Leg ulcers: atypical presentations and associated comorbidities

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Abstract

WoundsWest is an innovative Western Australian (WA) project under Ambulatory Care and Chronic Disease Management Reform undertaken in partnership with the Western Australian Department of Health, Curtin University of Technology and Silver Chain Nursing Association.

WoundsWest's Online Wound Management Education Program is a core component of WoundsWest. It involves the interdisciplinary development of an anticipated 16 online wound management education modules, which are designed to assist health professionals and health services to deliver best practice in wound management and reduce preventable wounds and adverse wound management outcomes. The development of these modules involves an extensive search of the literature to ascertain the evidence for best practice. In preparation for the development of the forthcoming online Leg Ulcer Module a considerable number of atypical leg ulcer presentations and associated comorbidities were identified. This paper outlines some of these presentations and comorbidities and reminds health professionals of the need for further diagnostic investigations when leg ulcer signs and symptoms are atypical, or the ulcer fails to heal in an orderly and timely manner.

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Introduction

Chronic ulceration of the lower legs is a relatively common condition amongst adults; one that causes pain, social distress and results in considerable healthcare and personal costs [1-3]. Since numerous factors lead to lower leg ulceration, it is essential that health professionals adopt an interdisciplinary approach to the systematic assessment of the individual in order to ascertain the pathogenesis, a definitive diagnosis and optimal treatment required. A correct diagnosis is essential to avoid inappropriate treatment that may delay wound healing, cause deterioration of the wound, or harm the patient.

Chronic leg ulcers affect 0.6-3% of those aged over 60 years, increasing to over 5% of those aged over 80 years [4, 5]. In Western Australia (WA) in 1994 leg ulcers were found to affect 1.1 per 1000 population (0.11% point prevalence) [6]. This study demonstrated that 24% of the ulcers were present for 1 year, 35% had a problem of ulceration for 5 years, 20% had experienced 10 or more episodes of ulceration and 45% of sufferers were housebound [7]. Furthermore, in 2005 it was estimated that the numbers of elderly Australians with leg ulcers would double over the next 25 years [8].

The common causes of leg ulceration are vascular disorders such as chronic venous insufficiency (CVI) or atherosclerotic disease of the arteries. Valvular incompetence in the deep veins causes the vessels to become distended and stretch to accommodate the additional blood flow. The valves are not able to effectively close, which results in retrograde blood flow, venous hypertension and lower leg oedema [9]. Atherosclerosis, on the other hand, is a progressive disease

that results from the deposition of cholesterol within the lumen of arteries. Atherosclerotic material narrows the lumen of the arteries to reduce blood flow, which causes ischemia and tissue necrosis [10]. However, individuals may not experience symptoms of arterial disease until 70% of the artery has been occluded [11,12]. Some individuals present with significant arterial narrowing combined with signs of venous incompetence and these are referred to as having a mixed arterial and venous aetiology [13]. Ulcers of mixed aetiology are common amongst the elderly [14].

It has been reported that ulcers related to venous insufficiency constitute 70%, arterial disease 10% and ulcers of mixed aetiology 15% of leg ulcer presentations [11]. The remaining 5% of leg ulcers result from less common pathophysiological causes and this latter group comprise considerable challenges in diagnosis, assessment and management [11, 15]. The purpose of this review is to highlight some of the atypical leg ulcer presentations identified during the development of the WoundsWest Leg Ulcer Module.

Microcirculatory or vascular disorders

Microcirculatory and vascular disorders that can result in atypical leg ulceration include: Raynaud's phenomenon, Martorell's ulcers and cutaneous vasculitis.

Raynaud's phenomenon

Raynaud's phenomenon is an episodic circulatory disorder where the peripheral microvasculature is overly sensitive to changes in external temperature. It typically causes colour changes (white and/or blue and red) of the extremities on exposure to the cold (even mild temperature changes if they occur suddenly) or stress. These changes cause pain, numbness or tingling sensations. The condition is commonly found in females and affects between 3 and 5% of the general population. While the pathogenesis of Raynaud's phenomenon is unclear, recent research concludes that a combination of abnormalities of vascular, intravascular and neural function may be contributory factors [16-18].

Raynaud's phenomenon is classified as either a:

1. *Primary condition*, which is idiopathic, benign and generally mild. A diagnosis is usually made when symptoms occur before 30 years of age, are present for 2-3 years and there is no evidence of any other underlying disorder. Individuals may develop painful ulcerations of the fingers and toe extremities.

2. *Secondary condition*, which generally occurs after 30 years of age as a result of an underlying disorder such as scleroderma. Presenting symptoms are generally more acute and severe. Individuals may develop persistent ulcers, infection and possibly gangrene that can lead to digit amputation.

While there is no current cure for Raynaud's phenomenon, care is aimed at minimising the incidence, extent and severity of attacks. Preventive measures are designed to identify and avoid triggers that exacerbate symptoms; for example, stress, cold, smoking, alcohol and caffeine intake. Individuals benefit from a temperate, controlled environment, lifestyle and dietary changes and smoking cessation. During an acute episode, relaxation therapy biofeedback may reduce vasoconstrictive spasms. Similarly, exercise, gentle massage of affected anatomical areas and exposing the affected extremity to controlled warmth may provide some relief. While vasodilation medications may be tried, antibiotics would be required for secondary infections [16-18].

Specific medications that have been identified as triggers for Raynaud's phenomenon include: β-blockers, adrenergic receptor agonists, ergotamine drugs, oestrogens, immunosuppressants, interferons, cocaine, amphetamines and nicotine [16-18].

Martorell's ulcer

Martorell's ulcers are rare conditions that are occasionally seen in patients with prolonged, severe or suboptimally controlled hypertension [19]. Ulcerations arise from tissue ischaemia, which results from increased vascular resistance and are generally located at the lower extremity of the leg above the ankle region. Ulcers tend to be necrotic and extremely painful, with the degree of pain disproportional to the size of the wound [19, 20]. Martorell's ulcers are more common in females between 55 and 65 years. The diagnosis is generally made by eliminating other aetiologies and histological examination, which demonstrate concentric intima thickening and hypertrophy of the media of small- and medium-sized arteries [16, 19, 20].

Cutaneous vasculitis

Cutaneous vasculitis represents a heterogeneous group of diseases characterised by protean clinical manifestations [21]. Vasculitis refers to the inflammation and destruction of blood vessel walls and can affect any blood vessel in any organ. Vasculitis of the skin usually results from the inflammation and ischemia of small- to medium-sized blood vessels [22, 23]. Although vasculitis is activated by many factors, current research suggests that the deposition of circulating immune complex is pivotal to the pathogenesis of most types of cutaneous vasculitis [23]. Immune complexes arise from hypersensitivity to auto-antibodies or from contact with foreign antigens [22].

