Chronic venous insufficiency and venous leg ulceration

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Venous ulcers are the most common form of leg ulcers. Venous disease has a significant impact on quality of life and work productivity. In addition, the costs associated with the long-term care of these chronic wounds are substantial. Although the exact pathogenic steps leading from venous hypertension to venous ulceration remain unclear, several hypotheses have been developed to explain the development of venous ulceration. A better understanding of the current pathophysiology of venous ulceration has led to the development of new approaches in its management. New types of wound dressings, topical and systemic therapeutic agents, surgical modalities, bioengineered tissue, matrix materials, and growth factors are all novel therapeutic options that may be used in addition to the "gold standard," compression therapy, for venous ulcers. This review discusses current aspects of the epidemiology, pathophysiology, clinical presentation, diagnostic assessment, and current therapeutic options for chronic venous insufficiency and venous ulceration. (J Am Acad Dermatol 2001;44:401-21.)

Learning objective: At the conclusion of this learning activity, participants should be familiar with the 3 main types of lower extremity ulcers and should improve their understanding of the epidemiology, pathogenesis, risk factors, clinical presentation, diagnostic assessment, and current therapies for chronic venous insufficiency and venous ulcers.

The 3 main types of lower extremity ulcers are venous, arterial, and neuropathic. Venous ulcers constitute the majority of all leg ulcers, whereas foot ulcers are more likely to be due to arterial insufficiency or neuropathy.[1] Up to 80% of leg ulcers are caused by venous disease, and arterial disease accounts for another 10% to 25%, which may coexist with venous disease. The incidence of arterial insufficency may likely increase with the aging of our population. Coexisting rheumatologic disease occurs in 10% to 15% of patients, whereas diabetes mellitus is present in 5% to 12% of patients.[2-5] Less commonly, trauma, pressure, and infectious agents are causes of leg ulcers.[6,7] Overlap of various causes as well as coexisting disease occurs because these conditions are not mutually exclusive.[8]

The course and prognosis for patients with leg ulcers differ based on their causes. Venous ulcers are not generally as painful, do not lead to amputation, and do not require surgical intervention as often as ulcers caused by arterial insufficiency.[9] However, their chronic course, unpredictable behavior, morbidity, and the associated economic burden have led to a renewed interest in the development of new approaches to improve the quantity or speed of healing.[9] In addition, the common assumption that venous ulcers are not painful has recently been challenged. As many as three fourths of patients with venous ulcers report pain, which in turn causes a significant decrease in patients' quality of life.[10,11] Although the exact pathogenic steps leading from venous hypertension to venous ulceration remain unclear, several hypotheses have emerged to explain the development of venous ulceration.[12,13]

There has also been a greater appreciation of the importance of moist wound healing, high compression therapy, and fibrinolytic agents,[14] as well as new data supporting the use of modalities such as bioengineered tissue,[15] matrix materials,[16] and growth factors.[17] This article highlights the epidemiology, pathophysiology, clinical presentation, and treatment of venous ulcers.

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EPIDEMIOLOGY

Venous leg ulcers are responsible for more than half of lower extremity ulcerations, with an overall prevalence ranging from 0.06% to 2%.[6,8] This variance may be due to contributory factors including the use of overall versus point prevalence; the inclusion or exclusion of foot ulcers; the age and sex distribution of the patient series; the methodology used to identify patients[6,18]; the patients' often inaccurate assessment of ulcer duration, healing, and recurrence; and the lack of a uniform definition of venous ulcer. In the United States, the most extensive survey was reported by Coon, Willis, and Keller[19] in 1973, who found an extrapolated figure of 400,000 to 600,000 venous ulcers for the entire US population. Similar data have been reported from Europe.[4,6,20] Most recently, Nelzen, Bergquist, and Lindhagen[6] reported leg ulcers in 827 of 270,800 inhabitants of Skorabury, Sweden. Fifty-four percent of these ulcers were due to venous insufficiency, resulting in a point prevalence of 0.16%.

This prevalence is accompanied by substantial costs. Venous disease accounts for 1% to 2% of the health care budgets of European countries.[21] A study in England analyzing the cost of dressing materials used in venous leg ulcers for a 4-month outpatient treatment has been estimated to be as high as $2500 US per patient.[22] Estimated annual costs of ulcer treatment in Sweden are $25 million,[23] whereas expenses in the United States may be between $1.9 billion and $2.5 billion.[24,25]

Venous ulcers impose a significant economic burden on Medicare. Olin et al[26] performed a retrospective cohort study of 78 patients who presented to the Cleveland Clinic Foundation (a large primary and tertiary referral center in the United States). The average duration of follow-up was 119 days (median, 84 days), the average number of visits per patient was 7, and a total of 14 patients (18%) required hospitalization. The average total medical cost per patient was $9685 (median, $3036). Home health care, hospitalizations, and home dressing changes accounted for 48%, 25%, and 21% of total costs, respectively. Total costs were related to duration of active therapy, ulcer size, and the presence of at least one comorbidity. These findings reflect an underestimate of venous ulcer costs because indirect costs (eg, time absent from work, forced early retirement) were not examined.

The female predominance of venous ulcers has been overestimated; however, after adjustment for age, a slight female predominance has been observed, with a female-to-male ratio of 1.6:1. Venous ulcers are more common with increasing age, with a peak prevalence between 60 and 80 years.[4,20] However, 72% of persons have their first ulcer by 60 years of age. Twenty-two percent of patients have their first ulcer by age 40 and 13% before 30 years of age.[6,9] Thus venous ulceration also affects work productivity and premature disability.[9,21] Once treated, many patients have a recurrence, which is reported to be as high as 72% of treated subjects. This high recurrence rate coupled with long ulcer duration of more than 1 year in more than half of patients helps explain the high prevalence of venous disease.[6] A subset of patients (up to 34%) have ulcers of extremely long duration, defined as more than 5 years.[4,20]

The majority of venous ulcers are located over the medial malleolus, with the remainder located elsewhere on the leg or foot. This area has been termed the gaiter area corresponding to the gaiter region of the boots of British soldiers (the medial malleolus). Either or both legs may be affected. One study found the left leg involved in 44% of cases, the right leg in 35%, and both legs in 21%, but this imparted no statistical significance. Venous ulcers are large, often larger (up to 550 cm^2 or circumferential) than ulcers of nonvenous origin (2.6 vs 1.2 cm^2).[6]

PATHOGENESIS

Normal anatomy and physiology

Venous blood flow of the lower extremity is divided into 3 components: the superficial, communicating, and deep veins. The superficial system comprises both the long and short saphenous veins and their tributaries. The long saphenous vein originates from the medial end of the dorsal venous arch of the foot and ascends the leg and thigh medially. It joins the femoral vein just below the inguinal ligament. The lesser or short saphenous vein originates from the lateral aspect of the dorsal venous arch, passes posteriorly to the lateral malleolus, and ascends subcutaneously in the mid posterior part of the calf. It then inserts into the popliteal vein near the popliteal fossa.

The superficial venous system is connected to the deep venous system through smaller communicating or perforator veins. The deep veins are categorized as either intramuscular or intermuscular. The deep system consists of 3 sets of paired tibial veins that merge to become the popliteal vein. At the level of the adductor canal, the popliteal vein is renamed the superficial femoral vein. This vessel joins the deep femoral vein in the femoral triangle to form the common femoral vein.

The superficial, communicating, and deep venous systems are equipped with one-way bicuspid valves that open only toward the deep system, allowing blood to flow in a cephalad direction and, normally,

prevent reflux. Blood is moved from the leg toward the heart primarily by the pumping action of the leg muscles.[27-29] At rest, in the erect position, the pressure in the superficial and deep systems approximates 80 mm Hg, which represents the hydrostatic pressure in the standing position.[27] Upon ambulation, the calf muscle contracts, the deep veins are compressed, and pressures rise transiently in the deep system, propelling blood in a cephalad direction. The valves close when pressure rises in the deep system, preventing retrograde flow and transmission of high pressure to the superficial system. The emptying of the deep system leads to a subsequent abrupt fall in deep vein pressure to 0 to 10 mm Hg, allowing the valves to open and driving flow from the superficial into the deep system.[27,28] Maintenance of an intact venous system and calf pump is essential in avoiding retrograde flow to the superficial system.[27]

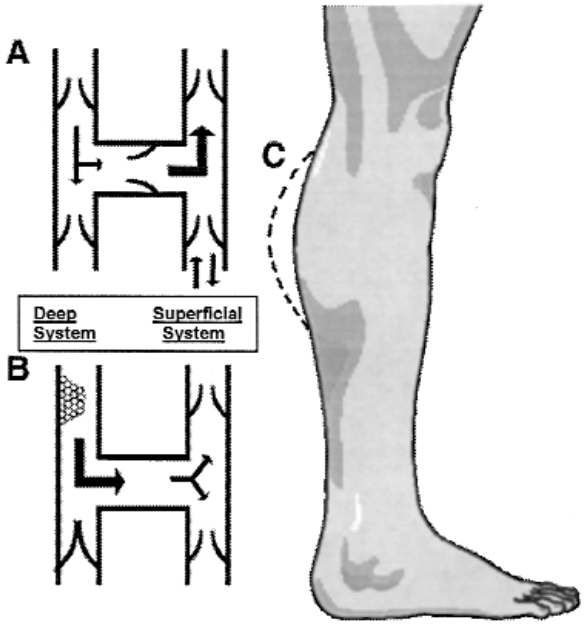

Fig 1. Pathophysiologic mechanisms involved in venous hypertension and ulcer formation. **A,** Dysfunction of valves in the superficial and/or communicating and/or deep system. **B,** Deep venous outflow obstruction (ie, thrombus formation). **C,** Muscle dysfunction and calf muscle pump failure.

