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TOPICAL REVIEW

Causes, investigation and treatment of leg ulceration

J.R.MEKKES, M.A.M.LOOTS, A.C.VAN DER WAL* AND J.D.BOS

*Departments of Dermatology and *Pathology, Academic Medical Center, University of Amsterdam, Meibergdreef 9, 1105 AZ Amsterdam, The Netherlands*

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Summary Chronic ulceration of the lower leg is a frequent condition, with a prevalence of 3–5% in the population over 65 years of age. The incidence of ulceration is rising as a result of the ageing population and increased risk factors for atherosclerotic occlusion such as smoking, obesity and diabetes. Ulcers can be defined as wounds with a 'full thickness depth' and a 'slow healing tendency'. In general, the slow healing tendency is not simply explained by depth and size, but caused by an underlying pathogenetic factor that needs to be removed to induce healing. The main causes are venous valve insufficiency, lower extremity arterial disease and diabetes. Less frequent conditions are infection, vasculitis, skin malignancies and ulcerating skin diseases such as pyoderma gangrenosum. But even rarer conditions exist, such as the recently discovered combination of vasculitis and hypercoagulability. For a proper treatment of patients with leg ulcers, it is important to be aware of the large differential diagnosis of leg ulceration.

Key words: aetiology, differential diagnosis, leg ulcer, treatment

Chronic ulceration of the lower leg including the foot is a frequent condition, causing pain, social discomfort, and generating considerable costs. Prevalence numbers (all ulcers) range from 1% in the adult population to 3–5% in the population over 65 years of age.[1,2] In a recent study, the prevalence of venous leg ulcers only in the over 65 years of age population in the U.K. was estimated to be 1–2%.[3] In Western countries, the incidence of ulceration is rising as a result of the ageing population,[3] and increased risk factors for atherosclerotic occlusion such as smoking, obesity and diabetes.[1,4–9]

Various definitions of the term ulcer exist but the two main criteria are 'full thickness depth', which implies that there are no sources for re-epithelialization left in the centre of the ulcer, and a 'slow healing tendency'. In most definitions, 'slow healing' is further specified by defining a time frame (present for more than 4 weeks) to separate chronic ulcers from acute wounds. In general, the slow healing tendency is not simply explained by depth and size, but caused by an underlying pathogenetic factor that needs to be removed to induce healing.

Although most leg ulcers are caused by venous insufficiency (approximately 45–60%), arterial insufficiency (10–20%), diabetes (15–25%) or combinations of these well known aetiological factors (10–15%),[4,5] rare underlying disorders may exist.

For a rational approach towards patients with leg ulcers, it is important to have detailed knowledge of the clinical picture, pathogenesis, diagnostic possibilities and treatment modalities of the common causes, but at the same time to be aware of the large differential diagnosis of leg ulceration. Because an incorrect diagnosis usually leads to incorrect treatment (a classic example is pyoderma gangrenosum treated with antibiotics), which may cause serious harm to patients, early careful assessment is crucial.

It is convenient to make a distinction between common causes and rare causes. The more common causes of leg ulceration (e.g. venous insufficiency, lower extremity arterial disease, diabetes) are listed in Table 1 and discussed below in some detail, with attention to the pathogenesis, diagnosis and (new) treatment modalities. Table 2 provides an overview of all causes of leg ulceration, including rare causes,

Correspondence: J.R.Mekkes.
E-mail: j.r.mekkes@amc.uva.nl

Table 1. Common causes of leg ulceration

Venous insufficiency (post-thrombotic syndrome)
Peripheral arterial disease (arteriosclerosis)
Diabetes (neuropathy and/or arterial occlusion)
Decubitus (pressure)
Infection (mostly *Streptococcus haemolyticus*)
Vasculitis (small vessel leucocytoclastic vasculitis)

grouped according to their main pathogenetic mechanism. Some of these entities will be discussed.

Common causes

Venous insufficiency

Venous ulceration is caused by increased pressure in the venous system. The main cause of venous hypertension is insufficiency of the valves in the deep venous system and the lower perforating veins. These veins and good functioning of their valves are necessary for the return of venous blood to the heart at each contraction of the calf muscles ('the muscle pump'). Intact valves but absent muscle contraction (immobility, paresis) may also cause oedema and ulceration, a condition known as dependency syndrome. Valve insufficiency may be acquired as in post-thrombotic syndrome or caused by congenital weakness of valves or vessels. The exact pathogenetic cascade leading from valve insufficiency to ulceration is still not fully elucidated.[4] The clinical symptoms of venous insufficiency are oedema, lipodermatosclerosis, hyperpigmentation, hyperkeratosis, and atrophie blanche preceding ulceration.[6] On a microvascular level, the observations are microlymphangiopathy, dilatation of larger lymph vessels,[10] dilatation and elongation of capillaries,[11] occlusion of capillaries by microthrombi[12] or white cells,[13] reduction of the number of functional capillaries,[10,11] increased capillary passage, leakage of plasma proteins and even erythrocytes, leading to iron accumulation in the interstitium, partly in siderophages, fibrin deposition, and ingrowth of fibroblasts along the fibrin fibrils.[12] The functional alterations are reduction, reversion and stagnation of blood flow in the capillaries of prenecrotic skin, increased pressure in the capillaries, increased blood flow in the deeper stratum reticulare capillary network, increased blood flow and arteriovenous shunting near ulcers, and decreased skin oxygen pressure in areas at risk.[11,14] Laboratory results can indicate anaemia, elevated erythrocyte sedimentation rate, iron deficiency, zinc deficiency, decreased fibrinolytic activity, increased plasma and full blood viscosity,[15] or clotting disorders predisposing to thrombosis.[16–18]

In the past, some of these observed phenomena, such as shunting of blood near ulcers, the fibrin cuff, iron accumulation, white cell accumulation, decreased fibrinolytic activity, binding of transforming growth factor-β and other growth factors by macromolecules such as fibrin or α-macroglobulin,[19] and various inflammatory responses to the vascular damage, were believed to be 'the final cause of venous ulceration'. To date, it is still not clear whether they represent causative factors or epiphenomena. Most authors believe that the haemodynamic changes on the microvascular level are sufficient to explain venous ulceration.[11,12,15,20,21] The capillaries, originally designed as a low-pressure system, are malformed by the increased tension in the venous system, and especially by the retrograde pressure waves during calf muscle contractions in deep venous insufficiency. The capillary changes (dilatation and elongation) lead to reduction of blood flow, disturbed rheological conditions,[15] sludging and aggregation of cells, and finally to microthrombi formation and occlusion of capillaries.[11,12] In addition, increased pressure in the venous system increases transendothelial and interendothelial capillary passage, resulting in a protein-rich oedema. Oedema in itself may contribute to tissue hypoxia because it simply increases the diffusion distance for oxygen around the nourishing capillaries.[14] In the end, this results in a fibrotic and oedematous skin area where a considerable number of capillaries are missing, while those remaining are malformed and dysfunctional. The slightest trauma or infection in these areas disturbs the balance between oxygen supply and demand and a chronic nonhealing ulcer develops.