The deposition of the immune complex activates the complement system and recruits inflammatory cells [23]. The release of histamine promotes the deposition of immune complexes while production of cytokine up-regulates adhesive molecules and results in infiltration of neutrophils,

oedema and bleeding. Thrombosis is also associated with activation of the complement system [23].

There are several classification systems for vasculitis and they include the American College of Rheumatology Classification, which comprises two subcategories [24]:

- Cutaneous small vessel vasculitis.
- Large-vessel necrotising vasculitis criteria.

The Chapel Hill Consensus Criteria (CHCC) proposes three subcategories [25]:

- Large-vessel vasculitis, which includes giant cell arteritis and Takayasu arteritis (skin lesions are uncommon).
- Medium-sized vessel vasculitis, which includes classic polyarteritis nodosa and Kawasaki disease (associated with mucocutaneous lymph node syndrome).
- Small vessel vasculitis, which encompasses: Wegener granulomatosis; Churg-Strauss syndrome; microscopic polyangiitis (polyarteritis); Henoch-Schönlein purpura; essential cryoglobulinaemic vasculitis; and, cutaneous leucocytoclastic vasculitis.

Unfortunately, current vasculitic classification systems do not provide consensus for research, clinical diagnosis and management of cutaneous vasculitis [23]. While most practitioners appear to favour the CHCC for classifying vasculitis, there is an apparent lack of agreement of specific disorders and an overlap among primary vasculitides when the various classification systems are adopted [23, 26].

Predisposing factors for vasculitis include: infection, certain medications and contact with allergens. A wide variety of bacterial, viral, fungal, protozoan and helminthic organisms have been implicated in the development of vasculitis [22]. Similarly, a wide range of medications have been implicated in causing vasculitis in some individuals and these include: insulin, penicillin, hydantoins, streptomycin, aspirin, sulphonamides, thiazides, phenothiazines, vitamins, phenylbutazone, quinine, streptokinase, tamoxifen, anti-influenza vaccine and serum oral contraceptives. Contact with chemical agents such as insecticides, petroleum products and food allergens (milk proteins and gluten) can also predispose susceptible individuals to vasculitis [16, 22].

Individuals with non-healing leg ulcers need to be referred to a specialist for appropriate diagnoses and management as vasculitis can 'mimic' other disorders [16, 21]. Common signs and symptoms associated with small- and medium-vessel cutaneous vasculitis include [24-27]:

- Palpable purpura.
- Necrosis.
- Livedo reticularis.
- Microlivedo.

Small-vessel disease results in smaller and more regular lesions, whereas medium-vessel disease results in irregular lesions due to vascular anastomosis.

Investigations aimed at eliminating other aetiologies and obtaining a definitive diagnosis of vasculitis include [15, 27]:

- Complete blood profile.
- Hepatitis profile – due to the strong association with hepatitis C.
- Serologic testing for streptococcal infection.
- Serum protein electrophoresis.
- HIV testing – for high-risk patients.
- Chest x-ray.
- Symptom-directed work-up for autoimmune disease and underlying malignance with age-appropriate screening.
- Multiple tissue biopsies.

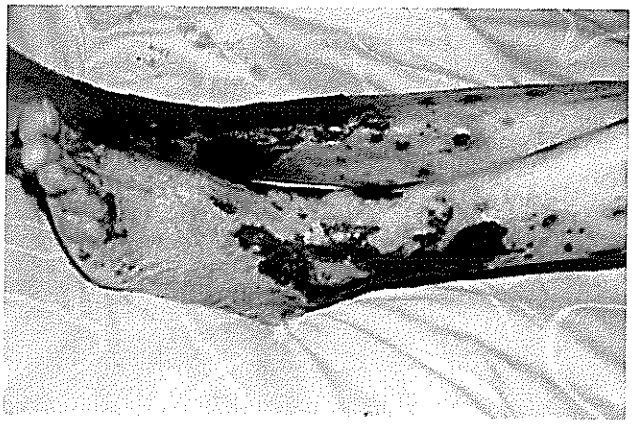

Figure 1. Cutaneous vasculitis (secondary to penicillin).

Haematological disorders

Ulcers related to haematological disorders generally result from microcirculatory occlusion [30, 31]. However, less common haematological disorders associated with ulcers include:

Essential thrombocythaemia

This is a chronic myelo-proliferative disease that affects platelet-producing cells [32]. The disorder clinically manifests as thrombocytosis with patients at increased risk of developing vascular complications such as thrombosis, myelofibrosis and transformation to acute myeloid leukaemia [32, 33]. Related risk factors for the disease include the presence of JAK2 gene and baseline leukocyte count [33, 34]. The leukocyte count has been identified as an independent predictor of major thrombosis in particularly acute coronary syndromes [33].

Primary polycythaemia

This is usually associated with occlusive vascular lesions such as ischaemic digits. A red cell mass more than 25% above the predicted value constitutes polycythaemia[35].

Sickle cell anaemia, a genetic disorder, commonly results in the formation of small, painful leg ulcers that arise when sickle-shaped inflexible red blood cells obstruct capillaries and restrict blood flow to an organ or the skin. African and Caribbean populations have a higher disposition for sickle cell disease[36]. Sickle cell anaemia has a leg ulcer incidence rate between 25.7% and 75%[37]. The ulcers are generally indolent, intractable and have a high probability of recurrence. Research shows that leg ulcers may be associated with the intensity of haemolysis[38]. Risk factors associated with leg ulcer development and sickle cell anaemia include[37,38]:

- High levels of lactate dehydrogenase and bilirubin.
- Age over 20 years.
- Male.
- Antithrombin III deficiency.
- Haemoglobin level < 6g/dL.
- Lower level of foetal haemoglobin.
- Presence of particular human leukocyte antigens.

Thalassaemia

Thalassaemia is an inherited disorder of haemoglobin. Thalassaemia major, also known as Cooley's anaemia, homozygous, beta thalassaemia or Mediterranean anaemia is a serious, inherited anaemia. Individuals with thalassaemia major cannot make enough satisfactory haemoglobin and, as a result, the bone marrow does not produce sufficient red blood cells. Individuals with thalassaemia minor are carriers of the disorder and only have mild anaemia[39,40]. In rare cases thalassaemia results in leg ulceration[40].