Pathophysiology

In a diseased venous system or failure of the calf muscle pump, venous pressure in the deep system upon ambulation may either fall minimally or not at all. This sustained ambulatory pressure has been termed *venous hypertension*.[13] Ultimately, venous hypertension in the deep veins may be transmitted to the superficial system.[28,30,31] Venous hypertension is also referred to as "chronic venous insufficiency" and occurs by 1 of 4 pathophysiologic mechanisms: (1) dysfunction of valves in the superficial and/or communicating veins because of congenital or acquired incompetence (Fig 1, *A*); (2) dysfunction of valves in the deep system because of congenital absence, inherent weakness, or thrombotic damage; (3) deep venous outflow obstruction rather than valvular incompetence (Fig 1, *B*); and (4) muscle dysfunction and calf muscle pump failure (Fig 1, *C*) from inflammatory conditions of the joints or muscles, fibrosis, or neuropathies.[27,28] Although venous ulcers can occur in patients with only perforator or superficial vein incompetence, they are usually associated with deep venous insufficiency.[32,33] Fewer than 10% of venous ulcers are due to deep venous incompetence alone.[34]

There is no general agreement on the sequence of pathogenic steps leading from venous hypertension or venous insufficiency to venous ulceration. Several hypotheses have been proposed to explain the development of venous ulceration.

Pericapillary fibrin cuffs and fibrinolytic abnormalities hypotheses

In 1982, based on histologic studies of lipodermatosclerotic skin, Browse and Burnand[35] postulated that the sustained venous hypertension within the venous system of the leg is transmitted to the capillary circulation, leading to distension of the capillary walls and leakage of macromolecules such as fibrinogen from within the capillaries into the dermis and subcutaneous tissues of the calf.[35] In the extravascular space, fibrinogen would polymerize to form pericapillary fibrin cuffs.[36-38] They suggested that this layer of fibrin forms a pericapillary physical barrier to the diffusion of oxygen and nutrients, resulting in cell death and ulceration.[35] Support for this hypothesis is the finding of pericapillary fibrin cuffs by direct immunofluorescence in lipodermatosclerotic nonulcerated skin, at the edges of venous ulcers, and within the ulcer bed.[27] In addition, Burnand et al[38] demonstrated in vitro that fibrin sheets impede the diffusion of oxygen. However, other data have not been consistent with this hypothesis. For example, the degree of fibrin deposition may have no relationship to the extent of venous insufficiency and transcutaneous oxygen tension, and venous ulcers heal without a diminution of fibrin cuffs.[37,39-41] Similarly, the severity of lipodermatosclerosis does not correlate with the degree of fibrin deposition.[42] Fibrin cuffs were found to be discontinuous and irregular around dermal capillaries,[43] thus making their role as a physical barrier

unlikely.[44] These observations suggest that fibrin cuffs are unlikely as a physical barrier to the diffusion of small molecules such as oxygen and other nutrients.[13,45,46] Although some studies in patients with chronic venous insufficiency have shown diminished cutaneous oxygenation,[8,38,41,44,47-49] oxygen pressure improves with the administration of oxygen,[50] suggesting that a diffusion barrier, rather than deficient transport, is responsible for low oxygen tissue pressure.[29] Roszinski and Schmeller[51] observed that although intracutaneous Po_2 in lipodermatosclerotic skin was lower than in normal skin, it did not drop to levels consistent with hypoxia. This suggests that hypoxia may not be the cause of ulceration in venous hypertension.[51] The transcutaneous oxygen levels in the perilesional skin have not been found to be predictive of healing.[52] In fact, a relative hypoxia may favorably contribute to normal healing through stimulation of angiogenesis.[53]

Nevertheless, in patients with venous disease, diffusion of substances out of capillaries into the extravascular space is in fact abnormally increased,[54,55] and fibrinogen, a large molecule, passes into the interstitial fluid at a rate significantly faster than normal.[54-56] In addition to and as a possible cause of local fibrinolytic abnormalities such as the fibrin cuff formations, systemic fibrinolytic and coagulation abnormalities are present in patients with venous disease.[36,57,58] One example is that fibrin deposited in acute wounds is removed within days, but persists in chronic wounds.[59] In addition, patients with venous disease and ulceration have been found to have prolonged euglobulin lysis time, elevated plasma fibrinogen levels,[43,60] increased levels of protein C,[61] fibrin-related antigens, D-dimer, D-monomer, and fibrin monomer.[62] A significant reduction of factor XIII activity has been observed in the blood of patients with venous ulcers.[63] Depletion of this factor may be either causal or indicative of fibrin deposition at the wound site.[64] These observations suggest simultaneous increased fibrin formation and decreased breakdown in many patients with venous disease as a consequence of formation of fibrin cuffs and possibly delayed healing.[28] It is unclear whether these fibrinolytic and coagulation abnormalities are primary or secondary to venous disease.[65] However, Stacey et al[66] showed that the pericapillary fibrin deposition preceded the development of clinically apparent lipodermatosclerosis.

Apart from providing a barrier, there are other reasons why fibrin and certain fibrinogen fragments may play an important role in the pathogenesis of venous ulceration and lipodermatosclerosis.[64] Pardes et al[43] showed that fibrin and fibrinogen have a direct down-regulatory effect on procollagen type I synthesis by dermal fibroblast cultures. Similarly, fibroblasts on fibrin gels synthesize less collagen. One possible hypothesis is that the persistence and continued deposition of fibrin and certain fibrinogen fragments may inhibit the capacity of fibroblasts to produce collagen and thus retard repair.[43] Alternatively, fibrin and fibrinogen receptor breakdown products are chemotactic for fibroblasts. Fibrin has been shown to lead to fibrosis in vivo through the release of fibrinopeptides that have stimulatory effects on the replication and migration of fibroblasts and monocytes.[13] Co-localization of fibrin with collagen in certain fibrotic conditions has been established.[59] Thus fibrotic tissue developing as a consequence of fibrin deposition may contribute to the inflammatory process in lipodermatosclerosis and may predispose the tissue to ulceration and prolong the healing process.[65]

Other hypotheses relating venous hypertension and venous ulceration do not necessarily exclude a role for fibrin cuffs and fibrinolytic abnormalities.

The growth factor "trap" hypothesis

Falanga and Eaglstein[13] proposed that fibrinogen, α_2-macroglobulin, and other macromolecules that leak into the dermis as a result of venous hypertension or capillary damage "trap" growth factors and other stimulatory or homeostatic substances. As a result, the trapped molecules may be unavailable for the maintenance of tissue integrity and the repair process. α_2-Macroglobulin is a well-recognized scavenger of growth factors such as transforming growth factor β (TGF-β). Higley et al[67,68] demonstrated markedly increased levels of TGF-β1, α_2-macroglobulin, and collagen-producing fibroblasts abnormally distributed within the fibrin cuffs surrounding the capillaries of the ulcer bed. An inappropriate interaction between these molecules and others may result in unavailability to repair minor traumatic wounds in the area and a propensity to actual ulcerations.

White cell trapping hypothesis

As a result of venous hypertension, there is a reduced pressure gradient between the arterial and venous systems with a postulated consequent reduced flow in the capillary bed between the systems. This could lead to erythrocyte aggregation[69,70] in the capillaries and leukocyte plugging of the capillaries.[12,71] Between 5%[72] and 20%[73] of leukocytes have been shown to accumulate in dependent extremities of healthy subjects. These acute changes are reversible when the leg is elevated.[8] This "trapping phenomenon" occurred to a greater degree ($\leq$ 30%[72]) when legs of patients with venous disease were held in a dependent position.[71] These investigators[71] proposed that white blood cell plugging in

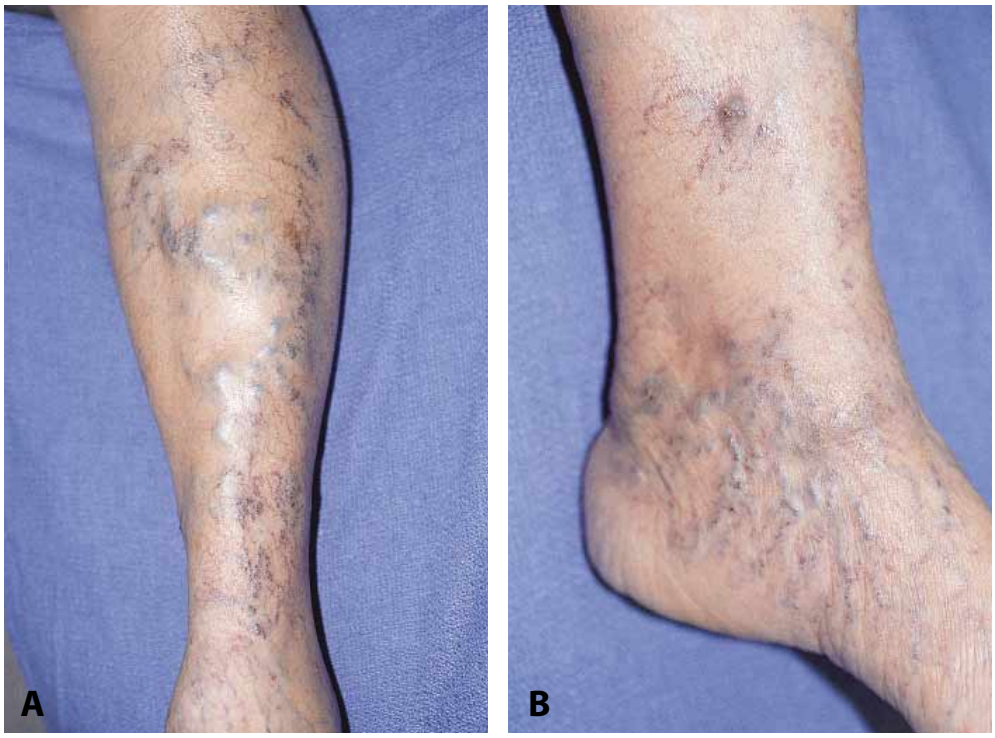

Fig 2. Varicosities are commonly the first sign of venous disease. **A,** Dilated long saphenous vein. **B,** Classic submalleolar venous flare.