The relative frequency of venous leg ulcers is diminishing as a result of improved community care, improved prevention, diagnosis and treatment of thrombosis, and an increase in arterial ulcers.[5,6,22] Still, the costs associated with venous leg ulcers are considerable, approximately £200 million yearly in the U.K.,[23] and $1 billion in the U.S.A.,[3,22,24] where the yearly costs for hard-to-heal ulcers may be up to $27 500 per patient.[25]

The mainstay of treatment (and prevention of new ulcers) is the control of oedema by adequate compression therapy. Provided that the patients are bandaged by experienced personnel, there are no differences between nonelastic, short stretch, two-layer or multilayer compression bandages.[5,26–28] Because many patients have ulcers of combined aetiology, e.g. venous

Table 2. Causes of leg ulceration

Venous insufficiency and dependency
Venous valve insufficiency in the deep (usually post-thrombotic) or superficial venous system
Venae communicantes insufficiency
Congenital hypoplasia/aplasia of venous valves
Weakness of the venous wall (collagen disorders)
Arteriovenous anastomosis, angiodysplasia
Compression or obstruction of veins (tumours, enlarged lymph nodes, pelvic vein thrombosis)
Ulcerating thrombophlebitis, ruptured varices
Dependency syndrome (immobility, arthrosis, rheumatoid arthritis, paresis, paralysis, orthopaedic malformations)
Arterial occlusion
Peripheral arterial disease (arteriosclerosis)
Arterial thrombosis/macrothromboembolism and microthromboembolism (fibrin, platelets)
Fat embolism (hypercholesterolaemia, hyperlipidaemia)
Detachment of cholesterol containing plaques from aorta, aneurysm or atrium (atrial fibrillation)
Thromboangiitis obliterans (Buerger disease)
Arteriovenous anastomosis (congenital/traumatic)
Trauma, rupture, infection, vascular procedures
Fibromuscular dysplasia
Microcirculatory disorders
Raynaud phenomenon, scleroderma
Hypertension: ulcus hypertensivum (Martorell ulcer)
Increased blood viscosity (increased fibrinogen level, paraneoplastic, paraproteinaemia, leukaemia)
Blood transfusion reactions
Physical or chemical injury
Pressure (decubitus), pressure by shoes, plaster of Paris, orthopaedic appliances, compression bandages
Trauma, burn wounds, freezing, electricity
Röntgen damage, intra-articular injection of Yttrium-90
Chemical (corrosive agents), sclerotherapy
Artificial (automutilation)
Infectious diseases
Erysipelas (bullosa), ecthyma, fasciitis necroticans (*Streptococcus haemolyticus*), ulcerating pyoderma (*S. aureus*), gas gangrene (*Clostridium*), ecthyma gangrenosum (*Pseudomonas*), septic embolism (*Meningococcus* and others), bacterial endocarditis, anthrax (*Bacillus anthracis*), Diphtheria (*Corynebacterium diphteriae*)
Osteomyelitis (several microorganisms)
Complications by secondary wound infections
Toeweb infection
Herpes, cytomegalovirus, lues maligna (lues III, gummata)
Leprosy, framboesia (yaws), ulcerating cutaneous tuberculosis, lupus vulgaris, atypical mycobacteria, Buruli ulcus (*Mycobacterium ulcerans*), papulonecrotic tuberculid
Tularaemia (*Franciscella tularensis*)
Leishmaniasis
Tropical ulcer (*Bacteroides, Borrelia vincenti* and other bacteria)
Madura foot, Maduramycosis (eumycetoma/mycetoma), chromoblastomycosis, coccidiomycosis, sporotrichosis, granuloma trichophyticum
Amoebiasis
Histoplasmosis
Bacillary angiomatosis
Neuropathic diseases
Diabetes, leprosy, alcohol neuropathy, tabes dorsalis, syringomyelia, spina bifida, paraplegia, paresis, multiple sclerosis, poliomyelitis
Vasculitis
Small vessel: small vessel-leucocytoclastic vasculitis, microscopic polyangiitis, Wegener granulomatosis, allergic granulomatosis (Churg–Strauss), Henoch–Schönlein purpura, essential cryoglobulinaemic vasculitis, erythema induratum Bazin, livedo reticularis, livedo vasculitis and Sneddon syndrome
Medium-sized: polyarteritis nodosa, Kawasaki disease
Large vessel: giant cell arteritis (polymyalgia rheumatica, Takayasu arteritis)
Haematological disorders
Sickle cell anaemia, other forms of anaemia, thalassaemia, hereditary spherocytosis, glucose-6-phosphate dehydrogenase deficiency, essential thrombocythaemia, thrombotic thrombocytopenic purpura, granulocytopenia, polycythaemia, leukaemia, monoclonal dysproteinaemia (Waldenström disease, myeloma), polyclonal dysproteinaemia (cryofibrinogenaemia, purpura,hyperglobulinaemia, cold agglutinins)

Table 2. (Continued)

