disease. Results from extravasation of blood and deposition of haemosiderin in the tissues due to longstanding ambulatory venous hypertension.[3] [7]
[Fig-3]

lipodermatosclerosis (common)

- Localised chronic inflammatory and fibrotic condition affecting the skin and subcutaneous tissues of the lower leg, especially in the supramalleolar region. Common in advanced disease. When severe it may even lead to contracture of the Achilles tendon. Results from capillary proliferation, fat necrosis, and fibrosis of the skin and subcutaneous tissues.[3] [7]
[Fig-3]

atrophie blanche (common)

- Localised, frequently round areas of white, shiny, atrophic skin surrounded by small dilated capillaries and sometimes areas of hyperpigmentation. Common in advanced disease.[3] [7]
[Fig-2]

leg ulcers (common)

- Venous ulcers are located in the gaiter area (between the malleolus and mid-calf) of the calf, proximal and posterior to the medial malleolus, and occasionally superior to the lateral malleolus.[3] [7]
- Ulceration may be healed or active.
[Fig-4]

Other diagnostic factors

leg fatigue, aching, and/or discomfort (common)

- Not present at the start of the day. Develop and worsen towards the end of the day and on prolonged standing, and improve on elevation.[3] [7]

heavy legs (common)

- Not present at the start of the day. Develops and worsens towards the end of the day and on prolonged standing, and improves on elevation.[3] [7]

leg cramps (common)

- Often associated with venous stasis and eczema.[3] [7]

telangiectasias (common)

- Early sign of CVI characterised by dilated intradermal venules <1 mm in diameter.[3] [7]

reticular veins (common)

- Early sign of CVI characterised by dilated, non-palpable, subdermal veins ≤ 3 mm in diameter.[3] [7]

dilated tortuous veins (common)

- Varicose veins are defined as dilated, palpable, subcutaneous veins < 3 mm in diameter.[3] [7]

dry and scaly skin (common)

- Eczematous skin changes are typical of venous stasis dermatitis.[3] [7]

skin burning and itching (uncommon)

- Often associated with venous stasis and eczema.[3] [7]

unilateral leg swelling (uncommon)

- An important subset of patients with CVI have iliac vein obstruction, more commonly on the left than the right. Such patients usually present predominantly with swelling and lack other features of CVI.[3] [7]

Diagnostic tests

1st test to order

Test	Result
duplex ultrasound <ul style="list-style-type: none"> • These results indicate venous reflux. • Duplex ultrasound imaging combines brightness-mode imaging and Doppler interrogation. It is the initial and most important primary diagnostic study. It can localise sites of obstruction and valvular reflux in both the deep and superficial venous systems. It should be noted that duplex ultrasound is operator dependent and that it is a reflux study and not an examination for acute DVT.[3] [7] 	retrograde or reversed flow, valve closure time > 0.5 seconds

Other tests to consider

Test	Result
ascending phlebography <ul style="list-style-type: none"> • Supplanted by duplex imaging, except when used by a specialist to evaluate treatment options for complex cases of CVI, such as those involving iliac vein obstruction.[3] [7] 	identifies obstruction site and level, presence, and location of collaterals
CT venography <ul style="list-style-type: none"> • Provides excellent anatomical detail, so is useful in evaluating congenital and complex or advanced CVI.[3] [7] 	reveals detailed venous anatomy
magnetic resonance venography <ul style="list-style-type: none"> • Provides excellent anatomical detail, so is useful in evaluating congenital and complex or advanced CVI.[3] [7] 	reveals detailed venous anatomy

Test	Result
CT abdomen and pelvis <ul style="list-style-type: none"> Used to rule out extrinsic compression as a cause for iliac vein compression.[3] [7] 	may reveal pelvic or abdominal mass in iliac vein obstruction
intravenous ultrasound <ul style="list-style-type: none"> Used in specialised centres as a secondary test to evaluate the significance of iliac vein obstruction in complex cases of CVI and is extremely useful in the diagnosis and therapy of iliac vein disease. 	reveals venous anatomy
air plethysmography <ul style="list-style-type: none"> Non-invasive investigation assessing venous function. Primarily used for research. Not frequently used outside of highly specialised centres or research settings.[3] [7] 	identifies reflux and obstruction