the capillaries of lipodermatosclerotic limbs during dependency accounts for the capillary closure noted on microscopic sections, causing local ischemia.[74] The aggregation of leukocytes not only contributes to the physical barrier, but also causes the release of certain mediators (including proteolytic enzymes such as collagenase and elastase, cytokines, free radicals, and chemotactic factors), which can cause further vascular permeability and release of large molecules such as fibrinogen into the pericapillary tissues.[12,28]

PATIENT HISTORY

The clinical history of patients with venous ulceration is characterized by the lack of specific symptoms. There is variable discomfort associated with venous ulcers, the severity of which varies unpredictably between patients and their particular ulcers. The surface area of the ulcer does not correlate well with the presence of pain. Deep ulcers, particularly around the malleoli, or small venous ulcers surrounded by atrophie blanche are the most painful. Patients with venous ulcers commonly complain of swelling and aching of the legs, often worse at the end of the day, which may be exacerbated by dependency and improved by leg elevation.[75] The grading of the pain is important because when pain is severe, one should consider the possibility of either infection or a different cause for the ulceration, such as vasculopathy. In addition to pain, odor and copious drainage from the wound and pruritus of the surrounding skin are common associated findings.[33] A history of ulcer recurrence, particularly at the same location, is characteristic. Patients may have a history of phlebitis, deep vein thrombosis, or silent thromboses, commonly during or after pregnancy or surgical interventions.[7]

RISK FACTORS FOR VENOUS LEG ULCERATION

Most epidemiologic studies on chronic venous insufficiency are cross-sectional surveys that suggest potential risk factors by describing their study population. However, these relationships could be due to the older age of the population with chronic venous insufficiency. Scott et al[76] conducted a prospective dual case-control study to address this issue. They found that in addition to being older, patients with chronic venous insufficiency tend to be obese. They also commonly report a history of significant leg injury such as a broken leg, stab or gunshot wound, or a crush injury as well as phlebitis. In contrast, patients with varicose veins tend to be younger, female, have a history of phlebitis, and have a family history of varicose veins. In their study, patients with

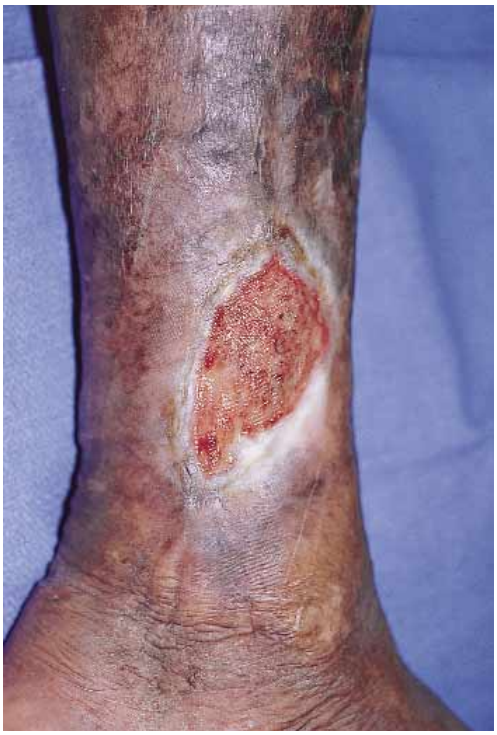

Fig 3. Ulcer in a typical location, above the medial malleolus. Note that the wound is shallow and has irregular borders and that the base is granulated and free of necrotic debris. A yellow, fibrinous base is commonly seen in early stages.

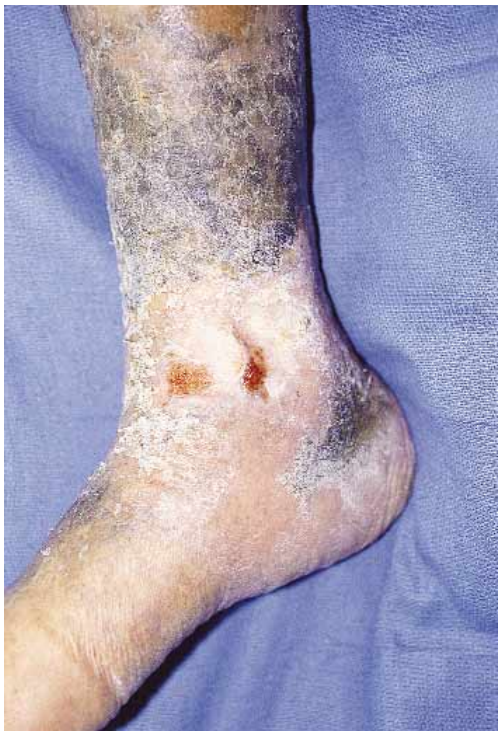

Fig 4. Chronic venous dermatitis is seen surrounding an ulcer in a typical location.

venous insufficiency were diagnosed with heart disease significantly more frequently than either the controls or patients with varicose veins. Scott et al[76] also reviewed the possible role of socioeconomic issues in venous ulcer development. They found that the only consistent significant indicator was a lack of medical insurance. Estimated family income or level of education was not predictive of ulcer development.

Insufficiency of the superficial, perforating, or deep veins of the legs are risk factors for leg ulceration. The degree and pattern of venous insufficiency are also predictive to ulcer formation.[77,78] Insufficiency of the superficial and perforating veins in combination carries a greater risk than insufficiency of the superficial veins alone. There is also a well-recognized association between deep venous thrombosis and venous ulceration, known as the postphlebitic syndrome.[79] However, the attributable risk of deep venous thrombosis for chronic venous insufficiency is unknown and requires further controlled prospective evaluation.[29] The possibility that previous leg injury may result in a subclinical deep venous thrombosis and finally in ulcer formation has also been raised. Other factors that may play a contributory role include chronic skin changes secondary to inadequate treatment of chronic venous insufficiency[80] and delayed treatment or failure to control edema.[81] Congenital absence of valves, previous surgery of varicose veins, primary valve or venous wall degeneration, and arteriovenous shunts may be important in the development of venous insufficiency.[29,35,82,83]

Factors such as type of employment and lifestyle can alter the course of venous ulcerations. Frequently, a job that requires long hours of standing tends to slow the healing of the wounds.[84]

CLINICAL PRESENTATION

One of the first obvious clinical signs of chronic venous insufficiency is varicose veins, although the recently described acute lipodermatosclerosis (see below) may precede the presence of varicosities.[85] The size of varicose veins may range from a submalleolar venous flare to various degrees of vessel dilation (Figs 2 and 3). Further progressive changes of chronic venous insufficiency include reddish-brown hyperpigmentation and purpura caused by extravasation of red blood cells into the dermis, collections of hemosiderin within macrophages, and melanin deposition.[7,86] Eczematous changes with redness, scaling, pruritus, and occasionally exudate, often referred as venous dermatitis, are commonly present. The dermatitis is caused or aggravated by

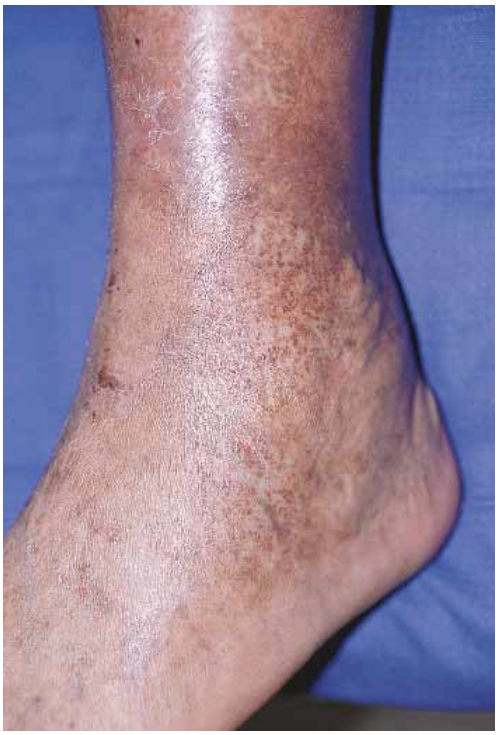

Fig 5. Changes of atrophie blanche: depressed ivory-white plaque surrounded with numerous telangiectatic capillaries. Although it is seen in the context of other disorders, nearly all patients with atrophie blanche show symptoms of venous incompetence.