Clotting disorders	Factor V Leiden, lupus anticoagulant, anticardiolipin (antiphospholipid syndrome), disturbed fibrinolysis, factor XIII deficiency (may be associated with colitis ulcerosa), antithrombin III deficiency, protein C or S deficiency, Marcoumar necrosis, large haematoma, purpura fulminans, diffuse intravasal coagulation
Metabolic diseases	Diabetes mellitus, necrobiosis lipoidica, porphyria cutanea tarda, gout, calciphylaxis, calcinosis cutis, homocysteinuria, prolidase deficiency, hyperoxaluria
Ulcerating tumours	Basal cell carcinoma, squamous cell carcinoma, malignant melanoma, metastasis, pseudoepitheliomatous hyperplasia, epithelioma (Marjolin ulcer), lymphoma, leukaemia, cutaneous T-cell and B-cell lymphoma, Hodgkin disease, sarcoma, lymphosarcoma, rhabdomyosarcoma, haemangiosarcoma, lymphangiosarcoma, Kaposi and pseudo-Kaposi sarcoma
Ulcerating skin diseases	Pyoderma gangrenosum, pemphigoid and other bullous diseases, panniculitis, periarteritis nodosa, erythema induratum (Bazin), malignant atrophic papulosis (Degos), erythema exudativum multiforme, sarcoidosis, erythema elevatum diutinum, Behçet disease, cutaneous discoid and systemic lupus erythematosus, scleroderma, lichen planus, keratosis actinica, contact dermatitis, fat necrosis/pancreatic fat necrosis, trench foot, insect bites, lymphoedema, lipoedema, myxoedema, erythermalgia/erythromelalgia, perniosis (chilblains), haemangioma, Stewart–Bluefarb syndrome
Drug reactions	Steroid ulcus (intralesional injection), vaccination ulcer (BCG), halogens, ergotamin, methotrexate, hydroxyureum, paravasal injection of cytostatic and other drugs, granulocyte-colony stimulating factor
Miscellaneous	Corpus alienum, orthopaedic fixation materials Klinefelter syndrome Rheumatoid arthritis, Felty syndrome Ulcus phagedenicum Acro-osteopathia ulceromutilans (Bureau–Barrière) Complement C3 deficiency Langerhans cell histiocytosis TAP 1 mutation

and diabetic, or venous and arterial, it is recommended that arterial insufficiency be ruled out before applying a compression bandage, especially when elastic bandages are used. This can be done by measuring the ankle–brachial pressure index (ABPI, see below), which should be over 0·8.[26,29] Especially in diabetic patients, who may have combined neuropathy and arterial insufficiency, compression therapy should be applied with caution. Simple reliance on the ABPI can produce a false sense of security as a result of non-compressible arteries due to calcification in diabetes patients.[30]

Surgical restoration or replacement of destroyed deep venous valves is still not a routine option.[31,32] Superficial incompetent veins can be ligated and/or removed, or embolized by sclerocompression therapy, but their role in the aetiology of venous leg ulcers is limited. Insufficient perforating veins, especially the lower Cockett veins are of haemodynamic importance because they transmit the high pressure to the overlying skin, and they can be ligated by (multiple) incisions or new subfascial endoscopic techniques,[33] but the value of this procedure in the presence of deep venous insufficiency is doubtful.[31,32] With the possible exception of pentoxifylline,[6,34] there is insufficient evidence that systemic drugs are beneficial.[23,35] Patients with resistant or large ulcers may require hospitalization, additional wound bed preparation and skin grafting. An old-fashioned but efficient method is full-thickness autologous skin grafting, using punch biopsy grafts.[36] Commercially cultured allogeneic skin grafts such as Apligraf© (Novartis, East Hanover, NJ, U.S.A.) have also been reported to accelerate healing,[37,38] especially in a subgroup of ulcers of long duration,[38] but more data are needed on cost-effectiveness, long-term results and recurrence rates.[39] The transplanted allogeneic cells do not survive; eventually they are replaced by the patient's own fibroblasts and keratinocytes, but the cell-seeded skin equivalents induce a healing tendency, probably through cytokine production.[38] For about a decade now it has been possible to culture an autologous dermal–epidermal skin equivalent from a small tissue specimen from the patient's upper leg, within 14–21 days.[36] These grafts will not be rejected, but the procedure is logistically complicated and expensive.

Lower extremity arterial disease

The incidence of critical leg ischaemia is increasing.[4,22,40] Risk factors for arteriosclerotic occlusion are diabetes (four- to fivefold increase of incidence of peripheral vascular disease), smoking, hyperlipidaemia, hypertension, obesity and age. Some influencing of risk factors is possible by education of the public, or by drug therapy (antihypertensive drugs, antilipaemic agents, transdermal nicotine, low-dose aspirin).[7,8,41] Arteriosclerotic occlusion usually affects the entire femoropopliteal trajectory including important distal branches (arteria peronea, tibialis anterior and tibialis posterior), and may lead to extensive distal damage. It may also affect only small-sized branches, leading to limited infarction of skin and subcutaneous tissue with a relatively good prognosis. The latter variant is not detected by a routine vascular examination. Large occlusions require surgical interventions, which may be revascularization by means of bypasses using the patient's own veins or artificial vein grafts, or by means of intravascular procedures such as balloon dilatation (percutaneous transluminal angioplasty), sometimes combined with thrombolysis and the placement of stents.[42] The average costs of a surgical intervention for critical leg ischaemia, including all necessary measures to secure graft maintenance during a 5-year follow-up period are US$35 000–47 000.[43,44] Femoropopliteal vein grafts have higher patency rates than femorocrural procedures.[38] Ideally, necrotic tissue can be excised in the same operation session, and in some cases, vascularized flaps can be used to close the defects. The efficacy of pharmacological treatment of existing disease with vasoactive or anticoagulative drugs is disappointing; antilipaemic agents are under investigation and may be useful. A future development, although still in the experimental phase, may be intravascular gene therapy with vascular endothelial growth factor, which may induce collateral neovascularization in inoperable ischaemic legs.[45]

Diabetes

Among diabetic patients, 2–3% will develop a foot ulcer each year, 15% will develop a foot ulcer during their lifetime.[9,46] The average costs per case from ulcer presentation to complete resolution may be £4730–10 930, and up to £20 800–31 800 when amputation is required.[47,48]