Haemolytic anaemia

This refers to the haemolysis of red blood cells in the blood vessels (intravascular haemolysis) or elsewhere in the body (extra-vascular). Bone marrow activity cannot compensate for the increased loss of red blood cells. Leg ulceration may occur when the condition is associated with sickle cell anaemia or thalassaemia[41,42].

Clotting disorders

Clotting disorders that can result in leg ulcers include: antiphospholipid syndrome, protein C and protein S deficiencies, factor V Leiden, lupus anticoagulant, factor XIII deficiency and antithrombin III deficiency[16].

Other haematological disorders

Other disorders associated with the development of leg ulcers include: leukaemia, hereditary spherocytosis, primary thrombocythaemia, thrombotic thrombocytopenic purpura, granulocytopenia, polycythaemia and polyclonal dysproteinaemia [16,31].

Metabolic disorders

Necrobiosis lipoidica

Necrobiosis lipoidica is a rare chronic condition that primarily affects individuals with diabetes and results in collagen degeneration, reduced collagen synthesis, atrophy and lipid deposits. Necrobiosis lipoidica occurs in about 0.7% of diabetic patients with ulcers developing in 13-35% of cases. This condition presents two to three times more commonly in women than men with the mean age of onset about 30 years [43,44].

Lesions generally develop on the pretibial area as small red-brown erythematous markings that gradually enlarge. Lesions may present as single or multiple, clearly demarcated, waxy, yellow-brown plaques with depressed centres, which are associated with granulomatous inflammation and collagen degeneration [43]. Ulcers may develop on one leg but invariably bilateral ulceration results [44]. Cutaneous changes include: atrophy, smooth and shiny skin, telangiectasia and loss of hair follicles. While the condition is generally painless, the ulcers within the lesions are usually painful [43].

Porphyria cutanea tarda

Porphyria cutanea tarda refers to a group of disorders that can be familial or acquired and which result in a deficiency in the function of the haem synthetic enzyme uroporphrinogen decarboxylase (UROD) [45]. Porphyria cutanea tarda generally arises following exposure to an agent or condition that impairs the hepatocytes' ability to produce hepatosiderin [45]. Possible precipitating factors include: alcohol, oestrogen, viral hepatitis, iron supplementation; human immunodeficiency viruses and haemochromatosis genes [45,46].

Cutaneous symptoms may include: fragile skin that heals slowly after minor trauma, blistering rash in sun exposed areas, sub-epidermal bullae, hyperpigmentation and hypertrichosis (principally of the forehead and upper cheeks) [45-47].

Gout

Gout is an inflammatory disorder of monosodium urate metabolism, which is characterised by the deposition of urate crystals in the joints and soft tissues. Monosodium urate crystals are powerful promoters of inflammation since they recruit neutrophils and stimulate the production of inflammation, pro-inflammatory cytokines and other inflammatory mediators. Increased longevity, dietary factors, lifestyle changes and increased prevalence of comorbidities are all risk factors associated with the development of gout. Gout is a heterogeneous disorder, which proceeds through four clinical phases where treatment is not provided [48]. The four phases of gout include:

1. *Asymptomatic hyperuricaemia* occurs where common symptoms of urate deposits, such as nephrolithiasis or kidney stones, are not present in individuals with elevated urate levels [47]. Hyperuricaemia arises from either an underlying genetic defect or is acquired through exposure to low-level lead levels, excessive alcohol or purine intake, renal disease, metabolic abnormalities, thiazides and low-dose acetylsalicylic acid [48].

2. *Acute or recurrent gout* arises from the powerful inflammatory response that occurs when urate crystals are deposited in joints or soft tissues. Commonly affected joints of the lower extremities include the knee, hallux (large toe), foot and ankle [49,50]. Clinical signs and symptoms include sudden severe pain, warmth and reduced range of movement [48].

3. *Intercritical gout* refers to the asymptomatic phase that occurs between acute episodes [48].

4. *Chronic tophaceous gout* is the formation of nodular uric acid crystals (tophi) masses that occurs within 10-20 years of poor management. Tophi occur in the elbows, hands, feet, ears, Achilles tendons and knees in 12% of patients after 5 years and in over 50% of patients after 20 years with gout [48].

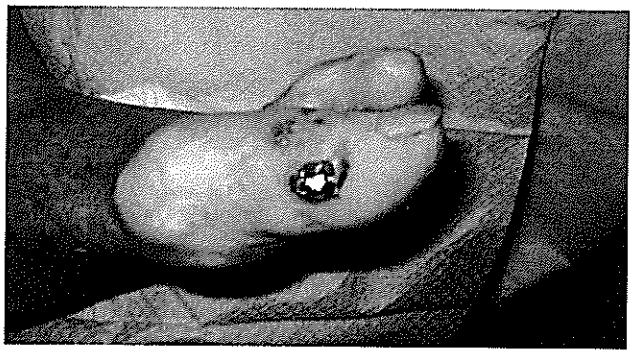

Figure 2. Chronic tophaceous gout.

Calciphylaxis

Calciphylaxis is a rare and potentially grave vasculopathy of the skin and subcutaneous tissue that has a female-to-male ratio of 3:1 [51]. This condition occurs as a complication of chronic kidney disease, particularly in diabetics and in secondary hyperparathyroidism associated with abnormal calcium metabolism. Calciphylaxis occurs in 1% of patients with chronic kidney disease and in 4% of individuals on dialysis, where onset is approximately 3 years after

commencing dialysis [51, 52]. Individuals with this condition have a survival rate of 45% at 1 year and 35% at 5 years, with infection being the principal cause of death [51-53].

Associated risk factors for calciphylaxis include: obesity, diabetes, female gender, low serum albumin, Caucasian race, length of time on renal replacement therapy, use of coumarin anticoagulants, Vitamin D analogs, calcium containing phosphate binders, iron substitution therapy, glucocorticosteroids, poor nutrition and recent trauma [51, 52, 54]. Lesions generally present as livedo reticularis principally over areas with significant amounts of subcutaneous fat, such as the abdomen, buttocks and thighs. However, lesions may also occur on the extremities of the digits that result in painful purpuric plaques, nodules, necrosis (which may be extensive) and eschar [52, 53]. Early diagnosis prior to the development of ulcers is vital for improving the prognosis [51-53].

Calcinosis cutis

Calcinosis cutis is a disorder whereby calcium and phosphorous salts are deposited in the dermis [55]. There are four main types and they include [55-57]:

1. *Dystrophic calcinosis cutis* arises from the deposition of calcium in the cutaneous tissue following injury, inflammation or necrosis and has been identified in numerous degenerative, collagen and vascular conditions.