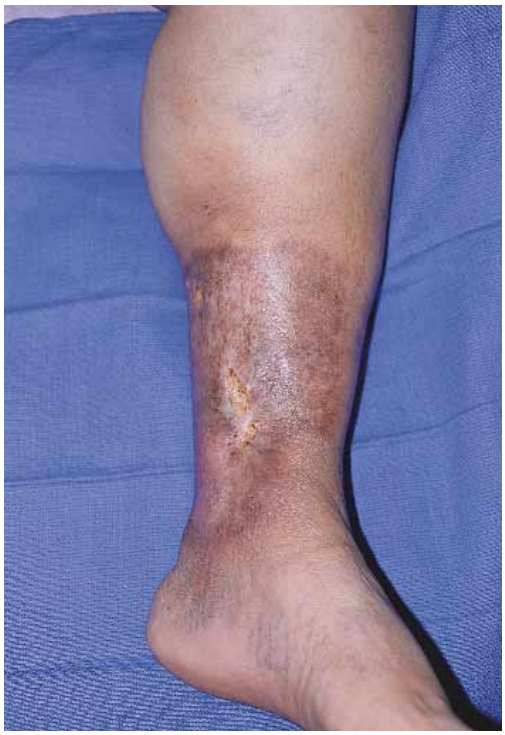

Fig 6. Advanced lipodermatosclerosis, characterized by an "inverted champagne bottle" appearance of the leg, with pigmentary changes and sclerotic, bound-down skin. The degree of induration correlates directly with delayed healing of the ulcer.

sensitization to applied topical medications to which patients with venous disease are particularly susceptible[27,33] (Fig 4). Dependent edema eventually develops toward the end of the day because of fluid leakage from local capillaries.[1] Atrophie blanche, defined as smooth, ivory-white atrophic plaques of sclerosis speckled with telangiectases, is described in up to 38% of patients with chronic venous insufficiency (Fig 5). Although atrophie blanche has been seen in the context of other vascular disorders and systemic conditions,[87-93] nearly all patients with atrophie blanche show symptoms of venous incompetence.[94] Ulceration of atrophie blanche lesions can be extremely painful; these ulcerated lesions also have a tendency toward slower healing.[94]

In long-standing venous disease, the surrounding skin may become indurated and fibrotic, involving eventually the entire lower third of the leg resulting in the appearance of an inverted bottle[7,85] (Fig 6). The induration is typically restricted to the medial leg and is sharply demarcated from proximal normal skin.[38,95] Atrophy of the epidermal surface and pigmentary change abnormalities are commonly seen.[1] Lipodermatosclerosis, a term used to describe these clinical findings, was initially called hypodermatitis sclerodermiformis by Huriez et al[96] and is likely the same as sclerosing panniculitis described later by Jorizzo et al.[97] Most authors agree that lipodermatosclerosis is highly associated with venous insufficiency or restricted to the legs of patients with venous insufficiency.[27,85] The severity of induration of lipodermatosclerosis may be prognostic because it has in some series been associated with poor wound healing.[52,98] An acute inflammatory stage of variable severity can precede the chronic phase of lipodermatosclerosis. The early stage, less commonly recognized, involves the leg above the malleolus (usually medially based) and is characterized by a more diffuse, not well-demarcated, extremely tender, erythematous, warm induration. This phase may develop without obvious clinical signs of venous disease and frequently leads to misdiagnosis as other clinical entities such as morphea, persistent cellulitis, erythema nodosum, and other panniculitides.[85] Lipodermatosclerosis frequently precedes the development of venous ulcers. However, lipodermatosclerotic skin is not invariably present, suggesting other or different mechanisms are likely involved in the pathogenesis of

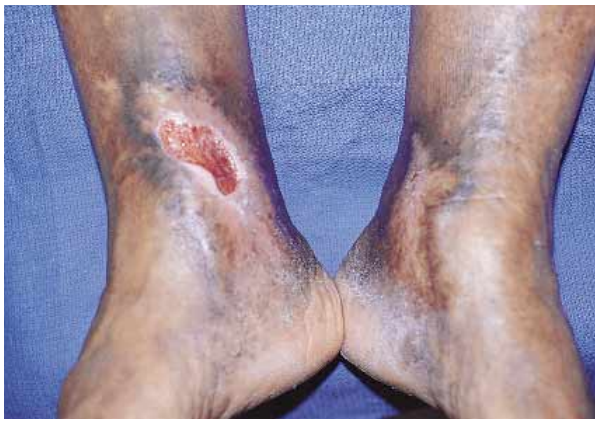

Fig 7. Majority of venous ulcers are located over the medial malleolus. Either or both legs may be affected. Notice surrounding hyperpigmentation and chronic dermatitic changes.

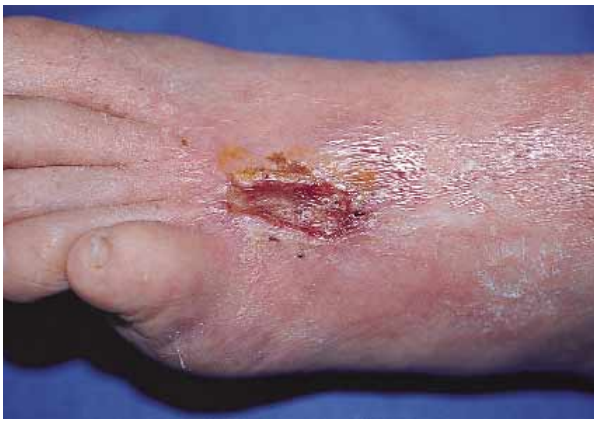

Fig 8. Venous ulcer involving the dorsum of the foot. An arterial origin was initially considered, but distal pulses were normal, ABI was 1.0, and angiogram showed no arterial disease.

venous ulcers.[27] In some studies, the degree of induration of lipodermatosclerosis correlates directly with delayed healing of the ulcer. Atrophie blanche can surround the venous ulcer in the presence or absence of lipodermatosclerotic skin. When seen separately, the degree of fibrinolytic abnormalities in any given patient may correlate with the presence of either lipodermatosclerosis or atrophie blanche.[99]

Venous ulcers may be single or multiple and, if left untreated, can involve the entire circumference of the leg.[29] They are characteristically located over the medial malleolus where the long saphenous vein is more superficial and has the greatest curvature (Fig 7). Trauma or infection may localize ulcers laterally or in more proximal locations; however, ulcers above the mid calf or on the foot commonly suggest another cause[1] (Fig 8). Venous ulcers generally have borders with irregular margins that are either flat or with a slight steep elevation. The wound bed of the venous ulcer tends to be shallow and rarely, if ever, shows necrotic eschar or exposed tendons. The presence of these should lead one to an alternative diagnosis.[33] A yellow, fibrinous bed is seen initially, but with appropriate therapy it usually evolves into a healthy granulation tissue base.[1]

DIFFERENTIAL DIAGNOSIS

Although most leg ulcers in large series are venous, the pathogenesis is not venous in all patients.[1] Other common causes are arterial and neuropathic; however, the cause of an ulcer is often multifactorial.[100]

Arterial ulcers typically appear round or punched out with a sharply demarcated border.[7,9,86] A fibrous yellow base or a true necrotic eschar with scant or absent granulation tissue is commonly seen. Necrotic tissue or the exposure of tendons and deep tissues also suggests an arterial etiology or prolonged pressure as the cause.[84,86] Associated findings of loss of hair, shiny and atrophic skin, abnormal toenails, cool feet, and weak or absent dorsalis pedis pulse also suggest arterial insufficiency. A prolonged capillary refilling time (>4-5 seconds) and the change in limb color with limb elevation are common findings. Although arterial ulcers frequently occur distally and over bony prominences, trauma may localize ulcers proximally, leading to diagnostic confusion with venous ulcers. The presence of claudication or in more severe cases rest pain is characteristic of arterial insufficiency. The ankle-to-brachial blood pressure ratio (ankle/brachial index [ABI]) measured by Doppler ultrasonography is an important tool to assess arterial circulation. An ABI of 0.9 or higher is normal, whereas an ABI of 0.5 or less indicates severe arterial disease.[101]

Neuropathic ulcers are associated with foot numbness, burning, and paresthesias or are occasionally asymptomatic.[7,86] Neuropathic ulcers are more common in, but are not limited to, patients with diabetes mellitus. Although patients with diabetes have an increased incidence of peripheral vascular disease, nearly 70% of diabetic foot ulcers are due to neuropathy with adequate vasculature. An abnormal, thickened callus develops at pressure areas, with eventual breakdown of the tissue resulting in ulcer formation.[102] Prolonged bacterial infection of these ulcers may be associated with underlying osteomyelitis.[103,104]

Inflammatory conditions such as pyoderma gangrenosum are less common. Pyoderma gangrenosum

is characterized by an ulcer with a characteristic, purplish-blue, undermined border and a cribriform base. Two thirds are associated with inflammatory conditions such as inflammatory bowel disease or rheumatoid arthritis or with hematologic malignancies.[105] Vasculitis may also cause chronic ulcers. Palpable purpura is the clinical hallmark of leukocytoclastic vasculitis; however, a polymorphous eruption that includes ulcers, necrotic areas, and livedo reticularis may be seen. Livedo reticularis (reticulated erythema) may be seen in other conditions, including cryoproteinemias and antiphospholipid syndrome.[9,106] Medium-sized vessel and large vessel vasculitis can also present with venous leg ulceration in combination with systemic involvement. Connective tissue diseases such as rheumatoid arthritis and systemic lupus erythematosus may also cause chronic relapsing ulcers of the lower extremities.[107]

Infectious organisms are also implicated in the formation of acute or chronic lower extremities ulcers and should be suspected when nonhealing ulcers do not conform to the usual pattern observed with more common conditions. Tissue culture, especially to look for fungal or atypical mycobacterial infections, will help elucidate the cause. Underlying diseases that result in immunosuppression predispose patients to such ulcerations.[100]

Biopsy of an ulcer is indicated to exclude basal cell or squamous cell carcinomas, which can occur in long-standing ulcers. Basal cell carcinomas arising from venous ulcers appear as exuberant granulation tissue rolling onto the wound edges.[108] Sibbald[1] recommends biopsy for those ulcers not improving after 6 weeks, for which edema control and bacterial balance of the wound have been achieved.