In the classic diabetic foot, distal sensorimotor and autonomic neuropathy is the major cause, often combined with arterial insufficiency caused by atherosclerotic occlusion of the tibioperoneal arteries, with sparing of the pedal arteries.[8,49] Approximately 60–70% have neuropathy only, 15–20% have peripheral vascular disease only, and 15–20% have a mixture of both.[50] The contribution of occlusive microvascular disease in the aetiology of diabetic foot ulcers has not been confirmed by histology, vascular casting or vascular resistance studies and therefore seems to be a misconception.[51] The frequency and severity of wound infection is increased in diabetes, which may be related to high glucose levels or impairment of granulocytic function and chemotaxis.[52] In addition, there seems to be prolonged inflammation, impaired neovascularization, decreased synthesis of collagen, an abnormal pattern of synthesis of extracellular matrix proteins, and decreased fibroblast proliferation.[53]

The main principles of treatment are relief of any pressure at the wound site, aggressive surgical debridement, adequate control of infection (beware of osteomyelitis), arterial reconstruction if necessary, and strict control of glucose levels. Pressure relief may be accomplished by total contact casting, which is the most extensively studied technique,[54] orthopaedic shoes or bed rest. Debridement of devitalized tissue at frequent intervals has been shown to heal neuropathic ulcers more rapidly.[55] There are few data to support the use of enzymatic or other non-surgical debridement strategies. Mild infections can be treated with oral antibiotics (e.g. flucloxacillin, clindamycin, amoxicillin–clavulanate, cefalexin, ciprofloxacin, or combinations, such as clindamycin + ciprofloxacin). Severe infections may require high-dose intravenous antibiotics (e.g. ceftazidime, imipenem–cilastatin, piperacillin–tazobactam, vancomycin, flucloxacillin + gentamicin, and many other combinations).

If the standard measures fail, some benefit may be derived from new therapeutic options such as recombinant human growth factors, bioengineered skin substitutes,[56] dressings made of extracellular matrix molecules such as collagen or hyaluronic acid, and a variety of synthetic dressings.[57] Although there is no evidence that any specific dressing type accelerates the healing process,[54] the beneficial effect of a moist wound environment has been well established. Randomized controlled clinical trials with growth factors in diabetic ulcers have shown efficacy of topically applied platelet-derived growth factor BB,[58] and granulocyte-colony stimulating factor.[59] The main effect of biological skin substitutes is to promote wound healing by stimulating the host to produce various cytokines. Dermagraft©

(Smith & Nephew, York, U.K.), a bioabsorbable polyglactin mesh seeded with cultured neonatal dermal fibroblasts, induced healing in 50% of diabetic ulcers after 8 weeks of treatment, vs. 7·7% in the control group;[60] however, no significant differences in ulcer recurrence rates were noted.[60] Apligraf© (Novartis), an allogeneic bilayered cultured skin equivalent, applied for 4 weeks, achieved complete wound healing at 12 weeks in 56% of patients with diabetic foot ulcers, vs. 38% in the control group.[61]

Recent research indicates that the incidence of both vascular and neurological complications of diabetes can be significantly reduced when intensified insulin therapy maintains blood glucose concentrations at near-normal levels.[57,62] Significant steps are undertaken towards fully automatic control of glucose levels by an implantable artificial pancreas.[63] Management of dyslipidaemia also deserves attention, and finally, patient education increases awareness of potential hazards (pressure, minor skin trauma) and reduces infection and ulcer recurrence.

Decubitus

Pressure ulcers develop when soft tissue is compressed between a bony prominence and an external surface for a prolonged period of time. Risk sites are the heel and malleoli, followed by the sacral and trochanter areas. It usually occurs in hospitalized patients that are temporarily or permanently unable to change their position due to circumstances such as general anaesthesia, sedation, coma, paresis/spinal injury or fractures. Additional risk factors are incontinence, bad nutritional state, increased body temperature, diabetes, peripheral arterial diseases and age.[64,65] Decubitus can be divided into four stages, depending on the extent of tissue damage: stage I, nonblanchable erythema; stage II, partial thickness loss of skin layers (blister, abrasion); stage III, full thickness loss exposing subcutaneous fat (superficial ulcer); stage IV, exposed muscle or bone (deep ulcer or necrosis).[22]

The prevalence of pressure ulcers ranges from 6·8–14·6% in home care settings and 5·1–15·6% in general hospitals, to 25–41% in geriatric nursing homes.[64,66] The costs generated by decubitus ulcers are enormous. Rough estimates indicate that the annual costs of pressure sore treatment in the U.K. are about £150 million.[22] Obviously, maximum attention should be given to preventive measures. It is generally recommended to have a decubitus protocol available to all staff which contains a validated scale for risk assessment. Depending on the risk assessment, preventive measures can be taken varying from frequent inspection, general measures to diminish pressure (spreading the body weight over an area as large as possible), frequent changes of position, and the use of special foam or air chamber mattresses, low-air-loss systems or air-fluidized mattresses.[65] Ulcer treatment consists of surgical removal of necrotic tissue, followed by the repeated application of dressings (saline soaked gauzes, hydrogels, hydrocolloids and many others) that further remove debris and induce granulation tissue formation.

Infectious diseases

Some microorganisms can cause tissue necrosis, such as the notorious β-haemolytic *Streptococcus pyogenes*. This bacteria causes a range of severe clinical symptoms varying from erysipelas, punched-out ulcers (ecthyma), deep cellulitis, to fasciitis necroticans, sepsis and multiorgan failure. Immediate high-dose antibiotic treatment is necessary, with special attention to the possibility of combined infections with *Staphylococcus aureus* and anaerobic species.

All chronic wounds are secondarily contaminated with bacteria, but in most cases, with the exception of the microorganisms listed in Table 2, they are not of pathogenetic importance. Wound cultures are often routinely performed, but give only information about the bacterial flora in the superficial layers. The decision to prescribe systemic antibiotics should be based on the combination of culture results and clinical criteria, such as signs of infection (fever, erythema, calor). In osteomyelitis, a common complication of neuropathic ulcers, efforts should be made to obtain representative cultures from the bone or deepest tissue layers, prior to antibiotic treatment, which should be given in high doses, preferably parenterally, and for at least 6 weeks.[67] The diagnosis has become easier after the introduction of labelled leucocyte scanning and especially, magnetic resonance imaging.

Acquired immune deficiency due to human immunodeficiency virus (HIV)-infection reintroduced ulcerative conditions that were thought to be eradicated, such as tertiary lues and ulcerating tuberculosis, and may be associated with atypical, large ulcers caused by herpes simplex or cytomegalovirus. In addition, bacillary angiomatosis, caused by *Rochalimae* species, and histoplasmosis must be included in the differential diagnosis of ulcerations occurring in HIV disease.[68,69] Increased world travel has brought tropical ulcerating infections to Western countries, especially

Leishmaniasis, but also atypical mycobacteria, ulcus tropicum[70] and deep mycotic infections.