Differential diagnosis

Condition	Differentiating signs / symptoms	Differentiating tests
Diabetic foot ulcer	<ul style="list-style-type: none"> Hx of diabetes. Foot wounds occur in the presence of peripheral neuropathy secondary to repetitive stress. Ulcers form on the plantar aspect of the foot or on the dorsal aspect of the digits from repetitive moderate stress. 	<ul style="list-style-type: none"> In the presence of concomitant diabetes and neuropathy, wound location is often the defining factor. Fasting plasma glucose ≥ 7 mmol/L (≥ 126 mg/dL) is diagnostic of diabetes.
Arterial ulcer	<ul style="list-style-type: none"> Hx of peripheral arterial disease. Ulcers secondary to arterial insufficiency are located on the distal margins of the foot and are frequently gangrenous or 'punched out' in appearance. 	<ul style="list-style-type: none"> Non-invasive vascular studies may help to exclude peripheral arterial disease, although wounds of mixed aetiology are not uncommon. A Doppler-derived ankle-brachial index < 0.92 is abnormal. If foot pulses are absent or diminished, the ankle-brachial index is < 0.8 and the patient has foot or leg ulcers. More detailed arterial imaging such as duplex arterial ultrasound can be performed to document the level and degree of arterial obstruction.
Squamous cell carcinoma (Marjolin)	<ul style="list-style-type: none"> Longstanding non-healing wound with irregular edges. 	<ul style="list-style-type: none"> Skin biopsy is diagnostic of squamous cell carcinoma.

Condition	Differentiating signs / symptoms	Differentiating tests
Pyoderma gangrenosum	<ul style="list-style-type: none"> Wound may increase in size and inflammation after surgical debridement. 	<ul style="list-style-type: none"> Skin biopsy is diagnostic of pyoderma gangrenosum.
Kaposi's sarcoma	<ul style="list-style-type: none"> Hx of immunosuppression (e.g., HIV infection, organ transplantation, immunosuppressive therapies). Raised purplish lesions that may be confused with venous lesions. 	<ul style="list-style-type: none"> Skin biopsy is diagnostic of Kaposi's sarcoma.
Lymphoedema	<ul style="list-style-type: none"> Usually unilateral. Characterised by a dorsal foot buffalo hump and loss of the web spaces between the toes (Stemmer's sign). 	<ul style="list-style-type: none"> Duplex ultrasound is normal or minimally abnormal.
Congestive heart failure	<ul style="list-style-type: none"> Hx of dyspnoea (on minimal exertion, orthopnoea, paroxysmal nocturnal dyspnoea) and weight gain. Bilateral pitting oedema with blebs and bullae in severe cases. Ulceration is rare. 	<ul style="list-style-type: none"> Chest x-ray: cardiomegaly, bilateral lower lobe shadowing, pleural effusion, enlarged hilar vessels, upper lobe diversion, fluid in horizontal fissure, Kerley B lines. Echocardiogram: systolic and diastolic dysfunction, evidence of underlying cause.
Renal disease	<ul style="list-style-type: none"> Bilateral oedema. Ulceration is rare. 	<ul style="list-style-type: none"> Serum electrolytes: elevated potassium. Serum urea and creatinine: elevated. Urinalysis: possible haematuria and proteinuria.
Hepatic disease	<ul style="list-style-type: none"> Bilateral oedema. Ulceration is rare. 	<ul style="list-style-type: none"> Liver function tests: results depend on underlying cause.

Diagnostic criteria

Venous Clinical Severity Score^[16] ^[17]

Each clinical feature is given a score of 0 (none), 1 (mild), 2 (moderate), or 3 (severe), depending on its severity. The total score is calculated to determine the overall severity of clinical disease present.