ASSESSMENT FOR VENOUS INSUFFICIENCY

In up to 76% of the cases, the diagnosis of venous ulceration may be made by clinical criteria alone.[109,110] Noninvasive methods are helpful for accurate diagnosis and anatomic and functional evaluation, but do not exclude overlapping causes for the ulceration.[9,110]

Measurement of the ABI by Doppler ultrasonography, as described earlier, is useful to exclude concomitant arterial disease because compression therapy in patients with undiagnosed arterial insufficiency can lead to ulcer worsening, gangrene, and limb amputation.[5] The ABI is unreliable in assessing arterial insufficiency in patients with diabetes mellitus, the elderly, and other conditions with calcified, noncompressible arteries.[111]

Continuous-wave Doppler studies are useful in providing information of the anatomic level of any superficial venous incompetence or obstruction; however, with this method, it can be difficult to differentiate superficial from deep venous insufficiency. Photoplethysmography and air plethysmography are simple noninvasive tests to measure the degree of venous reflux and the efficiency of the calf muscle pump. With the use of a tourniquet to occlude the superficial system, these tests help to assess a potential deep venous obstruction.[8,112]

Color duplex ultrasound scanning is currently the "gold standard" in evaluation of venous anatomy and physiology because of its accuracy, reproducibility, and noninvasive nature.[112,113] In addition, it has the advantage of visualizing other anatomic structures in the leg that can produce pain or swelling and mimic venous disease (eg, soft tissue masses, arterial aneurysms).[114]

Invasive phlebography is usually reserved for investigation before valvular surgery.[110] Immunofluorescence studies are highly sensitive in detecting the presence of pericapillary fibrin in the majority of venous ulcers; however, test specificity is not high.[37]

If there is suspicion of osteomyelitis, investigations such as bone scans, computed tomographic scans, and bone biopsies should be considered.[111]

TREATMENT

Treatment goals for patients with chronic venous insufficiency include reduction of edema, alleviation of pain, improvement of lipodermatosclerosis, healing of ulcers, and prevention of recurrence.[29] Better understanding of the pathophysiology of venous disease and leg ulceration has in turn suggested new approaches to the management of ulcer disease with new types of wound dressings, compression bandages, topical and systemic therapeutic agents, and surgical modalities.[8]

The primary role of treatment is to reverse the effects of venous hypertension. The simplest method is bed rest with leg elevation. However, this is usually impractical and difficult to enforce except in a hospital setting.[7] Unfortunately, inpatients are unable to spend the time needed in the hospital to reach complete re-epithelialization. Elevation of the legs above the heart level for 30 minutes, 3 to 4 times per day, allows swelling to subside and improves the microcirculation in patients with chronic venous insufficiency.[30,115] Leg elevation at night can be accomplished by propping up the foot end of the patient's bed on blocks 15 to 20 cm high.[116]

Mechanical therapy

Because leg elevation alone is usually not enough in more advanced disease, compression remains the cornerstone of therapy for patients with venous ulcers.

Patients who are compliant with compression therapy have a significantly improved ulcer healing rate and a decreased rate of recurrence; if the ulcers do recur, the interval to recurrence is more prolonged.[60,117,118] Compression is thought to either correct or improve venous hypertension, mainly owing to an improvement of the venous pump and lymphatic drainage.[119] Compression relieves the edema by raising the local hydrostatic pressure and decreasing the superficial venous pressure, in turn reducing the leakage of fluid and macromolecules. Although the acute effect of compressing a limb is a reduction of cutaneous blood flow,[119] edema reduction achieved with compression leads to an increase of cutaneous blood flow. This fact may be partly responsible for the increase in transcutaneous oxygen pressure that has been found by some authors.[39,40,119,120] Compression also improves blood flow velocity through unoccluded deep and superficial veins. Through an effect in lymph propulsion, continuous compression may improve clinically lipodermatosclerotic skin.[121] As demonstrated by isotopic lymphography, compression also enhances the lymph transport that is regularly reduced in deep vein thrombosis and in the postthrombotic syndrome.[122] Compression also enhances fibrinolysis.[123-125] Doppler ultrasonography and phlebography have demonstrated that reflux in the deep veins is decreased by external compression.[126] When there is not an anatomic abnormality of the valves, incompetent valves may become competent again by approximating the valve leaflets.[127] In addition to the mechanical effect, compression reduces the release of macromolecules into the extravascular space and thus prevents trapping of mediators important to wound healing.[64] The effectiveness of compression is enhanced by ankle movement. Walking and exercises should be encouraged.[128] Relative contraindications for compression include arterial insufficiency and uncompensated congestive heart failure.[129] Significant arterial insufficiency must be excluded by Doppler examination with determination of the ABI. Compression therapy is contraindicated in patients with a low ABI, and referral to a vascular surgeon for further testing and evaluation is indicated.[130]

Fletcher and Sheldon[131] recently reviewed 24 randomized controlled trials of compression/support system studies in venous disease. The authors found that many trials had limitations such as inadequate sample size and poor methodology. They were able to conclude that compression increases ulcer healing rates. They also found that compression alone is superior to a moist interactive dressing without compression and that high compression regimens are more effective than low compression.

The optimal pressure necessary to overcome venous hypertension is not well defined, but it is generally agreed that an external pressure of 35 to 40 mm Hg at the ankle is necessary to prevent capillary exudation in legs affected by venous disease.[132,133] Compression bandages may be harmful or useless if not applied correctly.[129,134,135] The best way to provide compression also remains controversial because multiple compression schemes have been advocated, as has the use of different materials.[119] However, given the limitation of our current knowledge and assuming that compression is successfully applied, the mode of application of compression appears less important.[131,136]

In compression therapy, two consecutive treatment phases can be distinguished. First is a therapy phase for the acute disease to reduce edema, which may help to heal venous ulcerations. For this phase, inelastic or rigid bandages as well as elastic and multilayered bandages can be used. The ideal bandaging system should help in decreasing the edema and be able to offer high working pressures (when the patient walks) and relatively low resting pressures (while the legs swing in relaxation).[137]

Rigid inelastic bandages mostly act as a support system because they give very little pressure at rest and high pressure with muscle contraction (high working pressures). The prototype of this bandage is the traditional Unna boot, a moist zinc-impregnated paste bandage.[119,138] Modified, less rigid Unna boots, also called short-stretch bandages, exhibit these properties. Examples include UnnaFlex (ConvaTec, Princeton, NJ) and Comprilan (Beiersdorf AG, Hamburg, Germany). Although there has been a gradual shift toward the use of elastic bandages in the last few years, there still seems to be a tendency to use a rigid bandage, such as the Unna boot, during the initial phase of edema reduction.[130,137] Unfortunately, the Unna boot does not accommodate changes in the volume of the leg associated with edema (as a consequence frequent reapplication is necessary) and is only effective in ambulatory patients. Unna boot can also cause an unpleasant odor that develops from wound exudate and has the potential to cause contact dermatitis.[84,86,137]

Long-stretch bandages, a type of elastic system, provide good working pressures but also higher resting pressures than short-stretch bandages. Therefore they are more useful after the initial stage when edema has been managed. Elastic compression bandages conform to the leg better, are easy to use, and allow for frequent dressing changes.[9] If applied in a spiral with 50% overlap between turns, producing a double layer bandaging at any point, they are able to provide sustained pressures.[24] The

major disadvantage of elastic wraps is their requirement of a substantial degree of sophistication for adequate application.[139] There are now 3 classes of elastic bandages, depending on the amount of pressure they exert.[140] Class I bandages are lightweight, comforming stretch products that have a simple dressing retention function. Class II are light support bandages and are sometimes called short or minimal stretch bandages because they behave as inelastic, rigid bandages. They are used to prevent the formation of edema in the treatment of venous leg ulcers and to provide support in the treatment of mild ankle sprains and strains. Class III are compression bandages, and, depending on the level of ankle pressures, they are further classified into classes IIIa (light compression bandages), IIIb (moderate compression bandages), IIIc (high compression bandages), and IIId (extra-high performance compression bandages). As a reference, class IIIc refers to bandages that achieve levels of compression on the order of 40 mm Hg on an ankle of average dimensions and are indicated for the treatment of severe varicosities, postthrombotic venous insufficiency, and the management of severe edema. Examples of type IIIc bandages, include Tensopress (Smith & Nephew), Setopress (Seton), and Surepress (ConvaTec).[140-142]

Multilayered bandage systems have recently been developed. Examples of prepackaged systems include those with 3-layered padding (Dynaflex, Johnson & Johnson, Arlington, Tex) and 4-layered padding (Profore, Smith & Nephew, New York, UK).[86] The 4-layered bandaging system was found to more quickly heal chronic venous ulcers that had failed to heal in many months of compression with traditional adhesive plaster bandaging.[114] A multilayered system can be adapted to a wide range of ankle circumferences and leg sizes and provides sustained pressures of 40 to 45 mm Hg at the ankle, graduating to 17 mm Hg below the knee. Although 3- or 4-layered elastic bandages cost more than the single-layered elastic bandage, they were shown to be less expensive in a comparative cost-analysis study because of faster healing rates.[117]