Vasculitis

Vasculitis denotes a heterogeneous group of diseases characterized by inflammatory vessel damage. Several subdivisions can be made, based on vessel size (large vessel, medium-sized, small vessel), infiltrate type (polymorphonuclear, mononuclear, granulomatous) or clinical presentation.[71] Cutaneous vasculitis may present as purpura, erythema, urticaria, noduli, bullae, or skin infarction leading to ulceration. Cutaneous ulceration is usually caused by medium-sized to small vessel leucocytoclastic vasculitis.[72] Persistent or progressive ulceration due to histologically confirmed vasculitis is an indication for immunosuppressive therapy.

Ulcerating vasculitis may be caused by antineutrophil cytoplasmic antibodies (ANCA), autoantibodies against antigens in neutrophils, such as myeloperoxidase and proteinase 3 (PR3). Using indirect immunofluorescence techniques, ANCA can be detected in a perinuclear pattern (often antimyeloperoxidase) or a cytoplasmic pattern (often anti-PR3). They were first identified in Wegener granulomatosis, later also in other types of small vessel vasculitis, now classified as ANCA-associated vasculitides (Wegener disease, microscopic polyarteritis, idiopathic glomerulonephritis and Churg–Strauss syndrome).[73,74]

Rare causes

Hypertension and ulcus hypertensivum Martorell

Hypertension is a known risk factor for atherosclerotic occlusion. In addition, antihypertensive drugs (beta-blockers) may interfere with wound healing due to peripheral vasoconstriction.[75] A rare condition exists called Martorell ulcer (Fig. 1), seen in patients with prolonged, severe or suboptimally controlled hypertension.[76] The ulceration is secondary to tissue ischaemia caused by increased vascular resistance. The ulcers are usually located at the lower limb, above the ankle region, contain black necrosis and are extremely painful. By definition, the distal arterial pulsations are normal, and the diagnosis is made by histological examination, which shows concentric intima thickening and marked hypertrophy of the media of small-sized and medium-sized arteries, and by exclusion of other conditions that may cause ulceration in this area. The differential diagnosis consists of arteriosclerotic occlusion of small-sized arteries, diabetic angiopathy, vasculitis, thromboembolic occlusion (e.g. in atrial fibrillation) and pyoderma gangrenosum. Treatment consists of reducing hypertension, avoiding beta-blockers, adequate control of pain, and local wound care.

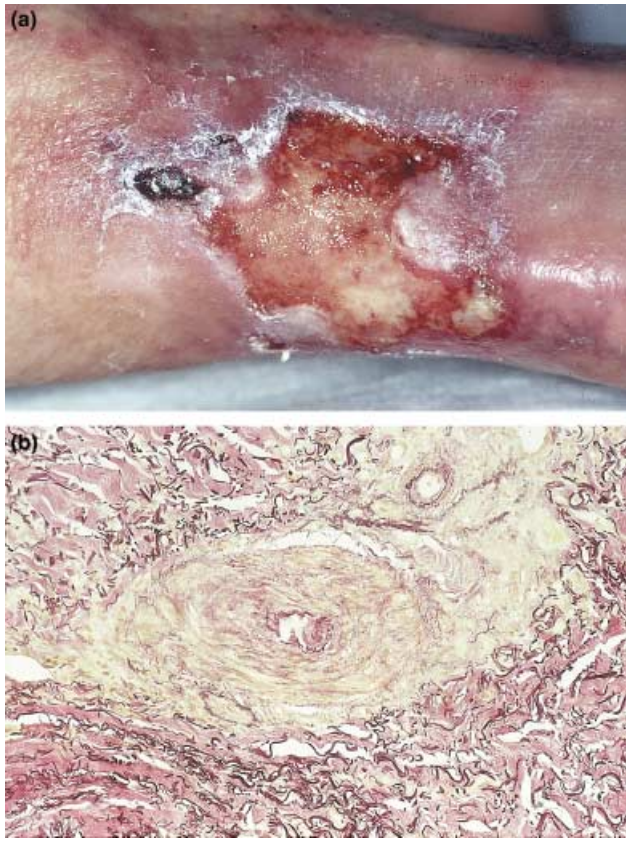

Figure 1. (a) Ulcus hypertensium (Martorell). (b) Histology: narrow lumen and hypertrophy of the media of a small-sized artery (Elastica van Gieson stain, original magnification ×40).

Felty syndrome

Felty syndrome (Fig. 2), defined by the triad of rheumatoid arthritis, splenomegaly and neutropenia, is associated with skin ulcers, probably caused by vasculitis. In general, the incidence of leg ulcers in rheumatoid arthritis is slightly increased.[77,78] In a minority of patients the ulceration is caused by vasculitis; other explanations are venous insufficiency and dependency (impairment of the venous pump caused by immobility and ankle joint dysfunction), deformities, trauma, ill-fitting shoes (pressure), neuropathy, coexisting arterial insufficiency or pyoderma gangrenosum.[78] If vasculitis

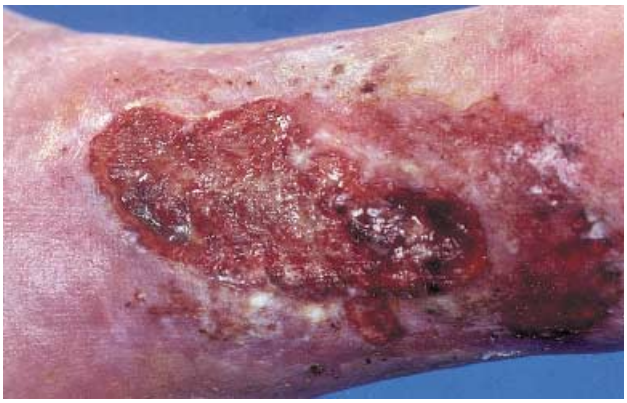

Figure 2. Vasculitis ulcer in a patient with Felty syndrome.

can be confirmed histologically, immunosuppressants are indicated.