- Pain
 - None (0 points)
 - Occasional, no use of analgesics (1 point)

- Daily, occasional use of non-narcotic analgesics (2 points)
- Constant use of narcotic analgesics (3 points).
- Varicose veins
 - None (0 points)
 - Few, scattered (1 point)
 - Multiple (2 points)
 - Extensive (3 points).
- Oedema
 - None (0 points)
 - In the evening, limited to ankle (1 point)
 - In the afternoon, above ankle (2 points)
 - In the morning, above ankle (3 points).
- Hyperpigmentation
 - None (0 points)
 - Limited (1 point)
 - Diffuse over lower third of leg (2 points)
 - Widespread (3 points).
- Inflammation and cellulitis
 - None (0 points)
 - Mild (1 point)
 - Moderate (2 points)
 - Severe (3 points).
- Induration
 - None (0 points)
 - Focal (1 point)
 - Less than lower third of leg (2 points)
 - Entire lower third of leg or more (3 points).
- Active ulcers
 - None (0 points)
 - One (1 point)
 - Two (2 points)
 - More than two (3 points).
- Ulcer duration
 - None (0 points)
 - <3 months (1 point)
 - 3 to 12 months (2 points)
 - Unhealed beyond 12 months (3 points).
- Ulcer diameter

- None (0 points)
 - <2 cm (1 point)
 - 2 to 6 cm (2 points)
 - >6 cm (3 points).
- Stockings
 - None (0 points)
 - Occasional use (1 point)
 - Used most days (2 points)
 - Constant use (3 points).

Step-by-step treatment approach

Graded compression stockings are the cornerstone of CVI treatment, supplemented by further specialised procedures, the choice of which depends on the specific associated clinical features.

Graded compression stockings

The mainstay of treatment for CVI-related oedema, stasis dermatitis, and small venous leg ulcers (VLU) is the use of graded compression knee-high stockings.[18] [19]

[Fig-4]

- As therapy may be lifelong, patient compliance is of critical importance. An estimated 30% to 65% of patients are non-compliant with compression therapy. Recurrence of VLUs in patients compliant with stocking use is half that in those who are non-compliant. Non-compliance with prescribed stockings is the primary cause of compression therapy failure.[20]
- A meta-analysis of 48 trials concluded that compression stockings were more effective in healing VLUs than no compression therapy.[21] For ulcer healing, multilayer dressings are more effective than single-layer dressings.[22] A single randomised controlled study suggested that 'progressive' stockings, which progressively apply maximal compression (23 mmHg at the level of the calf versus 10 mmHg at the ankle), were superior to a 'degressive' stocking (30 mmHg at ankle versus 21 mmHg at upper calf). The outcome measure used was a composite consisting of improvement in pain, deep and/or superficial venous thrombosis, pulmonary embolus (PE), and ulceration of skin.[13]
- In a meta-analysis of 5 randomised trials of patients with DVT comparing venous compression to controls, any post-thrombotic syndrome occurred in 26% of compression-treated patients versus 46% of controls (relative risk = 0.54). Similarly, mild to moderate post-thrombotic syndrome occurred in 22% of compression-treated patients versus 37% of controls (relative risk = 0.52) with severe post-thrombotic syndrome occurring in 5% and 12%, respectively (relative risk = 0.38).[23]
- Stockings must be put on first thing in the morning and should be removed only when the patient is recumbent (usually just before going to bed).
- There are 3 classes of compression stockings: class 1 stockings (low compression) control oedema; class 2 (medium compression) and class 3 (high compression) are usually required for more advanced CVI.
- Thromboembolic disorder (TED) stockings are inadequate for controlling CVI and should not be prescribed for this condition, because the pressure at the ankle is insufficient at less than 20 mmHg.
- Patients with severe CVI or previous ulcers generally require lifelong graded compression stockings of 30 to 40 mmHg or higher.
- A randomised controlled trial, comparing thigh-length with below-knee compression stockings for the prevention of post-thrombotic syndrome, found that thigh-length stockings do not offer better protection against post-thrombotic syndrome than below-knee stockings, and they are less well tolerated.[24]

Pharmacotherapy

Eczematous skin changes and mild stasis dermatitis

- It is generally felt that applying a simple moisturising cream to combat skin dryness and flaking is beneficial.