Pneumatic compression devices based on an intermittent inflation of air bags may also be used for the relief of edema[143,144] and to promote wound healing.[49,145] They were developed for the prophylaxis of deep venous thrombosis, especially in bedridden elderly or inactive patients or those with severe lymphedema.[119,146,147] They should also be considered when a venous ulcer does not respond to treatment with standard compression dressings.[86] Orthotic compression devices are another alternative for patients who require compression, but need frequent dressing changes or for those who find other compression bandages uncomfortable or difficult to use. They consist of multiple adjustable Velcro straps from the instep to the knee, can be easily applied and removed, and can be adjusted for patient comfort.[148]

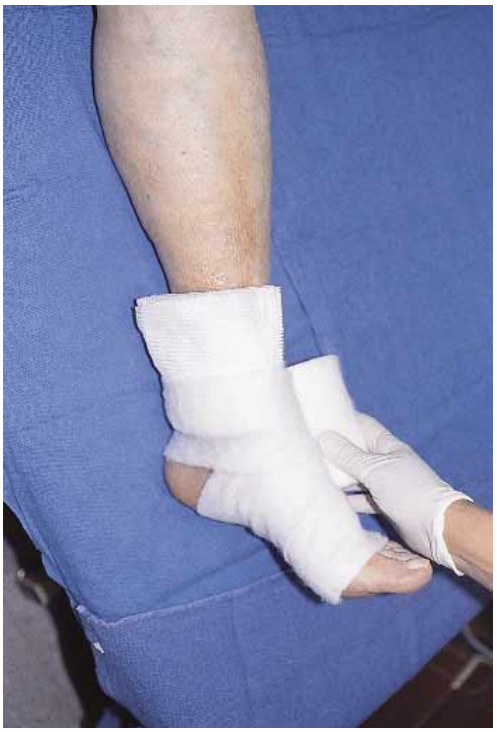

Fig 9. Example of localized supplemental pressure being applied to a venous ulcer. Extra layers of gauze are placed between the primary dressing and compression bandages. Localized supplemental pressure is used in ulcers located in "concave" regions of the leg, which may not receive adequate pressures during compression therapy.

Whatever bandaging system is used, it should be adapted to account for different ankle sizes.[24] At times the extra padding of dressing materials is necessary and should be specially considered when venous ulcers are not responding well to compression therapy.[27] Typically, these ulcers are located in the concave areas of skin near or below the malleolus. Because of the difficulty in applying compression to these areas, extra padding is used to ensure that therapeutic pressures are achieved locally[25,149] (Fig 9). In addition, patients with the classic "inverted champagne bottle"–shaped leg also benefit from the extra padding to the narrow areas to achieve more consistent graduated compression.[24]

For the second or maintenance phase, elastic materials such as graded compression stockings or compression bandages can be used to maintain integrity of the healed ulcer.[119] Because the stockings are made of elastic material, they are equivalent to

Table I. The 3 common types of leg ulcers

	Venous	Arterial	Neuropathic
Ulcer location	Medial malleolus; trauma or infection may localize ulcers laterally or more proximally	Distal, over bony prominences; trauma may localize ulcers proximally	Pressure points on feet (eg, junction of great toe & plantar surface, metatarsal head, heel)
Ulcer appearance	Shallow, irregular borders; base may be initially fibrinous, but later develops granulation tissue	Round or punched-out, well-demarcated border, fibrinous yellow base or true necrotic eschar; bone and tendon exposure may be seen	Callus surrounding the wound and undermined edges are characteristic; blister, hemorrhage, necrosis, and exposure of underlying structures are commonly seen
Physical examination	Varicose veins, leg edema, atrophie blanche, dermatitis, lipodermatosclerosis, pigmentary changes, purpura	Loss of hair, shiny, atrophic skin, dystrophic toenails, cold feet, femoral bruit, absent or decreased pulses, prolonged capillary refilling time	No sensation to monofilament; bone resorption, claw toes, flat foot, Charcot joints
Frequent symptoms	Pain, odor, and copious drainage from the wound; pruritus	Claudication, resting ischemic pain	Foot numbness, burning, paresthesias
ABI	>0.9	ABI <0.7 suggests arterial disease; calcification of vessels gives falsely high Doppler readings	Normal, unless associated with arterial component
Risk factors	Deep venous thrombosis, significant leg injury, obesity	Diabetes, hypertension, cigarette smoking, hypercholesterolemia	Diabetes, leprosy, frostbite
Complications	Allergic contact dermatitis, cellulitis	Gangrene	Underlying osteomyelitis
Treatment pearl	Compression therapy, leg elevation	Pentoxifylline, vascular surgery assessment if ABI <5	Vigorous surgical debridement, pressure avoidance

long-stretch bandages. After healing, patients should be encouraged to wear graded compression stockings for the rest of their lives to prevent ulcer recurrence. Each garment has a standard compression value graduated up the stocking, from a maximum at the ankle to a minimum at the thigh.[119,148] There are 4 classes of compression stockings based on the compression exerted at the ankle. Compression class I stockings exert an ankle pressure of 20 to 30 mm Hg and are indicated for varicose veins, mild edema, or leg fatigue. Compression class II stockings are 30 to 40 mm Hg and are indicated for moderate leg edema, severe varicosities, and moderate venous insufficiency. Compression classes III (40-50 mm Hg) and IV (≥ 60 mm Hg) are indicated for severe edema or elephantiasis and severe venous insufficiency with secondary postthrombotic edema. Elasticity of these stockings decreases with time and washing, and they should be replaced at least every 6 months.[148] Assuming proper measurement and fitting of hose (custom-fitted), specific instructions on how to put on compression stockings may enhance compliance. Despite adequate recommendations, arthritic, obese, or elderly patients do not have the strength or mobility to pull on the stockings. Most medical supply stores should have aids, which can facilitate application. Some examples of these include Stocking Donner (Beiersdorf-Jobst), Easy Slide (Sigvaris), and the Circaid garment (Circaid Medical Products, Inc, Coronado, Calif).[137,150]

The question of who can best be treated by compression therapy alone and who should be considered a candidate for an alternative therapy has recently begun to be studied. A recent retrospective cohort study determined the association of several risk factors with the failure of a venous leg ulcer to heal within 24 weeks of compression therapy.[151] The authors found significant associations with a larger wound area, greater duration of the wound, history of venous ligation or venous stripping, history of hip or knee replacement, ABI of less than 0.80, and the presence of fibrin on more than 50% of the wound surface. Other studies need to be designed to confirm the importance of these newly identified clinical parameters and to help wound care specialists to determine who can best be treated with compression therapy

alone, and who should be considered a candidate for another treatment. Alternatively, the finding of healing rates at 3 to 4 weeks of treatment to be predictive of eventual heal represents another predictive approach.

Wound debridement

It is commonly accepted that leg ulcers should be debrided of necrotic and fibrinous debris to allow formation of good granulation tissue and adequate epithelialization[152-154]; however, some have recently questioned the need for this procedure.[155] Good data do not exist to prove the benefit of debridement for venous ulcers; nevertheless it remains a part of the standard of care. There are several methods of wound debridement, including autolytic, chemical, mechanical, surgical, and biologic.[156-158]

Autolytic debridement. Compression therapy is the key to healing venous ulcerations, and the role of special dressings underneath the compression bandaging is not entirely clear. It may still be likely in venous ulcers that wound occlusion itself promotes re-epithelialization and it clearly reduces associated pain, enhances autolytic debridement, and provides an additional barrier to bacteria.[159-161] Few randomized studies have been performed comparing the dressings, but most clinicians agree that maintenance of a moist wound environment accelerates wound healing compared with the desiccated environment caused by air exposure.[162,163] Five basic types of occlusive dressings are available, each with its own advantages and disadvantages. These include hydrogels (eg, IntraSite gel, Nu-Gel, Vigilon), alginates (eg, Sorbsan, Kaltostat, Algiderm), hydrocolloids (eg, Comfeel, DuoDerm, Restore), foams (eg, Allevyn, Curafoam, Lyofoam), and films (eg, OpSite, Tegaderm). The choice of dressing is usually determined according to the type of wound, the amount of exudate, cost considerations, and patient and physician preference.[86] In two randomized controlled studies of different contact dressings, in combination with the multilayered bandage, no material was found significantly better than a simple nonadherent dressing.[164,165] Kikta et al[166] showed that the rate of ulcer healing was no different in patients treated with Unna boots as compared with those treated with occlusive hydrocolloidal dressings, but patients preferred the latter therapy because of ease of ulcer care. However, the application of a hydrocolloid alone without adequate compression is unlikely to yield satisfactory results in the outpatient setting. Mulder, Bolton, and Lydon[167] demonstrated lysis of fibrin cuffs treated with hydrocolloid dressing, but whether this is of clinical importance is not known.

Chemical debridement. To promote the removal of necrotic tissue and the formation of healthy granulation tissue, several enzyme-debriding agents have been advocated.[168-172] Application of specific proteolytic enzymes to venous ulcers could accelerate the removal of fibrin cuffs and trapping by other macromolecules.[173]

Several enzyme-debriding agents are commercially available in the United States, including collagenase (Santyl, Knoll Pharmaceuticals), papain (Panafil, Rystan Company, Inc, and Accuzyme, HealthPoint Medical), and trypsin (Granulex, Dow Hickham Pharmaceuticals).[154,156] The dressings are changed one to several times a day following manufacturer's recommendations. A recently published report of a double-blind randomized study showed that Elase was ineffective in debriding venous ulcers.[174] Topical application of tissue plasminogen activator appears to be a promising therapy; however, it is unclear whether this treatment works by fibrin removal.[175] Compelling evidence of the clinical efficacy of these agents from randomized, large-scale, controlled studies is lacking.[156,176] Some have even questioned whether these agents truly provide an additional benefit over more standard therapies.[155,177]

Mechanical debridement. There are several methods of mechanical debridement including application of wet-to-dry dressings, hydrotherapy, irrigation, and dextranomers.[157] The major disadvantage of mechanical debridement is its nondiscriminatory removal of viable tissue along with necrotic material.[158] There are no studies indicating that whirlpool or irrigation actually enhances wound healing, although many clinicians would argue that they are helpful.[156] Dextranomer is a very hydrophilic structure with a highly absorptive capacity, especially useful for wounds with heavy exudate. Its major drawback is the possibility of causing dehydration of the wound bed. Sharp surgical debridement is a rapid way to remove necrotic tissue or eschar, indicated in only specific situations and almost never in venous ulcers because these are usually free of frank necrosis or eschar tissue.[130] This may be accomplished with a curet, forceps, scalpel, or sharp scissors.