2. *Metastatic calcinosis cutis* is a rare condition arising in end-stage renal failure where calcium is deposited in the skin and subcutaneous tissue. It is generally widespread and large deposits are found symmetrically distributed near large joints such as the knees, elbows and shoulders. Calcium deposition occurs less frequently in the skin than in visceral organs such as the lungs, kidneys, blood vessels and stomach.

3. *Iatrogenic calcinosis cutis* is known to occur after extravasation of calcium-containing intravenous solutions and electroencephalographic and electromyography examinations that use electrodes with calcium chloride paste. Calcification is localised to the site of an invasive procedure.

4. *Idiopathic calcinosis* is associated with calcified nodules of the scrotum, sub-epidermal calcified nodules and milia like calcinosis conditions. In this instance calcification is generally localised to a specific area.

Leg ulcers are generally asymptomatic, but may be tender and present with numerous, dense, pale dermal papules, plaques, nodules or subcutaneous nodules. The lesions may also be enclosed by a yellowish/whitish gritty substance that ulcerates. Lesions over joints can restrict mobility, while vascular calcification may cause diminished pulses and, in severe cases, cutaneous gangrene [55-57].

Neuropathic disorders

There are numerous disorders that can result in neuropathy of the lower legs and associated ulceration due to insensate injury, burns or pressure ulcers. The following disorders are less typical neuropathic presentations than those commonly associated with paraplegia and diabetes mellitus.

Hansen's disease (leprosy)

Hansen's disease is caused by the *Mycobacterium leprae* organism that predominantly affects the skin and peripheral nerves [58]. Transmission occurs from person to person through respiratory droplet transmission [31, 59]. The three mechanisms associated with causing neuropathy include [60]:

- Damage from the direct effects of *Mycobacterium leprae* that result in neurofilament damage and demyelination.
- Inflammation and immune-mediated processes.
- Oedema and mechanical processes impair the function of Schwann cells, increasing their susceptibility to injury. Additionally, nerve fibres and blood vessels may be compressed leading to ischaemia and further injury.

Approximately 30% of people with Hansen's disease will develop nerve damage that results in peripheral nerve sensory loss, usually in the hands, feet and eyes [58, 60, 61]. Skin damage can present as thickened, cracked skin that becomes infected and ulcerates [58, 62]. Additional skin changes may include: erythematous changes (papules and nodules) or hypo-pigmented plaques and alopecia [58, 59, 62].

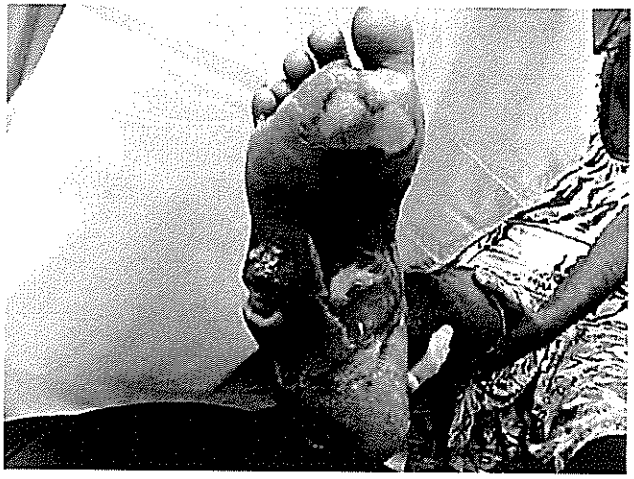

Figure 3. Hansen's disease (evidence of chronic and traumatic injury due to loss of protective sensation)

Alcoholic neuropathy

Alcoholic neuropathy is characterised by Wallerian degeneration of the axons, reduced myelination of neural fibres and in chronic cases, neural regeneration. Ethanol migrates into the cell's membrane to increase membrane fluidity and impair signal transduction proteins [63, 64]:

This peripheral nerve damage may arise from nutritional deficiencies of thiamine, niacin, folate and protein[63,64].

Signs and symptoms of alcohol neuropathy include[63,64]:

- Peripheral neuropathy – an early symptom.
- Paresthesia or decreased pain and temperature sensation – this presents as a stocking-glove distribution.
- Plantar ulceration.
- Pain.
- Weakness, particularly of the feet but it may extend proximally to the arms and causes difficulty for the patient when climbing or walking.
- Autonomic symptoms which include: motility disturbance of the gastrointestinal tract, urinary incontinence, diarrhoea and abnormal sweat patterns.

Tabes dorsalis

Tabes dorsalis is a slow but progressive condition arising from spinal cord damage that occurs 15-30 years after untreated primary syphilis. Due to early diagnosis and therapeutic intervention, tabes dorsalis is now a rare condition. Clinical signs and symptoms may include[65,66]:

- Loss of proprioception.
- Stabbing pains in the legs.
- Paresthesia.
- Decreased deep tendon reflexes.
- Progressive ataxia.
- Bowel and bladder incontinence.
- Presence of Argyll Robertson pupil – The pupil is able to change its focal length but does not respond to light.
- Destructive bone and joint processes, in particular, those of the lower limbs, lumbar spine and hips.
- Patients may have a single painless, swollen and deformed joint.
- Peripheral neuropathy.
- Joint changes generally precede neurological changes.
- Soft tissue swelling.

Leg ulcers generally arise from trauma to areas of sensory loss.

Syringomyelia

Syringomyelia refers to the abnormal formation of fluid-filled cavities or syrinxes in the spinal cord tissue or central canal, which occurs in about 40-65% of individuals with Chiari I malformations[67]. The exact pathogenesis of syringomyelia is unknown; however, individuals present with numerous sensory, motor and autonomic symptoms that can cause the following cutaneous manifestations[67-69]:

- Painless ulcers of the extremities.
- Oedema.
- Hyperhydrosis.

Individuals can develop painless ulcers of the extremities as a result of trauma due to impaired sensation. However, pressure ulcers of the lower limb may be confused with leg ulcers arising from other aetiologies.

Spina bifida

Spina bifida relates to the failure of the caudal neural tube to fuse in the foetus during the first trimester of pregnancy as a result of multiple causes and encompasses a broad range of abnormalities[70]. A subset of these abnormalities, more accurately referred to as meningomyelocoeles, present with caudal lesions that affect the spinal cord, vertebrae and the skin. As a result of these lesions, spina bifida patients experience numerous skin problems that may include[70,71]:

- Burns and ulcers from insensate extremities.
- Pressure ulcers on the lower limb that may be confused with leg ulcers of other aetiologies.
- Frequent post surgical wound infections.
- Moisture lesions from incontinence.