Venous leg ulcers

- Long-term therapy with non-specific local unguents or topical antibiotic ointments or creams is of no benefit and may damage adjacent skin. The use of such therapies is also strongly discouraged because of allergic reactions and the potential for breakdown of the dermal barrier.
- Pentoxifylline, micronised purified flavonoid fraction (MPFF), and the prostaglandin E1 (PGE1) analogue alprostadil[25] have shown some benefit in VLU healing in randomised clinical trials.
- Pentoxifylline is used to treat claudication. A meta-analysis of 5 trials showed a minimal benefit to VLU healing with oral pentoxifylline (odds ratio 1:3) compared with compression therapy and placebo.[26]
- A meta-analysis of prospective randomised trials of MPFF in the treatment of VLU compared compression and local care with and without the addition of oral MPFF.[27] At 6 months, the chance of ulcer healing was 32% better in patients treated with adjunctive MPFF than in those managed by conventional therapy alone (relative risk reduction 32%, CI 3% to 70%). This difference was present from month 2 (relative risk reduction 44%, CI 7% to 94%) and was associated with a shorter time to healing (16 weeks versus 21 weeks; $P = 0.0034$). These data suggest that MPFF may be a useful adjunct to conventional therapy in large and longstanding VLU. Diosmin (an MPFF) is available in some European, Asian, and South American countries and in Canada, but not in the US or the UK.
- A systematic review determined that, while data were limited by heterogeneity and small sample sizes, pentoxifylline and micronised purified flavonoid fraction (MPFF) were both reported to have demonstrated clinical benefits when used in conjunction with compression therapy.[28]
- The requirement for intravenous infusion of alprostadil limits its widespread applicability, and topically applied PGE1 has shown no benefit.
- The following systemically given drugs are ineffective in healing VLU: aspirin, ifetroban, stanozolol, antibiotics, and hydroxyrutosides.
- Topically applied growth factors have not been systematically shown to be efficacious in speeding up VLU healing.

Leg pain

- A Cochrane Collaboration review evaluated 7 studies of horse chestnut seed extract (HCSE) for treatment of mild CVI, specifically for leg pain. The reviewers concluded that HCSE could be a potentially effective treatment in this population.[29]

Invasive procedures

Superficial venous reflux

- Saphenectomy: a randomised controlled trial of saphenectomy (surgical stripping) and compression versus compression alone in patients with significant reflux in the great or small saphenous vein on duplex ultrasound showed 89% to 93% initial ulcer healing rates in both groups (P value reported as not significant). Ulcer recurrence rates at 4 years were 52% in the compression only group compared with only 24% in those who underwent saphenectomy and compression, a difference that was statistically significant.[30] These findings strongly suggest that saphenectomy confers long-term benefit in patients with CVI who also have superficial venous reflux.

- Endovenous laser therapy or radiofrequency ablation of the great saphenous vein (GSV): these procedures can be done with outpatients under local tumescent anaesthesia and have generally replaced surgical stripping for most patients requiring GSV ablation. Following endovenous ablation, compression stockings should be worn for 24 hours per day for 1 to 3 days, then during the day for 1 to 2 weeks. Postoperatively, normal activities can be resumed, but strenuous leg activity (e.g., running, weighted leg exercises, cycling) should be avoided for 1 week. Continued use of compression stockings during the day is recommended following ablative procedures on the superficial system if there is on-going evidence of reflux (i.e., deep system insufficiency). A randomised controlled trial comparing endovenous laser ablation therapy with saphenopopliteal junction ligation plus attempted stripping/excision for the treatment of small saphenous vein insufficiency has reported similar 2-year outcomes, but with the possible benefit of fewer short-term sensory deficits with endovenous laser ablation therapy.[31]
- Foam sclerotherapy: this technique can also be used to ablate the GSV.[32] The sclerosant agent is mixed with air to produce foam, which is then injected into the vein under ultrasound guidance. The foam displaces blood in the vein and causes spasm of the vein and endothelial injury, resulting in thrombosis of the vessel. Retinal or cerebral emboli (causing migraine but rarely stroke) may occur with the use of foam in 2% to 6% of patients, but these adverse sequelae are almost always minor and transient.[33]
- A meta-analysis of over 12,000 legs investigated the success rate of these therapies as determined by duplex ultrasound, documenting successful vein excision or ablation and lack of residual reflux.[33] Measured in this manner, after a mean follow-up of 32 months, the relative effectiveness rates were 77% for foam sclerotherapy, 78% for surgical stripping, 84% for radiofrequency ablation, and 94% for laser ablation. The major complication of these techniques was DVT, occurring in 1% to 3% of patients.