Growth factors

Studies on wound fluid suggest that the effects produced by occlusive dressings might be a consequence of their ability to keep fluid-rich growth factor activity in contact with healing tissues.[178] The idea that keeping growth factors in contact with healing tissues might speed healing has focused recent investigations on the use of exogenous polypeptide growth factors.[179-182] Investigations at the University of Miami found that topical application of human recombinant epidermal growth factor was safe but failed to significantly enhance re-epithelialization of venous ulcers. However, these

authors found a greater reduction in ulcer size and more ulcers healed as compared with the placebo group, but this was not statistically significant.[46] Alternatively, using a porcine model of epithelialization, Cazzamoga et al[183] found that topical application of the growth factor inhibitor Suramin reduced the speed of epithelialization of occluded wounds by 20% when placed on the initial day of wounding, which suggests the importance of growth factors in healing.[183] These results are encouraging, and interesting research on the use of growth factors continues. Platelet-derived growth factor, which is the only topical growth factor available on the market, is approved for use in diabetic ulcers. Whether this agent is useful for venous ulcers has not yet been determined.

Topical antibiotics

Care must be used with any topical preparation because patients with chronic venous insufficiency have an increased susceptibility to contact dermatitis. If a severe contact dermatitis develops, a short course of systemic steroids may be needed.

The use of topical antibiotics is controversial, with the potential of the emergence of resistant organisms.[184,185] Topical antiseptics have been shown to have cellular toxicities that exceed their bactericidal activities and have been found to impair wound epithelialization.[186-188] Recently, cadexomer-iodine preparations have been shown to be safe, to have useful antimicrobial properties, and to be effective in wound debridement, stimulation of granulation tissue, and overall wound healing.[189] Hillstrom[190] reported a mean decrease of 34% in venous ulcer size from cadexomer iodine treatment, whereas the wounds in the control group actually increased in size. Similarly, Holloway et al,[191] evaluating wound closure in 75 patients with venous disease, reported double the rate of healing for cadexomer iodine treatment compared with the control group.

Systemic therapy

Systemic pharmacotherapy for venous leg ulceration may be useful as an adjuvant to standard compression therapy.[192] Most medications used as adjuvant therapy possess mechanisms of action that address one or more of the factors that have been identified in the pathophysiology of venous leg ulceration.[8] A frequent dilemma is determining when an ulcer is infected or merely colonized with bacteria because wound swab cultures usually reveal polymicrobial growth. Tissue quantitative cultures are helpful, but usually not available. The presence of more than 10^5 bacteria per gram of tissue may impede wound healing and regeneration.[192-195] Systemic antibiotics have not been shown to improve the healing rates of venous ulcers and should be reserved for ulcers with clinically apparent cellulitis.[196] An additional complexity is distinguishing infection from contact dermatitis in an edematous and erythematous leg. Although an increase in C-reactive protein levels has been correlated with clinical signs of infection in the context of venous ulceration, the value of this test needs further evaluation.[197]

Given the persistence and importance of systemic fibrinolytic abnormalities and the presence of pericapillary fibrin cuffs in venous ulceration, fibrinolytic therapeutic modalities have merited great investigative interest. Stanozolol, an androgenic steroid with fibrinolytic properties, has been found to be helpful in the treatment of acute and chronic lipodermatosclerosis.[198-200] Jarret et al[201] showed clinical improvement and enhanced fibrinolysis in 3 patients after 3 months of therapy. Similarly, Browse et al[202] reported a reduction in pain and skin induration in 14 patients with lipodermatosclerosis whom they treated with stanozolol and compression stockings. Burnand et al[199] compared stanozolol with elastic stockings and placebo with elastic stockings. They found both treatments were helpful in alleviating the thickness and pain of lipodermatosclerosis, but stanozolol and compression were superior.[203,204] Kirsner et al[85] have successfully treated patients with acute and chronic lipodermatosclerosis, observing generally a decrease in pain and discomfort after 3 weeks of stanozolol therapy. Although lipodermatosclerosis is alleviated by stanozolol, no studies have demonstrated an increase in the rate of healing of ulcers within affected skin.[57,205,206] Stanozolol is a safe agent, and most of its side effects are minor and reversible. Peliosis, hepatitis, and hepatocellular carcinoma are probably the most rare but feared of the serious side effects.[207] Other side effects include sodium retention with concomitant edema and hypertension, hirsutism, acne, liver function and lipid abnormalities, and dysmenorrhea, all of which are reversible.[203,204] Patients to be treated with stanozolol should undergo blood pressure measurement, prostate examination, liver function tests, lipid profile, test for prostate-specific antigen, complete blood cell count, and kidney function tests.

It was hoped that ifetroban, a thromboxane receptor antagonist, would stimulate venous ulcer healing. However, a double-blind randomized study that included 150 patients failed to demonstrate increased effectiveness of this therapy over compression therapy alone.[208]

The effectiveness of pentoxifylline in healing venous ulcers may be due, at least in part, to the fibrinolytic action of this agent.[209] Pentoxifylline may

also work by reducing leukocyte adhesion to the vascular endothelium[210] and by its antithrombotic effects.[211] These actions of pentoxifylline are probably mediated by effects on cytokine production.[212] In a controlled trial, Colgan et al[192] reported complete healing of the target ulcer in 23 of the 38 patients treated with pentoxifylline 400 mg 3 times a day. However, in a more recent randomized, double-blind, placebo-controlled trial of 200 patients with confirmed venous ulcers, administration of 400 mg of pentoxifylline 3 times a day was not more effective than placebo.[213] It may be that higher doses of pentoxifylline are needed. This concept was supported by a recent study of 131 patients that showed that pentoxifylline 800 mg 3 times a day accelerated the healing rate of venous ulcers and was more effective than the conventional dose (400 mg 3 times a day).[209,214]

An increased rate of venous ulcer healing with the use of oral enteric-coated aspirin (300 mg) daily has been reported. Whether ulcer healing was promoted by inhibiting platelet aggregation or by reducing inflammation has yet to be determined.[215]

Daflon, a micronized and purified flavonoidic fraction, has been shown to be of benefit in symptomatic disturbances of venolymphatic origin. This medication appears to work by decreasing the white blood cell plugging to endothelial cells, reducing the capillary increased permeability and increasing red blood cell velocity. Daflon at a daily dose of 1000 mg/day was used in addition to compression stockings in 105 patients with venous ulcers in a multicenter trial for a 2-month period. This study showed that Daflon was of benefit in patients with venous ulceration by accelerating healing of ulcers smaller than 10 cm. However, a longer follow-up is needed to further evaluate the efficacy of this drug.[216] Recent work from Italian investigators found that sulodexide, a heparin-like molecule with profibrinolytic and antithrombotic activity, speeds healing of venous ulcers in combination with compression therapy compared with compression alone.[217]

Surgery

Surgical treatment of venous ulcers may be directed toward modifying the cause of venous hypertension or treating the ulcer itself by a graft. There are no specific indications for when skin grafting for lower extremity ulcers should be used. Larger or refractory ulcers are two instances when grafting should be considered.[218] Even if grafts do not take, they likely stimulate wound healing, and in very painful ulcerations skin grafting may rapidly and markedly relieve pain.[219] However, grafted ulcers are at risk as they are commonly contaminated, subject to trauma, and when in a dependent position, may have vascular compromise.[220]

Nevertheless, split-thickness skin grafts (STSGs) have been successfully used for the treatment of chronic leg ulcers, with healing rates up to 75%.[221-224] Kirsner et al[221] used STSGs to treat 36 ulcers of various causes and observed that 78% were either completely or partially healed at follow-up. Importantly, they observed that if patients remained healed for 3 months, long-term success improved. Trier, Peacock, and Madden[222] had a 54% complete healing rate in a study of 100 patients grafted over 17 years. Similarly, they reported finding a similar critical 3-month period postgrafting after which, if the graft was intact, it tended to remain so. Harrison[225] treated 34 patients with venous ulcers with STSGs and obtained long-term follow-up in 28. He found that major medical problems/medications, multiple hospital admissions, immobility, local leg problems such as dermatitis, chronicity of ulceration, and patients who lived alone were risk factors that predisposed patients to a less successful outcome. Despite the success rates reported with STSGs for chronic wounds, there are a significant percentage of patients who do not heal with grafting. Possible contributing factors include noncompliance,[221,222] a local fibrin deficiency in the wound bed preventing the adhesion of the graft,[226] or the presence of microthrombi in the dermal vessels leading to ischemia and impairment of graft take.[57] Pinch grafting is a useful option for smaller wounds. They have the advantage of leaving several millimeters between each graft to allow exudate to drain out and not lift the graft from the ulcer's surface.[149] Meshed grafts are useful for large highly exudative ulcers because they also allow exudate to escape through the graft interstices.[227]

Superficial vein surgery (ligation or sclerosis of the long and short saphenous systems, with or without communicating vein ligation or sclerosis) has been shown to be of value in decreasing the rate of recurrence only if the deep veins are competent, but this benefit is not obtained when the deep veins are incompetent.[218,228] Superficial vein surgery has not been shown to improve the healing rate of venous ulcers.[218]

Radical excision of the ulcer bed, the fibrotic suprafascial tissues, and the diseased superficial and perforating veins as well as coverage of the large soft tissue defect with a free flap have been successfully used in a few cases. Whether this intervention is needed is not known. However, the magnitude of the surgical technique definitively limits its application.[229,230]

New therapies

The tissue-engineered skin equivalent Apligraf has been recently approved by the Food and Drug Administration and is approved in other countries

for use in venous ulcers. In a trial recently published by Falanga et al,[231] patients with venous ulcers were randomized to receive compression therapy with or without Apligraf. Two hundred seventy-five patients were evaluated in this prospective, multicenter, controlled study. The authors found that significantly more patients healed at 6 months when treated with Apligraf plus compression therapy than with compression alone (63% vs 49%; $P = .02$). In addition, the median time to complete wound closure was significantly shorter with Apligraf (61 vs 181 days). Apligraf was particularly effective in difficult-to-heal ulcers—ulcers of more than 6 months' duration and larger and deeper ulcers. Apligraf was both safe and nonimmunogenic in this trial.