Spina bifida is preventable in approximately 70% of cases through the provision of maternal peri-conceptional folic acid supplements[70].

Multiple sclerosis

Multiple sclerosis (MS) is a progressive, degenerative, chronic inflammatory disease of the central nervous system that arises early in adult life[72-74]. Associated causes include genetic and environmental factors[72]. Genetic factors are associated with an increased risk of developing multiple sclerosis if a first-degree relative has MS and siblings of an individual with MS have a 3% lifetime risk. MS patients present with numerous sensory and motor symptoms that can potentially lead to pressure ulcers, leg ulcers and foot ulcers[74-77].

Autoimmune disorders

Rheumatoid ulcers

Cutaneous lesions are common initial features of individuals with rheumatoid arthritis and may include rheumatoid nodules, digital gangrene, palpable purpura, ecchymosis and ischaemic ulcers[53]. Approximately 10% of individuals with rheumatoid arthritis will develop leg ulcers[53,78]. This is particularly evident in those patients with long-

standing, seropositive disease. Rheumatoid leg ulcers may be associated with venous insufficiency, trauma, arterial insufficiency, vasculitis, Felty's syndrome (swollen spleen, decreased white blood cell count and repeated infections) and pyoderma gangrenosum [53, 79, 80]. Treatment is determined following a definitive diagnosis of any of these conditions. The application of an appropriate dressing that incorporates moist wound healing principles is advised. Compression therapy may be indicated for the management of venous insufficiency and a vascular referral is essential where arterial insufficiency is identified [9, 10].

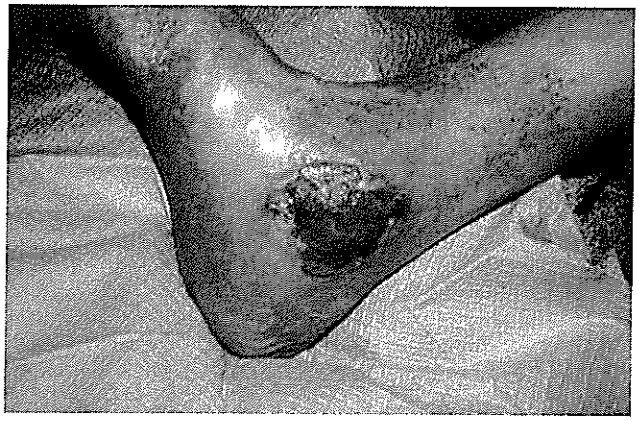

Figure 4. Rheumatoid ulcer on medial malleolus.

Scleroderma

Scleroderma is a rare chronic autoimmune connective tissue disease with an unknown aetiology [18]. The term is derived from the Greek 'sclero' meaning hard and 'derma' meaning skin. It is frequently associated with rheumatic diseases [18]. Raynaud's phenomenon is also a common symptom [81]. Scleroderma is described as being localised or systemic [18, 82, 83].

Localised scleroderma generally only affects the skin and occasionally the underlying subcutaneous tissue and muscles [84, 85]. Localised scleroderma is associated with about 10% of all new cases of scleroderma and primarily affects children [18]. While this condition is generally restricted to the skin and subcutaneous tissue, widespread fibrosis results in growth defects [18].

The two principal presentations of skin induration resulting from localised scleroderma include [18, 83]:

- Morphea presentations are firm, whitish, oval-shaped plaques with a surrounding purplish hue that are generally confined to a single area of the body such as the trunk or they may be more widespread.
- Linear scleroderma generally present as streaks on the extremities and is seen relatively commonly in children [81]. Lines that occasionally appear on the head and scalp are described as *en coup de sabre* or 'sword' marks [18, 84]. The indurations may also involve muscles and bone, leading to atrophy and furrowing of the skin [81, 84].

Systemic sclerosis is a chronic disorder of unknown aetiology that is reported to occur in about 90% of all cases [18, 85, 86]. The disorder is characterised by impaired fibroblast function, micro-vascular disease and activation of the immune system that results in excessive collagen production and fibrosis of the skin and organs [86, 87].

Two common clinical forms of systemic sclerosis include:

- Limited scleroderma (lcSSc) involves the skin distal to the elbows and knees.
- Diffuse cutaneous SSc (dcSSc) involves the skin proximal to the elbows and knees including the trunk.

Cutaneous symptoms associated with systemic sclerosis include thickening of the skin, finger ulcerations and joint contractures [87].

Pyoderma gangrenosum

Pyoderma gangrenosum is a relatively uncommon condition of unknown aetiology, characterised by idiopathic, primarily sterile, painful, inflammatory neutrophilic dermatosis [88, 89]. Recurrent cutaneous ulcerations with mucopurulent or haemorrhagic exudate may present [88, 89]. Pyoderma gangrenosum is frequently associated with rheumatic disorders, neoplasia or inflammatory bowel disease [90]. Research shows that approximately 50% of patients have an underlying disorder that may include: ulcerative

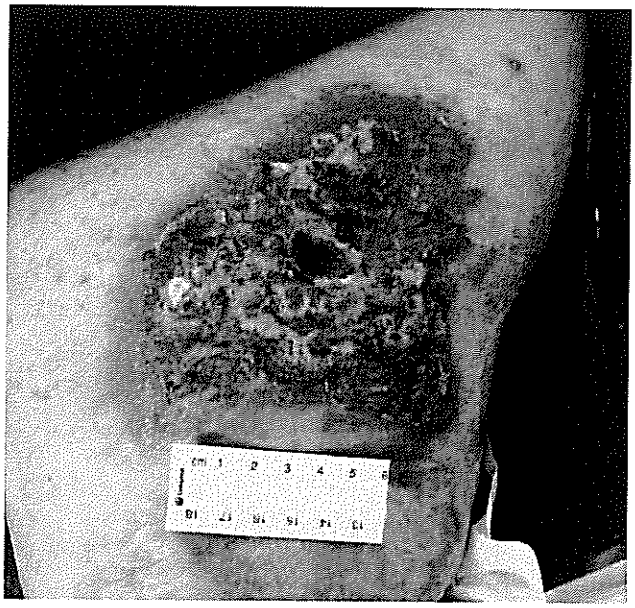

Figure 5. Pyoderma gangrenosum on thigh.