Raynaud phenomenon and scleroderma

Patients with Raynaud phenomenon or scleroderma may develop painful ulcerations at the acra of the fingers and toes. The exact pathogenesis is unknown, but microvascular damage, associated with increased serum levels of endothelial adhesion molecules and endothelium-associated cytokines plays an important role.[79] In scleroderma, ulceration is more severe (sometimes leading to gangrene and amputation of digits) and may occur at other regions of the body. Infection and osteomyelitis are common complications. Treatment consists of preventive measures, local wound care, antibiotics if necessary, and vasodilating drugs such as nifedipine, angiotensin-converting enzyme inhibitors, or intravenous prostacyclin may be tried.[80]

Haematological disorders

Several forms of anaemia (sickle cell anaemia, thalassaemia, hereditary spherocytosis, glucose-6-phosphate dehydrogenase deficiency) have been associated with lower leg ulceration. In sickle cell anaemia, an increased number of activated endothelial cells has been found in the circulation, and it is hypothesized that an interaction between sickle cells and endothelial cells causes increased expression of endothelial cell adhesion molecules, which promotes thrombotic vaso-occlusion.[81] In addition, in the other haematological conditions (e.g. essential thrombocythaemia, thrombotic thrombocytopenic purpura, polycythaemia, leukaemia, dysproteinaemia), microvascular thrombosis is the most likely pathogenetic factor.

Clotting disorders

Hypercoagulable disorders may cause ulceration, either indirectly as a consequence of venous thrombosis, or directly by thrombus formation in small arteries, arterioles, capillaries or venules.[82,83] A growing number of hereditary or acquired conditions predisposing to thrombosis have been identified (Table 2), such as the antiphospholipid syndrome, deficiency of antithrombin III, protein C or protein S,[84] or abnormal clotting factors (factor V Leiden, factor II mutant).[16,17,83] It is not the laboratory abnormalities, but the specific clinical picture that determines whether a patient should be treated with anticoagulant drugs.

Combinations of vasculitis and clotting disorders

This combination (Figs 3 and 4) may be more frequent than the current literature suggests. The two rare conditions together predispose for necrosis. Vasculitis damages the vascular wall, but does not always lead to ulceration. An additional hypercoagulable state may lead to extensive microvascular thrombi formation. For factor V Leiden such a sequence of events is likely. The vascular damage initiates the coagulation cascade, prothrombin is converted to thrombin, and thrombin activates factors V and VII. Coagulation is normally controlled by circulating antithrombin III, and locally by thrombomodulin, which is present on endothelial cells and binds thrombin (Fig. 5). The thrombin–thrombomodulin complex activates protein C. Activated protein C (and protein S) inactivates factors Va and VIIa, but the mutant factor V Leiden ($^{506}R \rightarrow {}^{506}Q$) is resistant to inactivation by protein C. As a consequence, the local protection mechanism against thrombosis does not work adequately.

Hydroxyurea ulcer

Hydroxyurea is a cytostatic drug used in chronic myeloproliferative disorders. A rare complication is the development of painful ulcers (Fig. 6), usually localized on the malleoli.[85] The ulcers do not develop immediately; there may be an interval of 2–15 years between the start of hydroxyurea treatment and the first ulceration. The ulcers are very therapy resistant, and often it is necessary to discontinue hydroxyurea treatment.

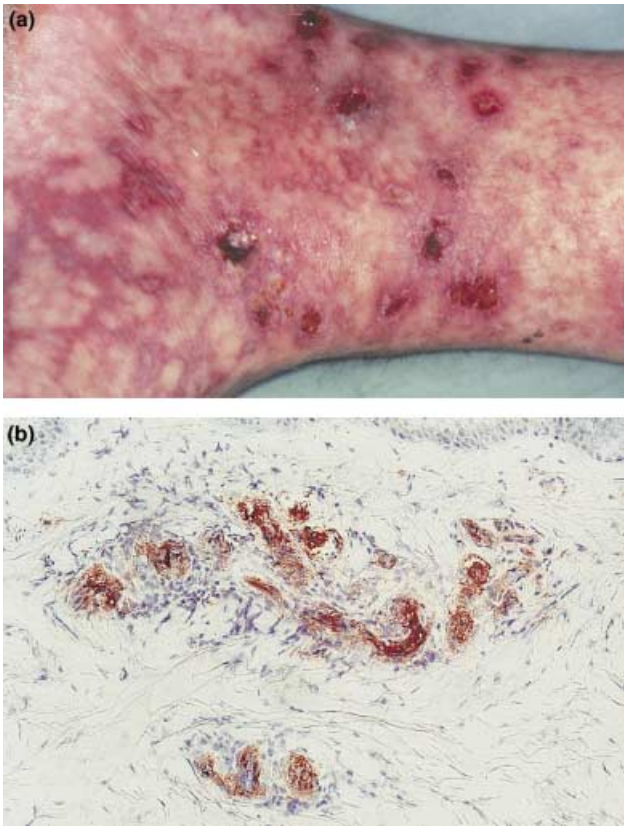

Figure 3. (a) Leucocytoclastic vasculitis in combination with factor V Leiden. (b) Histology: microvascular occlusion by platelet-rich thrombi (CD61 staining for thrombocytes, original magnification ×40).