Angiomata and varicosities

- These lesions may occasionally cause symptoms of sufficient severity to warrant laser or radiofrequency ablation or injection sclerotherapy, which may be liquid or, increasingly, foam sclerotherapy. It should be noted that foam sclerotherapy is not approved in all countries for this use.

Perforating vein incompetence

- The role of perforating vein interruption with subfascial endoscopic perforator (ligation) surgery is controversial and its efficacy uncertain.[34]
- Many centres are now ablating perforating veins with laser or radiofrequency ablation.

Iliac vein obstruction

- An important subset of patients with CVI have iliac vein obstruction, more commonly on the left side than the right. In selected patients (determined by a vascular specialist), symptoms may be substantially improved by percutaneous iliac angioplasty and stenting. These procedures are performed in significant numbers only in selected centres, and the indications for such procedures are still developing.[35]

Deep venous reflux

- Venous valvular reconstruction (either with leaflet repair or axillary valve transplantation) is rarely performed, and its use is generally confined to selected centres. Results are far better when

performed in patients with primary rather than post-thrombotic venous reflux.[36] The operation is generally reserved for patients in whom conventional therapy has failed.

Treatment details overview

Consult your local pharmaceutical database for comprehensive drug information including contraindications, drug interactions, and alternative dosing. (see [Disclaimer](#))

Ongoing (summary)		
Patient group	Tx line	Treatment
all symptomatic patients	1st	graded compression stockings
	adjunct	moisturiser
	adjunct	pentoxifylline or diosmin
■ with superficial venous reflux	plus	endovenous ablation or saphenectomy
■ with angiomata and varicosities	adjunct	endovenous ablation or injection sclerotherapy
■ with perforating vein incompetence	plus	endovenous ablation
■ with iliac vein obstruction	adjunct	percutaneous iliac angioplasty and stenting
■ with deep venous reflux	adjunct	venous valvular reconstruction
■ with leg pain	adjunct	horse chestnut seed extract

Treatment options

Ongoing

Patient group	Tx line	Treatment
all symptomatic patients	1st	<p>graded compression stockings</p> <ul style="list-style-type: none"> » The mainstay of treatment for CVI-related oedema, stasis dermatitis, and small venous leg ulcers is use of graded compression knee-high stockings.[18] [19] » Shown to be more effective in healing venous ulcers than no compression therapy.[21] For ulcer healing, multilayer dressings are more effective than single-layer dressings.[22] » Stockings must be put on first thing in the morning and should be removed only when the patient is recumbent (usually just before going to bed). » In general, there are 3 classes of compression stockings: class 1 stockings (light compression) control oedema; class 2 (medium compression) and class 3 (high compression) are usually required for more advanced CVI. Patients with severe CVI or previous ulcers generally require lifelong graded compression stockings of at least 30 to 40 mmHg.
	adjunct	<p>moisturiser</p> <ul style="list-style-type: none"> » Applying a simple moisturising cream to combat skin dryness and flaking in eczematous skin changes and mild stasis dermatitis is generally thought to be beneficial.
	adjunct	<p>pentoxifylline or diosmin</p> <ul style="list-style-type: none"> » Pentoxifylline and the PGE1 analogue alprostadil[25] have shown some benefit in VLU healing in randomised clinical trials. » Pentoxifylline is used to treat claudication. A meta-analysis of 5 trials showed a minimal benefit to VLU healing with oral pentoxifylline (odds ratio 1:3) compared with compression therapy and placebo.[26] A later systematic review determined that, while data were limited by heterogeneity and small sample sizes, pentoxifylline demonstrated clinical benefits when used in conjunction with compression therapy.[28]

Ongoing

Patient group

Tx line

Treatment

» A meta-analysis of prospective randomised trials of MPFF in the treatment of VLU compared compression and local care with and without the addition of oral MPFF.[27] A later systematic review determined that, while data were limited by heterogeneity and small sample sizes, micronised purified flavonoid fraction (MPFF) has demonstrated clinical benefits when used in conjunction with compression therapy.[28] The data suggest that MPFF may be a useful adjunct to conventional therapy in large and longstanding VLU.

» Diosmin (an MPFF) is available in some European, Asian, and South American countries and in Canada, but not in the US or the UK.