Several case reports and pilot studies have demonstrated that topical application of granulocyte-macrophage colony-stimulating factor promotes healing of leg ulcers.[232-235] In a recent report, Jaschke, Zabernigg, and Gattringer[235] observed complete healing in 90.4% of 52 venous ulcers treated with granulocyte-macrophage colony-stimulating factor and compression therapy, with an average healing time of 19 weeks and a 6% relapse rate 1 year after healing. A noncontact radiant heat bandage (Warm-up Active Wound Therapy, Augustine Medical, Eden Prairie, Minn) was found to be safe and efficacious for the inpatient treatment of recalcitrant chronic venous ulcers in 17 patients.[236] Similarly, monochromatic infrared energy was effective in healing leg ulcers of different origins.[237] Controlled studies are needed to confirm the actual benefits of these therapies.

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CME examination

Identification No. 801-103

Instructions for Category I CME credit appear in the front advertising section. See last page of Contents for page number.

Questions 1-30, Valencia IC, Falabella A, Kirsner RS, Eaglstein WH. J Am Acad Dermatol 2001;44:401-21.

Directions for questions 1-15: Give single best response.

1. Each of the following statements is true regarding the epidemiology of venous ulcers *except*
   a. up to 80% of leg ulcers are caused by venous disease.
   b. variance of prevalence of venous ulcers may be due to inclusion or exclusion of foot ulcers and history of healing and recurrence.
   c. contributing factors to the overall burden of venous ulcers include the impact on work productivity and premature disability.
   d. a slight female predominance has been observed.
   e. Venous ulcers are more common with increasing age and only 10% of patients have their first ulcer by 40 years of age.

2. Each of the following statements is true regarding the normal venous system of the leg *except*
   a. the venous system is divided into 3 components: the superficial, communicating, and deep systems.
   b. blood is moved from the leg toward the heart primarily by the pumping action of the leg muscles.
   c. in the erect position, the pressure in the superficial and deep systems approximate 120 mm Hg at rest.
   d. on ambulation, the calf muscle contracts and pressure rises transiently in the deep system.
   e. an intact venous system and calf pump are essential in avoiding retrograde flow to the superficial system.

3. Mechanisms involved in venous hypertension include each of the following *except*
   a. most commonly caused by dysfunction of valves in the superficial and/or communicating veins with a normal deep system
   b. muscle dysfunction and calf muscle pump failure
   c. congenital absence or inherent weakness of valves in the superficial or deep systems
   d. dysfunction of valves in the deep system with or without deep venous outflow obstruction
   e. fewer than 10% of venous ulcers are due to deep venous incompetence alone

4. Which of the following statements is true regarding the hypothesis of pericapillary fibrin formation?
   a. The degree of pericapillary fibrin deposition correlates with the extent of venous insufficiency.
   b. Consistent data have shown that fibrin cuffs are a physical barrier to the diffusion of oxygen and other nutrients.
   c. The severity of lipodermatosclerosis does correlate with the degree of fibrin deposition.
   d. The transcutaneous oxygen level in the perilesional skin has been found to be predictive of ulcer healing.
   e. Diffusion of large molecules out of capillaries into the extravascular space is abnormally increased.

5. Which of the following statements is true regarding the pathogenesis of venous ulcers?
   a. An increased activity of factor XIII has been observed in patients with venous ulcers.
   b. Accumulation of fibrin is persistent in both acute and chronic wounds.
   c. Fibrosis may develop as a consequence of fibrin deposition.
   d. Entrapment of growth factors and other stimulatory substances may favor the repairing process.
   e. Decreased levels of transforming growth factor $\beta 1$ and α_2-macroglobulin have been found in the pericapillary fibrin cuffs.

6. Patient history of venous ulcers includes each of the following *except*
   a. alleviation of pain by leg elevation
   b. correlation of the size of the ulcer with the presence of pain
   c. characteristic aching and swelling at the end of the day
   d. ulcer recurrence at the same location common
   e. odor and copious drainage from the wound are common

7. Risk factors associated with venous leg ulcerations include each of the following *except*
   a. history of deep venous thrombosis
   b. significant leg injury
   c. previous surgery of the leg
   d. older age and obesity
   e. female gender

8. Which of the following clinical features is characteristic of venous insufficiency?
   a. Varicosities always precede the development of venous ulcers.

b. The so-called "venous dermatitis" is commonly due to the application of topical agents.
c. Atrophie blanche is only seen in the context of venous incompetence.
d. Lipodermatosclerosis is invariably present in venous insufficiency.
e. The severity of lipodermatosclerosis does not correlate with ulcer healing.

9. Clinical findings of venous ulcers include each of the following *except*
   a. majority located over the gaiter area
   b. are significantly more common on the left leg
   c. can involve the entire circumference of the leg
   d. characteristically have flat, irregular edges
   e. can be surrounded by areas of atrophie blanche or lipodermatosclerosis

10. Which of the following statements is *true* regarding leg ulcers?
    a. Arterial ulcers always localize distally on the leg.
    b. A yellow fibrinous bed is rarely seen in venous ulcers.
    c. The majority of diabetic foot ulcers are associated with peripheral vascular insufficiency.
    d. Necrotic eschar or exposed tendons suggest an arterial origin.
    e. None of the above

11. Which of the following statements is *false* regarding the diagnosis of leg ulcers?
    a. An ankle/brachial index greater than 0.5 rules out an arterial ulcer component.
    b. Clinical criteria alone are sufficient to diagnose venous ulceration in the majority of cases.
    c. The ankle/brachial index is unreliable in conditions with calcified arteries.
    d. Color duplex ultrasound scanning is the "gold standard" in evaluating venous disease.
    e. Invasive phlebography should be reserved for investigation before valvular surgery.

12. Treatment goals for patients with venous insufficiency include each of the following *except*
    a. reduction of edema
    b. prevention of recurrence
    c. alleviation of pain
    d. alleviation of lipodermatosclerosis
    e. all of the above

13. Which of the following statements regarding mechanical therapy for venous insufficiency is *true*?
    a. It does not decrease rate of recurrence.
    b. Compression relieves the edema by lowering the local hydrostatic pressure.
    c. Compression enhances fibrinolysis.
    d. Walking and exercises should be discouraged while receiving compression therapy.
    e. Compression has no effect on blood flow velocity.

14. Which of the following statements is *false* regarding compression therapy?
    a. It increases blood flow velocity.
    b. It reduces the release of macromolecules into the extravascular space.
    c. It reduces reflux in the deep veins.
    d. Arterial insufficiency is a relative contraindication.
    e. Low compression is as effective as high compression in ulcer healing.

15. Factors associated with failure of venous ulcers to heal with compression therapy include
    a. multiple limb ulcers
    b. deep vein thrombosis
    c. low venous flow index
    d. history of venous ligation or stripping
    e. presence of varicosities or dermatitis

Directions for questions 16-20: For each numbered item, choose the appropriate lettered item.

a. Rigid bandage
b. Class II elastic bandages
c. Maintenance phase
d. Pneumatic compression
e. Localized supplemental pressure

16. Bed-ridden elderly patients
17. Ulcers in the concave areas
18. Mild sprains and strains of the ankle
19. Unna boot
20. Compression stockings

Directions for questions 21-25: For each numbered item, choose the appropriate lettered item.

a. Occlusive dressings
b. Proteolytic enzymes
c. Mechanical debridement
d. Surgical debridement
e. Cadexomer-iodine

21. Whirlpool
22. Chemical debridement
23. Autolytic debridement
24. Dextranomers
25. Collagenase

Directions for questions 26-30: For each numbered item, choose the appropriate lettered item.

a. Stanozolol
b. Ifetroban
c. Daflon
d. Cadexomer-iodine
e. Sulodexide

26. Heparin-like molecule
27. Micronized flavonoidic fraction
28. Thromboxane receptor antagonist
29. Peliosis hepatitis
30. Antimicrobial properties

Answers to CME examination

Identification No. 801-103

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1. e
2. c
3. a
4. e
5. c
6. b
7. e
8. b
9. b
10. d
11. a
12. e
13. c
14. e
15. d
16. d
17. e
18. b
19. a
20. c
21. c
22. b
23. a
24. c
25. b
26. e
27. c
28. b
29. a
30. d