Table 1: Pyoderma gangrenosum types and characteristics [88, 90, 92, 94]

Type	Clinical description
Ulcerative	Ulceration with rapidly expanding purulent wound bed
	Generally present as numerous small pustules that rapidly expand and break down
	Forms painful ulcers with enlarging surrounding erythema
	Ulcers may present with a violaceous undermined border
	Generally involves lower extremities or trunk
	Arise de novo or from a pathergic response to trauma
	Wound bed may be crusted or have a granular appearance
Genital	May occur in the vulva, penile or scrotal area
Pustular	Presents as painful pustules on trunk or extremities
	Pustules often symmetrical in shape
	Discrete painful pustules with an erythematous halo on legs and upper trunk
	Pustules may be self-limited
	Commonly associated with fever, arthralgias or inflammatory bowel disease
	May also develop into an ulcerative form in patients with inflammatory bowel disease
Bullous	Frequently occurs on arms and face
	Painful superficial bullae with inflamed borders
	Evolves rapidly into painful vesicles and enlarging bullae that have a central area of necrosis and erosion
	Surrounding area presents as a halo of erythema
	Develop into superficial ulcers of lesser depth than ulcerative type
Vegetative	Evolves slowly as superficial ulcerations
	Presents as a chronic non-painful ulceration
	Absence of violaceous undermined borders
	Wound base non-purulent
Peristomal	Painful pink-purple papules that develop into ulcers with a violaceous undermined border
	Multiple fistulous tracts
	May occur in patients with ulcerative colitis or Crohn's disease with ileostomy or colostomy
Vesiculopustular	Lesions are vesicular and pustular
	Present on trunk and extremities
Infantile	Generally occurs in perianal and genital areas of infants

colitis, Crohn's regional enteritis, hepatitis C, seronegative rheumatoid arthritis, spondylitis, monoclonal gammopathies, leukaemia, lymphoma and myelodysplastic syndrome [88, 90-93].

Pyoderma gangrenosum usually occurs on the lower extremity, particularly in the pretibial area, although other sites may be involved, including the breast, trunk, hand, head, neck and peristomal skin [88, 90]. There are five prototypic forms of pyoderma gangrenosum (Table 1) [88, 90, 92]. Extra-cutaneous manifestations can also occur and involve the: heart, eyes, lymph nodes, spleen and liver [88, 94]. Pyoderma gangrenosum initially presents as a follicular pustule that rapidly grows and causes tissue necrosis, ulceration and erythematous oedema of the surrounding skin [88, 90]. Ulcers display undermining with violaceous or bluish, raised borders and secondary infections commonly develop [88, 90]. A classic symptom of pyoderma gangrenosum is severe ulcer pain. Diagnosis is determined by the history of the disease, clinical presentation, histopathology and exclusion of other diseases such as vasculitis, which have a similar appearance [88, 94]. Pyoderma

primarily occurs in individuals between the ages of 20 and 50 years, with women more frequently affected than men[88].

Kaposi's sarcoma

Kaposi's sarcoma is an angio-proliferative, soft tissue disease that generally affects the skin. It may involve the lymphatic system, lungs and the gastrointestinal tract; bone, however, is rarely involved. There are four distinct clinical forms of Kaposi's sarcoma and they are[95-97]:

Classic Kaposi sarcoma is benign, progresses slowly and predominantly affects elderly Mediterranean or eastern European males [98, 99]. It is unrelated to the human immunodeficient virus (HIV). The classic forms presents with violaceous nodules and plaques that develop on the lower extremities[95].

Lymphadenopathic Kaposi sarcoma is an aggressive form that generally affects young adults and children and is endemic to parts of Africa[99]. It is a rapidly progressive tumour that develops within months to years with bone, lymph node and visceral involvement[95, 99].

Iatrogenically immunosuppressed individuals, in particular organ transplant recipients, develop this form of Kaposi's sarcoma, which generally affects males more than females[95].

Aggressive epidemic sarcoma is the commonest malignancy diagnosed in individuals infected with HIV[95]. This sarcoma was first described in the early 1980s among young HIV-positive patients aged 30-40 years and is reported to occur in about 25% of HIV-infected homosexual men. However, since the advent of antiretroviral therapy, it is now estimated to occur in only 5-7% of the same population[95, 96]. Kaposi's sarcoma is an aggressive and lethal tumour with a survival time of about 1 year in HIV-infected patients who have severe and untreated immunodeficiency[96].

Kaposi's sarcoma initially presents as pinkish, red or brown-black, well-circumscribed, asymptomatic plaques on the skin[96, 97]. In individuals not infected with HIV, Kaposi's sarcoma is generally limited to the lower extremities[96, 97, 99]. However, in the advanced stage of Kaposi's sarcoma, the lymphatic system is compromised, which causes oedema with disseminated skin involvement[96].

Allergic ulceration

Numerous local and systemic allergic responses are manifested on the skin. An allergy is a hypersensitivity reaction initiated by specific immunologic mechanisms[100] as a result of contact with or ingestion of an animal, vegetable, mineral or chemical agent. Dermatitis is the term that encompasses local skin inflammation[100]. The terms dermatitis and eczema are frequently used synonymously[101].

The Nomenclature Review Committee of the World Allergy Organisation proposed the term eczema to replace the term atopic eczema or dermatitis syndrome[100]. Eczema is a skin condition that arises from a genetically determined skin barrier defect[101]. The underlying inflammation in children and young adults with the atopic constitution is dominated by an IgE-antibody-associated reaction that is called atopic eczema[100]. The classification of atopy and atopic eczema is derived from IgE sensitisation and is identified through IgE-antibody determination and skin testing. In chronic cases, the inflammation is less influenced by IgE antibody and, principally, by lymphocytes[100]. Eczema, without the signs of atopic syndrome has a 45%-64% prevalence rate in pre-school children[100]. Children with non-atopic eczema have less risk of developing asthma as adolescents than atopic children with eczema, but have increased risk of developing atopic eczema[100].