» The requirement for intravenous infusion of alprostadil limits its widespread applicability, and topically applied PGE1 has shown no benefit.

Primary options

» **pentoxifylline**: 400 mg orally three times daily

OR

Secondary options

» **diosmin**: consult specialist for guidance on dose

■ **with superficial venous reflux**

plus

endovenous ablation or saphenectomy

» Saphenectomy (surgical stripping) confers long-term benefit in patients with CVI with associated superficial venous reflux. Patients with significant great or small saphenous vein reflux on duplex ultrasound have ulcer recurrence rates at 4 years of 24% with saphenectomy and compression and 52% with compression alone.[30]

» Endovenous laser therapy or radiofrequency ablation of the great saphenous vein can be done with outpatients under local tumescent anaesthesia and have replaced surgical stripping for most patients. Following endovenous ablation, compression stockings should be worn for 24 hours per day for 1 to 3 days, then during the day for 1 to 2 weeks. Postoperatively, normal activities can be resumed, but strenuous leg activity (e.g., running, weighted leg exercises, cycling) should be avoided for 1 week. Continued use of compression stockings during the day is recommended if there is on-

Ongoing

Patient group	Tx line	Treatment
		<p>going evidence of reflux (i.e., deep system insufficiency).</p> <p>» A randomised controlled trial comparing endovenous laser ablation therapy with saphenopopliteal junction ligation plus attempted stripping/excision for the treatment of small saphenous vein insufficiency has reported similar 2-year outcomes, but with the possible benefit of fewer short-term sensory deficits with endovenous laser ablation therapy.[31]</p> <p>» The major complication of these techniques is DVT, occurring in 1% to 3% of patients.[33]</p>
■ with angiomata and varicosities	adjunct	<p>endovenous ablation or injection sclerotherapy</p> <p>» These lesions may occasionally cause symptoms of sufficient severity to warrant laser or radiofrequency ablation or injection sclerotherapy, which may be liquid or, increasingly, foam sclerotherapy.</p>
■ with perforating vein incompetence	plus	<p>endovenous ablation</p> <p>» Many centres are now ablating perforating veins with laser or radiofrequency ablation.</p>
■ with iliac vein obstruction	adjunct	<p>percutaneous iliac angioplasty and stenting</p> <p>» An important subset of patients with CVI have iliac vein obstruction, more commonly on the left than the right. In selected patients (determined by a vascular specialist), symptoms may be substantially improved by percutaneous iliac angioplasty and stenting. These procedures are performed in significant numbers only in selected centres, and the indications for such procedures are still developing.[35]</p>
■ with deep venous reflux	adjunct	<p>venous valvular reconstruction</p> <p>» Venous valvular reconstruction (either with leaflet repair or axillary valve transplantation) is rarely performed, and its use is generally confined to selected centres. Results are far better when performed in patients with primary rather than post-thrombotic venous reflux.[36] The operation is generally reserved for patients in whom conventional therapy has failed.</p>
■ with leg pain	adjunct	<p>horse chestnut seed extract</p>

Ongoing

Patient group	Tx line	Treatment
.....		<p>» A Cochrane Collaboration review evaluated 7 studies of horse chestnut seed extract (HCSE) for treatment of mild CVI, specifically for leg pain. The reviewers concluded that HCSE could be a potentially effective treatment in this population.[29]</p> <p>Primary options</p> <p>» horse chestnut seed extract: consult specialist for guidance on dose</p>

Emerging

Balneotherapy

One single-blind, randomised, multicentre controlled trial assessed the efficacy of spa therapy in 425 people with advanced chronic venous disorders.[37] The study concluded that the frequency of leg ulcers was not reduced after a 3-week spa therapy course. The study also demonstrated that spa therapy provides a significant and substantial improvement in clinical status, symptoms, and quality of life of patients with advanced venous insufficiency for at least 1 year.

Spray-applied cell therapy

Results from one phase II double-blind, randomised, controlled trial of 205 people with venous leg ulcers suggest that dosing of growth-arrested allogenic neonatal keratinocytes and fibroblasts in a fibrin vehicle is associated with a higher proportion of healing when compared with vehicle alone.[38] These promising results warrant further studies in this area.