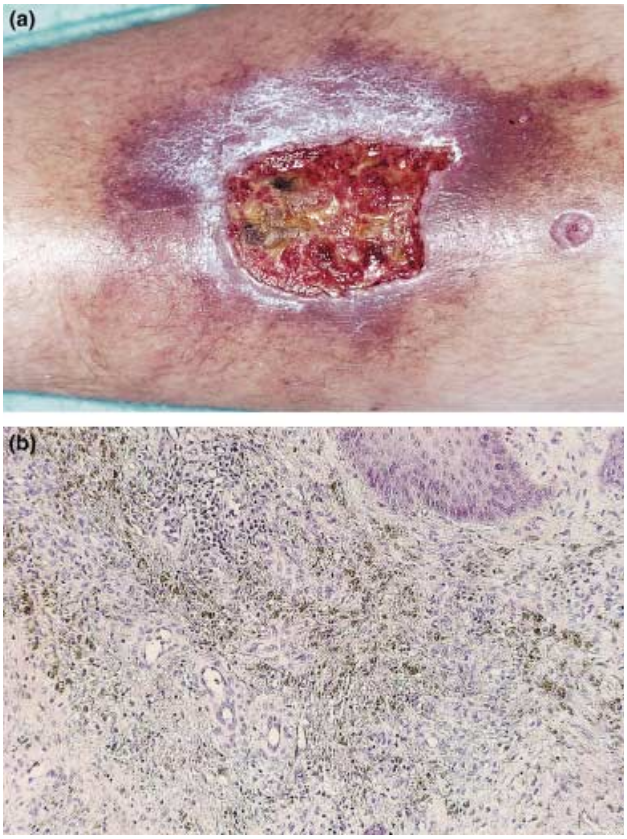

Figure 4. (a) Antineutrophil cytoplasmic antibody (myeloperoxidase)-associated vasculitis combined with factor V Leiden. (b) Histology: iron deposition and reactive angioendotheliomatosis (haematoxylin and eosin, original magnification ×40).

Antiphospholipid syndrome

This rare syndrome is characterized by the presence of circulating autoantibodies against phospholipid compounds. It is associated with an increased risk for venous or arterial thrombosis, thrombocytopenia and habitual abortus. The cutaneous symptoms (ulceration, livedo reticularis, acrocyanosis, Raynaud phenomenon, capillaritis and thrombophlebitis) can all be explained by vascular thrombosis. The two most frequently found antibodies are lupus anticoagulant and anticardiolipin. The presence of lupus anticoagulant (Fig. 7) is often accompanied by a prolonged prothrombin time and activated partial thromboplastin time, hence the confusing term anticoagulant, but it is associated with an increased risk for thrombosis.[18,86] Antiphospholipids have been found in a growing number of diseases, especially autoimmune diseases (systemic lupus erythematosus, autoimmune thrombocytic purpura and haemolytic anaemia, rheumatoid arthritis, Sjögren syndrome, giant cell arteritis, dermatomyositis, Behçet disease, polyarteritis nodosa), malignancies, haematological disorders (myelofibrosis, von Willebrand disease, paraproteinaemia), infections (lues, lepra, tuberculosis, mycoplasma, borreliosis, HIV, endocarditis, hepatitis) and neurological disorders (Sneddon syndrome, myasthenia gravis, multiple sclerosis).[86]

Malignancies

Many tumour types (Table 2), including metastases, may present with skin ulceration as the first symptom. The two most frequent ulcerating tumours of the skin are basal cell carcinoma (ulcus rodens) and squamous cell carcinoma, which may occur anywhere on the body, with a preference for sun-exposed skin. Malignancies (predominantly squamous cell carcinoma, sometimes fibrosarcoma) can also develop secondarily in chronic leg ulcers, especially in ulcers of longer

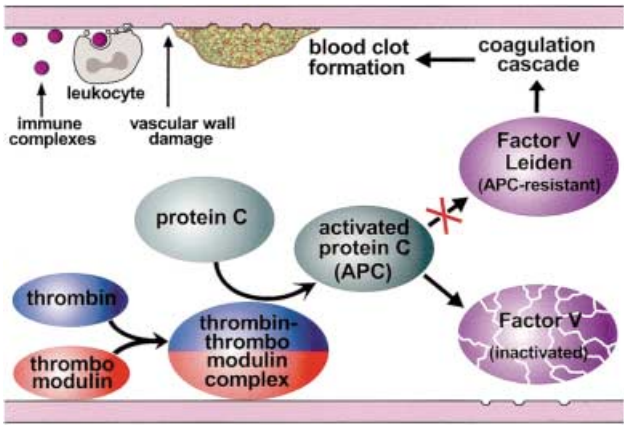

Figure 5. Schematic representation of the role of factor V Leiden in vascular thrombosis. In leucocytoclastic vasculitis, endothelial cells are damaged by leucocytes. The vascular damage initiates the coagulation cascade; prothrombin is converted to thrombin. Thrombin activates factors V and VII. Activated factors V and VII further accelerate the coagulation cascade, and a blood clot is formed. Coagulation is normally controlled by circulating antithrombin III, and locally by thrombomodulin, which is present in endothelial cells and binds thrombin. The thrombin–thrombomodulin complex activates protein C. Activated protein C (APC) is able to inactivate factor V, which will inhibit blood clot formation, but the mutant factor V Leiden ($^{506}R \rightarrow {}^{506}Q$) is resistant to inactivation by protein C (APC resistant) and will further induce the coagulation cascade. Consequently, the local protection mechanism against thrombosis is not working adequately.

duration, probably as a consequence of the continuously increased cell division in and around the ulcer.

Ulcerating skin diseases

Several skin disorders present with ulceration as the first symptom (Table 2). The most impressive ulcerating dermatosis is pyoderma gangrenosum, which is often not recognized.[87] Pyoderma gangrenosum causes deep necrotic ulcers, usually with an elevated violaceous border, and the ulceration is progressive if left untreated. It may be provoked by wounding the skin, hence its occurrence around scars, anus praeter, and donor sites used for grafting the original lesions. The diagnosis is made on the clinical picture. The aetiology is unknown; it is associated with colitis ulcerosa and morbus Crohn, and many other internal diseases (arthritis, paraproteinaemia, myeloma, leukaemia, polycythaemia vera, paroxysmal nocturnal haemoglobinuria, lupus erythematosus, malignancies, hepatitis, Wegener granulomatosis, diabetes, Sneddon–Wilkinson disease, Behçet syndrome). Only treatment with sulphasalazine, prednisone, ciclosporin or other immunomodulatory drugs will stop the process.

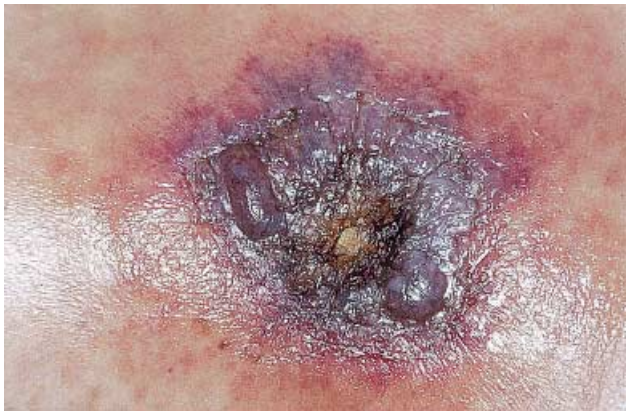

Figure 6. Necrotic ulcer on the medial malleolus caused by hydrea (hydroxyurea).