Contact dermatitis, a common skin disease, occurs when there is close contact with low-molecular-weight chemicals or irritants that potentially provoke a locally induced skin inflammatory reaction[100, 102]. Contact dermatitis demonstrates both acute and chronic responses of irritant and allergic contact dermatitis[102]. Where the reaction is mediated by an

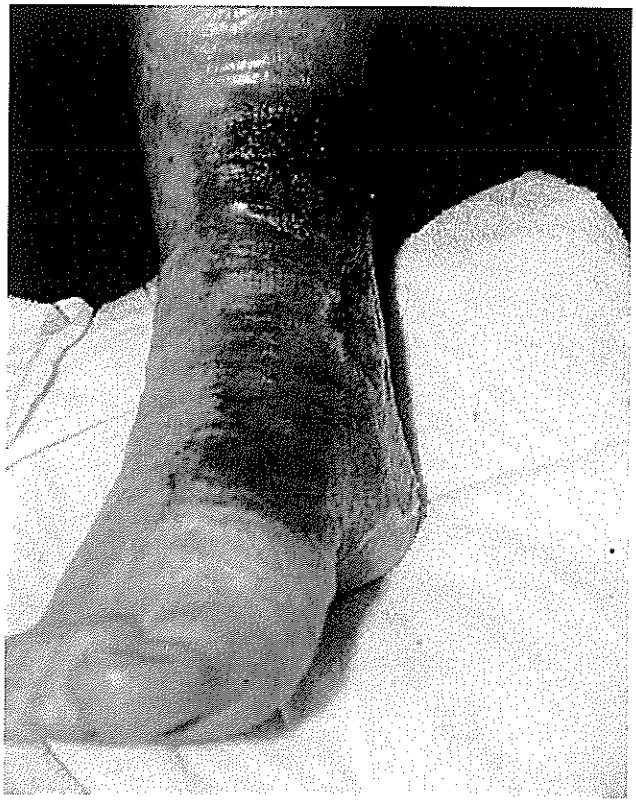

Figure 6. Allergic ulceration to chlorhexidine impregnated dressing used to treat an infected venous leg ulcer.

immunological mechanism, it is known as allergic contact dermatitis [100]. Products containing preservatives, perfumes, solubilisers and sunscreens have been associated with allergic contact dermatitis. Potential allergens include: lanolin, propylene glycol, vitamin E and topical antibiotics [101, 103]. In a study of venous leg ulcer patients, positive patch tests were revealed in 68% of patients and multiple allergies occurring in 51% of cases [101]. Common allergens included fragrances, which accounted for 30.5%, antimicrobials 19.5%, topical corticosteroids 8% and several dressing additives [104].

Skin irritation, a main source of occupational hand eczema, arises where skin function is impaired when lipids are removed from the stratum corneum due to repeated hand washing or direct contact with irritants [102]. The skin displays increased transepidermal water loss and dryness [102]. Exposure may also arise through oral uptake and is known as systemic allergic contact dermatitis. Where an immune mechanism does not develop, the term non-allergic contact dermatitis is used [100]. 'Other forms' of dermatitis encompass nummular dermatitis, photosensitive dermatitis, dyshidrotic eczema and seborrheic eczema [100].

Malignant leg ulcers

Malignant wounds arise from the infiltration of the skin by a primary tumour or metastatic tumour. Synonymous terms used to describe malignant wounds include tumour necrosis, fungating wounds, ulcerating cancerous wounds, or malignant cutaneous wounds. A primary tumour is a local invasion, which results from the direct extension of a tumour to the surface of the skin [105, 106]. It initially appears as an inflammatory area with induration, redness, heat and/or tenderness. The skin may have a *'peau d'orange'* appearance that adheres to underlying tissue [105]. Ulceration of the skin occurs as the tumour spreads and there is tissue destruction [105-107].

Metastatic tumours result when cells detach from the primary site and travel via blood and/or lymphatic vessels or even a tissue plane to a distant organ, including the skin [105-107]. Large amounts of necrotic material may be present in malignant wounds and this can account for malodour.

Basal cell carcinoma (BCC)

BCC is a common and prevalent skin tumour found in Caucasians. The appearance and morphology of BCCs are varied and can present as: superficial, cystic, nodular, ulcerated (rodent ulcer), sclerosing, keratotic or pigmented [108, 109]. BCCs are slow-growing lesions that arise from the basal cells, located at the base of the epidermis [109, 110]. They are locally invasive, malignant epidermal skin tumours that mostly occur in adults [110]. Individuals generally affected have fair complexions, blonde or red hair, light eye colour and solar-damaged skin with poor tanning ability (skin type I) [108].

BCCs are more common in men than in women and the male-to-female ratio is approximately 2:1 [108]. Contributing factors are history of excessive exposure to carcinogenic ultraviolet radiation [110]. The rate for BCC is 19 times less in dark pigmented races than in Caucasians [108].

The incidence of BCC varies depending on geographical location. Individuals who live nearer to the equator or in areas with high UV radiance are at a greater risk of developing BCCs [108]. The highest incidence of BCC has been reported in Australia, USA and Europe [109]. The tumour infiltrates tissue through irregular finger-like outgrowths that remain adjoined to the primary mass [109]. Metastases are rare and morbidity results from local tissue invasion and destruction chiefly on the face, head and neck [109]. The term 'rodent ulcer' has also been applied to a BCC, which has an ulcerated portion as it appears to have been eaten by a rodent [111].

Squamous cell carcinoma (SCC)

Primary cutaneous SCCs are malignant lesions that arise from keratinising cells [112]. SCCs are locally invasive and have the potential to metastasise to other organs of the body. Table 2 provides a list of some causative factors associated with the development of SCC [113].

SCC lesions appear as growing keratotic lesions that may ulcerate and develop secondarily infections [114]. As these lesions can develop in chronic leg ulcers, a biopsy ulcer should be taken if the edges are raised [114].

Table 2: Causative factors for the development of squamous cell carcinoma [113].

- Accumulative exposure to UV radiation
- Immunosuppression therapy
- Chronically injured or diseased skin
- Xeroderma pigmentosum
- Human papilloma virus
- Chemical carcinogen exposure
- Organ transplantation
- Radiation dermatitis
- Arsenic
- Leukaemia
- Lymphoma ulcers
- Sinus
- Osteomyelitis
- Actinic keratosis
- Bowen's disease

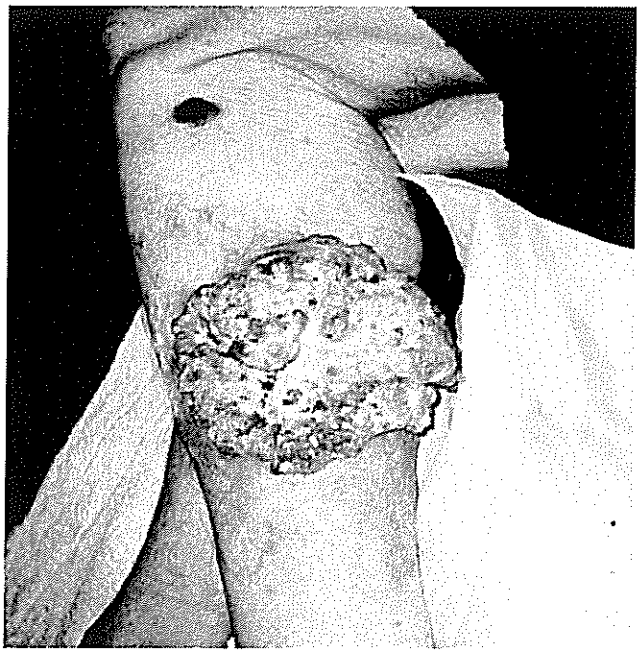

Figure 7. Squamous cell carcinoma.