Other emerging therapies

A number of initial trials support some benefit to patients with CVI from a number of agents, including venoactive drugs (VADs), calcium dobesilate, and red-vine-leaf extract.[39] [40] [41] Pain, oedema, and leg volume appear to be reduced, but further trials with better stratification of disease type and severity are needed before the use of these agents can be recommended.

Recommendations

Monitoring

Venous stripping or ablation is helpful in patients with CVI who have documented superficial venous reflux.^[30] Following venous stripping and ligation, patients generally undergo a repeat duplex ultrasound only if symptoms recur, whereas after endovenous laser or radiofrequency ablation, a duplex ultrasound is generally performed within 72 hours in order to document successful ablation and lack of a DVT. Repeat evaluation is recommended if initial results are inadequate, symptoms persist, or varicosities recur.

Patient instructions

The patient should be reassured that the condition is not limb threatening and that it differs from the circulatory problems that are due to diabetes and peripheral arterial occlusive disease.

All patients with documented CVI should be advised to wear graded compression stockings. These stockings must be put on first thing in the morning and should be removed only when the patient is recumbent (usually just before going to bed). The importance of compliance with compression therapy must also be emphasised, as an estimated 30% to 65% of patients are non-compliant with compression therapy. The recurrence of venous leg ulcers in patients compliant with stocking use is half that in those who are non-compliant, and non-compliance is the primary cause of compression therapy failure.^[20] Patients should be advised that thromboembolic disorder stockings are inadequate for controlling CVI, as they provide insufficient compression at the ankle.

Patients with severe CVI or previous ulcers should be advised that they may require lifelong graded compression stockings. Following endovenous ablation, patients are usually advised to wear compression stockings for 24 hours per day for 1 to 3 days, and then during the day for 1 to 2 weeks. Postoperatively, patients can return to normal activities, but they should avoid strenuous leg activity such as running, weighted leg exercises, or cycling for 1 week. Continued use of compression stockings during the day is recommended following ablative procedures on the superficial system if there is on-going evidence of reflux (i.e., deep system insufficiency).

Complications

Complications	Timeframe	Likelihood
saphenectomy and endovenous-related DVT	short term	low
Saphenectomy and endovenous ablation (laser and radiofrequency) are associated with a 1% to 3% rate of DVT occurrence. ^[33]		
haemosiderin deposition	long term	high
Secondary to changes in the microcirculatory system, with the capillaries becoming elongated, fibrotic, and leaky.		
Hyperpigmentation (usually a reddish-brown discoloration) of the ankle and lower leg is also known as brawny oedema. It results from extravasation of blood and deposition of haemosiderin in the tissues due to longstanding ambulatory venous hypertension.		
venous ulceration	long term	medium

Complications	Timeframe	Likelihood
<p>Increased dilation of the venous system and increased pressure may lead to venous hypertension. The typical constellation of findings that ensue include oedema, lipodermatosclerosis, and eventual ulceration. Perforator incompetence may also contribute to ulceration.</p> <p>Treatment of the superficial axial system, if involved, will help.[30] Perforator treatment is considered if perforating veins are involved.</p>		
lipodermatosclerosis	long term	medium
<p>Secondary to changes in the microcirculatory system, with the capillaries becoming elongated, fibrotic, and leaky. Characteristically results from capillary proliferation, fat necrosis, and fibrosis of the skin and subcutaneous tissues.</p>		
haemorrhage	long term	low
<p>Erosion of varices can lead to bleeding that may require surgical intervention.</p>		
infection	long term	low
<p>Uncommon in patients compliant with compression therapy and good skin care and hygiene.</p>		

Prognosis

Physicians should note, and the patient should be reassured, that CVI is not limb threatening and that it differs from the circulatory disorders of diabetes and peripheral arterial occlusive disease. Patients with severe CVI (CEAP C4-6) or previous ulcers generally require lifelong graded compression stockings of at least 30 to 40 mmHg. Compliance with compression therapy markedly reduces, but does not eliminate, long-term sequelae. The recurrence of venous leg ulcers in patients compliant with stocking use is half that in those who are non-compliant, and non-compliance is the primary cause of compression therapy failure.[20]

Diagnostic guidelines

Europe

Clinical practice management of chronic venous disease

Published by: European Society for Vascular Surgery (ESVS)

Last published: 2015

Summary: This guideline covers the diagnosis and management of chronic venous disease.