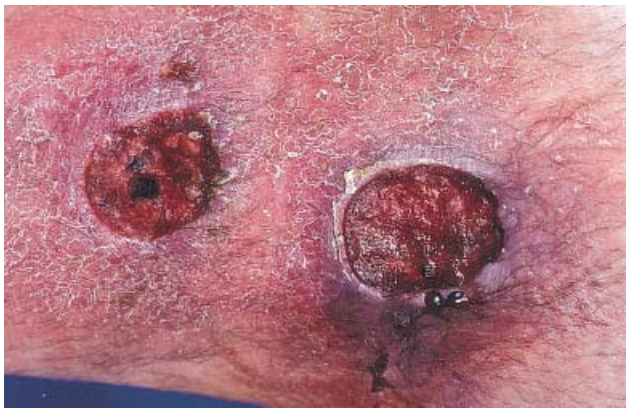

Figure 7. Ulcers caused by lupus anticoagulant.

In some skin diseases ulceration is a common feature, e.g. vasculitis, panniculitis, periarteritis nodosa, erythema induratum (Bazin),[88] malignant atrophic papulosis,[89] calciphylaxis;[90] in other conditions ulceration may occur, e.g. scleroderma, lichen planus, necrobiosis lipoidica, insect bites, lymphoedema, lipoedema, erythromelalgia,[91] perniosis (chilblains), haemangioma, Stewart–Bluefarb syndrome.[92]

Klinefelter syndrome

Klinefelter syndrome (XXY karyotype) is associated with lower leg ulceration, mostly of venous origin. Recent studies suggest that an increased level of plasminogen activator inhibitor-1 is involved in the pathogenesis.[93]

Diagnostic approach in patients with leg ulcers

The localization may give the first clue; venous leg ulcers predominantly occur in the gaiter area, above

the malleoli, arterial ulcers at the toes, on the shin and over pressure points, diabetic ulcers over pressure points, especially the distal metatarsal joints.[41] Venous insufficiency can often be diagnosed without additional vascular investigations, on the presence of typical skin signs such as oedema, haemosiderin pigmentation, hyperkeratosis and atrophie blanche.

Suspicion of arterial disease requires a routine vascular work-up, starting with clinical examination, palpation of arteries, assessment of skin colour and temperature, and calculation of the ABPI for the arteria dorsalis pedis and tibialis posterior. In healthy subjects, the ABPI is around or above 1·0, but an ABPI above 0·8 is still considered normal, and a safe threshold to apply compression therapy in venous leg ulcer patients.[6,26,29] An ABPI below 0·5 indicates arterial insufficiency.[6] If high systolic pressures are measured, one should consider the possibility that the arteries are difficult to compress due to calcium deposits. This can make the ABPI unreliable.[6,29,30] Toe pressure and transcutaneous oxygen pressure measurement, Duplex scanning and finally, diagnostic angiography, can complete the vascular work-up. A new diagnostic method is magnetic resonance angiography.

Diabetes is readily detected by routine laboratory investigations, which in the case of ulcer patients should include serum glucose (and, if elevated, HbA_{1c}), cholesterol and triglycerides, iron, haemoglobin, erythrocyte sedimentation rate and differential leucocyte counts. In the case of diabetes, neuropathy may be assessed by measuring the thresholds for perception of vibration (using a biothesiometer) and light touch (using Semmes–Weinstein monofilaments). And, although not as sensitive as MRI, plain radiography of bones suspected for osteomyelitis is useful.

An irregular border, black necrosis, erythema or bluish or purple discoloration of adjacent skin are suggestive for vasculitis. Histological examination of a skin specimen, taken from vital skin adjacent to the ulcer can confirm the diagnosis. Numerous specialized staining techniques are available to detect vascular pathology, microorganisms, malignancies, dermatological disorders or (metabolic) storage diseases. Therefore the pathologist should receive detailed information about the clinical problem and the differential options that are still open. If vasculitis is suspected, additional laboratory investigations (Table 3) should be performed to identify underlying disorders associated with vasculitis.

Table 3. Laboratory screening tests for vasculitis

Urine analysis for proteinuria, haematuria, cylindruria
Routine and immunohistopathology of skin biopsies
Erythrocyte sedimentation rate, haemoglobin, differential blood count, kidney and liver function
Antinuclear antibodies, rheumatoid factor
Complement C4, circulating immune complexes
Paraproteins, immunoglobulin fractions
Antineutrophil cytoplasmic antibodies
Serological tests and cultures for underlying infections

Table 4. Laboratory screening tests for clotting disorders

Activated partial thromboplastin time
Prothrombin time
Thrombin time
Factor V (Leiden) mutation ($^{506}R \rightarrow {}^{506}Q$)
Factor II (prothrombin) mutation ($^{20210}G \rightarrow {}^{20210}A$)
Antithrombin III
Protein C and protein S
Lupus anticoagulant
Anticardiolipin

Clinical signs of a hypercoagulable state, such as repeated thrombophlebitis or unexplained thrombosis at young age, are an indication for screening for clotting disorders (Table 4). Whether all patients with skin necrosis caused by vasculitis should be screened routinely for hypercoagulability needs to be further documented in larger patient series. It seems wise to consider the possibility of its existence, and this also pertains to the other relatively rare conditions listed in Table 2.[68–70,76,81–104]

In interpreting Table 2, one should realize that the majority (90–95%) of ulcers are venous, arterial, diabetic, or of mixed aetiology, and that the other conditions are rare. They should be taken into consideration only if an ulcer cannot be categorized under one of the common causes (Table 1), or fails to respond to adequate treatment, or in case of additional suggestive clinical signs or laboratory abnormalities.

With good knowledge of the large differential diagnosis of leg ulceration, and with the efforts and the specialized skills of all specialities involved, the expanding diagnostic and technical possibilities, and the enormous arsenal of wound care products available to us, including the new biotechnology-based products such as cultured skin and growth factors, it should be possible to overcome or at least control the burden of leg ulceration in our ageing population.

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