Melanoma

Melanomas are aggressive skin cancers that arise from the melanocyte cells that produce pigment [115, 116]. Males have nearly 1.5 times the risk of developing melanomas than females [116]. Common sites for males are the back and the arms and legs for females [116]. The typical presentation is a pigmented lesion associated with recent changes in size, shape or colour [115, 117, 118]. The most publicised means of identifying potentially atypical pigmented skin lesions is the 'ABCDE' mnemonic: asymmetry, border irregularity, colour variegation, diagnosis based on a full-thickness excisional biopsy and evolution of a pigmented lesion [118, 119].

Marjolin's ulcers

Marjolin's ulcers are rare, malignant transformations arising from chronic wounds [120, 121]. Jean Marjolin named this condition in 1828, when he noted malignant degeneration of a burn scar [122]. Marjolin's ulcers usually consist of SCCs that arise from sites of previous damage such as: burns, scars, sinuses, pressure ulcers, trauma, chronic venous stasis ulcers, urethral or anal fistulas and osteomyelitis sites [122]. Marjolin's malignancies rarely encompass BCCs or melanomas [120].

The incidence of Marjolin's ulcers varies, but it has been estimated that 1.7% of chronic wounds undergo malignant degeneration and that a Marjolin's ulcer has a 30%-40% rate of metastasis [122]. However, its behaviour is more aggressive when arising in pressure ulcers as compared to burns or osteomyelitis and it is more aggressive than other skin cancers of the same cell type. While the aetiology of Marjolin's ulcers is not clear, it is believed to arise from the constant mitotic activity of epidermal cells trying to resurface a wound [120].

As Marjolin's ulcers may have a latent transformation time of 25-40 years, it is essential that a biopsy is performed on all chronic ulcers; particularly ulcers that occur at the site of a previously healed burn or traumatic injury and where osteomyelitis has developed [120]. Biopsies need to be taken from multiple sites to reduce the risk of a sampling error delaying the correct diagnosis [120, 122].

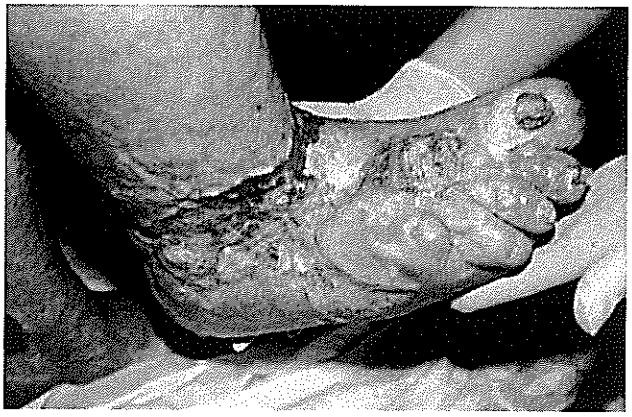

Figure 8. Marjolin's ulcer – a squamous cell carcinoma in a chronic foot ulcer associated with rheumatoid disease and lymphoedema.

Infectious ulceration

All chronic wounds are contaminated with bacteria although not all organisms are pathogenic. Table 3 lists some of the organisms and infections associated with tissue necrosis:

The pathogenic ability or virulence of a micro-organism needed to cause disease is determined by its capacity to find a susceptible host, gain access to appropriate tissue/s and evade the host's defence mechanisms [124]. Wounds are generally infected by extracellular rather than intracellular infections [126]. Pathogens may rely on the production of extracellular enzymes to invade deeper into host tissue. Microbial toxins that cause tissue damage include: exotoxins, which are released from viable bacteria, and endotoxins and integral cell wall components,which are released following microbial cell death and lysis. These toxins are dose-dependent and can cause either local or systemic reactions. Exotoxins are generally more toxic than endotoxins and affect specific target cells [126]. Qualitative and quantitative bacteriology analysis of wound swabs, tissue biopsy specimens or tissue aspirate specimens will be required to confirm a diagnosis [124, 126]. Where osteomyelitis is suspected, representative cultures need to be obtained from the bone or deepest tissue layers. Diagnosis may be aided by labelled leukocyte scanning or magnetic resonance imaging. Topical and systemic treatment should be employed as indicated by the findings [16, 123].

Table 3. Organisms and infections associated with tissue necrosis [16, 123-125]

β-haemolytic *Streptococcus pyogenes*
Erysipelas
Fasciitis necroticans (*Streptococcus haemolyticus*),
Ulceration pyoderma (*S. aureus*)
Gas gangrene (*Clostridium*)
Ecthyma gangrenosum (*Pseudomonas*),
Septic embolism
Anthrax (*Bacillus anthracis*),
Diphtheria (*Corynebacterium diphteriae*)
Osteomyelitis
Toe-web fungal infection
Lues maligna (lues III, gummata)
Buruli ulcer (*Mycobacterium ulcerans*)
Tularaemia (*Franciscella tularensis*)
Leishmaniasis
Tropical ulcer (*Bacteroides, Borrelia vincenti and other bacteria*)
Amoebiasis
Histoplasmosis
Bacillary angiomatosi

Factitious ulceration

Factitious wounding refers to those wounds that are created by a deliberate act of force by an individual, aimed at causing damage to their own body. Factitious wounding may be ritualistic or repetitive and is generally impulsive [127]. Individuals generally offer fraudulent clinical histories with feigned signs and symptoms. Research demonstrates that manipulation of the skin or wounding is the most common form of fictitious injury [128]. Individuals cause factitious wounding for numerous reasons that may include: self-distraction, communication within the self, potential for endorphin stimulation that produces mood changes, alerting others to internal pain and feelings of hopelessness or desperation [127]. Diagnosis can be particularly difficult to ascertain as some individuals' fraudulent clinical histories and feigned signs and symptoms are very informed and realistic [127, 129-132].

Conclusion

This review has outlined some of the atypical conditions that may predispose an individual to leg ulceration and that were identified in the development of the online WoundsWest Leg Ulcer Module. The conditions described are unusual, occur infrequently and can be difficult to diagnose and manage.

When leg ulcers fail to respond to treatment or heal in an orderly and timely manner, clinicians should be prompted to conduct further diagnostic investigations, refer to specialists as indicated and ensure a multidisciplinary approach to care is being employed.

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