Varicose veins: diagnosis and management

Published by: National Institute for Health and Care Excellence

Last published: 2013

Summary: This guideline provides evidence-based recommendations on the diagnosis of varicose veins in adults aged 18 years and over.

North America

Practice parameter for the performance of peripheral venous ultrasound examinations

Published by: American Institute of Ultrasound in Medicine; American College of Radiology; Society of Radiologists in Ultrasound

Last published: 2015

Summary: Intended to assist practitioners performing non-invasive ultrasound evaluation of peripheral venous structures.

Oceania

Australian and New Zealand clinical practice guideline for prevention and management of venous leg ulcers

Published by: Wounds Australia (Australian Wound Management Association); New Zealand Wound Care Society

Last published: 2011

Summary: Present a comprehensive review of the assessment and diagnosis of venous leg ulcers, based on the best evidence available up to January 2011.

Treatment guidelines

Europe

Clinical practice management of chronic venous disease

Published by: European Society for Vascular Surgery (ESVS)

Last published: 2015

Summary: This guideline covers the diagnosis and management of chronic venous disease.

Europe

Varicose veins: diagnosis and management

Published by: National Institute for Health and Care Excellence

Last published: 2013

Summary: This guideline provides evidence-based recommendations on the management of varicose veins in adults aged 18 years and over.

Ultrasound-guided foam sclerotherapy for varicose veins

Published by: National Institute for Health and Care Excellence

Last published: 2013

Summary: NICE interventional procedure guidance makes recommendations on the safety and efficacy of ultrasound-guided foam sclerotherapy for varicose veins.

Endovenous mechanochemical ablation for varicose veins

Published by: National Institute for Health and Care Excellence

Last published: 2013

Summary: NICE interventional procedure guidance makes recommendations on the safety and efficacy of endovenous mechanochemical ablation for varicose veins.

Recommendations for the referral and treatment of patients with lower limb chronic venous insufficiency (including varicose veins)

Published by: Venous Forum of the Royal Society of Medicine

Last published: 2011

Summary: Evidence-based, expert view recommendations for the referral and treatment of CVI.

North America

Management of venous leg ulcers

Published by: Society for Vascular Surgery; American Venous Forum

Last published: 2014

Summary: Provides evidence-based recommendations on the management of venous leg ulcers.

Practice guidelines for superficial venous disease (treatment of superficial venous disease of the lower leg)

Published by: American College of Phlebology

Last published: 2014

Summary: Provides recommendations (based on best-available evidence and expert consensus) on the management of superficial venous disease of the lower leg.

The care of patients with varicose veins and associated chronic venous diseases: clinical practice guidelines of the Society for Vascular Surgery and the American Venous Forum

Published by: Society for Vascular Surgery; American Venous Forum

Last published: 2011

Summary: Recommendations for the care of patients with varicose veins of the lower limbs and pelvis, and the management of superficial and perforating vein incompetence in patients with associated, more advanced chronic venous diseases (CVDs), including oedema, skin changes, or venous ulcers.

North America

Recommended reporting standards for endovenous ablation for the treatment of venous insufficiency: joint statement of the American Venous Forum and the Society of Interventional Radiology

Published by: American Venous Forum; Society of Interventional Radiology

Last published: 2007

Summary: Research guidelines providing recommended reporting standards for physicians performing clinical research studies evaluating endovenous ablation in the treatment of lower extremity venous reflux.

Oceania

Australian and New Zealand clinical practice guideline for prevention and management of venous leg ulcers

Published by: Wounds Australia (Australian Wound Management Association); New Zealand Wound Care Society

Last published: 2011

Summary: This guideline presents a comprehensive review of the treatment of venous leg ulcers, based on the best evidence available up to January 2011.

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Images



Figure 1: Serial images of severe CVI (C6) and chronic ulceration of the right lower extremity

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Figure 2: Atrophie blanche in a patient with CVI

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Figure 3: Lipodermatosclerosis and leg ulcer with hypercoagulable state and recurrent episodes of DVT

From the collection of Dr Joseph L. Mills; used with permission



Figure 4: Serial images of recurrent venous ulcer with resolution at 3 months

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