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Lower-extremity ulcers: diagnosis and management

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Summary

Chronic wounds of the lower extremities are occurring with increasing prevalence. They affect millions of individuals annually, representing both a significant health risk and a large economic burden. Chronic wounds are associated with increased mortality and substantial morbidity due to infection, pain, limitation of daily activities, and psychosocial consequences. To manage these wounds effectively, clinicians must be able to diagnose and manage their aetiology. Diagnosis starts with determining whether the wound is one of the four most common chronic wounds: venous leg ulcers, diabetic foot ulcers, pressure ulcers and arterial ulcers. Moreover, despite many recent advances in wound care, the challenge of managing chronic wounds is complicated by the lack of consistently accepted diagnostic methods and wound-care standards. We present a comprehensive yet condensed approach to managing lower-extremity ulcers, from diagnosis to basic management.

What's already known about this topic?

- Increasing in prevalence, the 4 most common chronic wounds are diabetic foot ulcers, venous leg ulcers, pressure ulcers and arterial ulcers. These wounds represent a significant socioeconomic burden due to the high cost of wound care, long time to heal, morbidity, high complication rate and impact on patients' and relatives' quality of life.
- Part of the problem is that non-specialized care providers lack familiarity and consistency in the use of standardized diagnostic methods and treatment strategies.

What does this study add?

- Non-specialized care providers, including dermatologists should have a strong knowledge foundation on these common chronic wounds to increase diagnostic accuracy and implementation of standard of care methods.
- This review presents a comprehensive, complete review from the diagnosis and pathophysiology to the differential diagnosis and standard of care treatment of these ulcers.

Wounds, in particular chronic wounds, represent a clinical challenge to healthcare providers and an unmet medical need for patients. In the U.S.A. alone, chronic wounds affect an estimated 7 million patients annually, costing the US healthcare system upwards of $25 billion each year.[1] Patient care is partially driven by basic, translational and clinical research discovery, and despite significant underfunding from US federal sources, wound-healing research has been increasingly productive.[1] However, more often, patient care is driven by professional education. While improved wound care has occurred, practice gaps exist and chronic wounds will continue as an even greater public health concern as the population ages and the incidence of risk factors for chronic wounds, such as diabetes mellitus, continues to rise. To combat the increasing number of patients with wounds and wound-healing problems, more and better-trained clinicians are needed.

Chronic ulcers differ from acute ulcers in that they fail to progress through a normal, orderly and timely sequence of

tissue-repair processes, resulting in a longer time to restore normal anatomical and functional integrity.[2,3] Open wounds make an individual vulnerable to infection, which is, in part, responsible for the increased morbidity and mortality associated with chronic diabetic foot ulcers (DFUs) and pressure ulcers (PUs).[4,5] Moreover, patients also experience increased morbidity from associated pain, drainage and foul odour, impaired mobility and psychosocial consequences.[6,7] Dealing with patients with a chronic wound starts with making an accurate diagnosis.

Principal causes of chronic wounds

Discerning the cause of a chronic wound starts with determining whether the wound is one of the four common chronic wounds, and wound location is often quite helpful.[8] For example, the most common chronic leg wound is the venous leg ulcer (VLU),[9,10] accounting for approximately 80% of all leg ulcers and typically affecting older individuals.[11] The most common chronic foot wound is the DFU.[12] In the U.S.A., approximately 30 million individuals have diabetes mellitus (DM), and their lifetime risk of developing a foot ulcer is as high as 25%.[13] The prevalence of DFU in diabetics is 4–10%,[14] and approximately 20% of all diabetes-related hospital admissions and 85% of amputations in diabetic patients are due to a complicated DFU.[15]

Independent of location, the most common chronic wound is the PU, which presents predominantly over high- and prolonged-pressure areas.[12] The elderly or infirm, or individuals with impaired mobility are the most common groups to develop PUs, given their higher likelihood of prolonged immobilization.[16] Hospitalized patients develop PUs frequently, and the overall higher incidence of PUs in selected hospitalized patient populations has been used as a marker for poor-quality care.[17–19] Ulcers secondary to arterial disease (arterial or ischaemic ulcers, AUs) are the fourth most common chronic wound type and tend to be distal on the lower extremity or anteriorly on the leg. Severe peripheral vascular disease is seen with advancing age and in patients who smoke or have DM, hypertension, hyperlipidaemia or a family history of vascular disease.[20] These patients usually have evidence of significant atherosclerotic disease in other vessels and are at risk for development of AUs.[21,22]

Table 1 Risk factors for development of chronic ulcers

Venous leg ulcers
Age > 55 years[77]
Male sex[77]
Presence of reflux in deep and perforator veins, deep obstruction and combination of reflux and obstruction[77]
History of superficial/deep-vein thrombosis and pulmonary embolism[77]
Previous ulcer history[78]
Parental history of ankle ulcers[77] and family history of venous insufficiency[79]
Number of pregnancies (for women)[79]
Severe lipodermatosclerosis[78]
Time since first ulcer episode ≥ 2 years[78]
Skeletal or joint disease in lower extremities[77]
Higher body mass index[77]
Physical inactivity[77]
Diabetic foot ulcers
Presence of sensory neuropathy[80,81]
Previous ulcer or amputation[80]
Concomitant peripheral arterial disease[80,81]
Long duration of diabetes mellitus[81]
Male sex[82]
Insulin use[83]
Charcot deformity and hammer/claw toe deformity[83]
Reduced skin oxygenation and foot perfusion (transcutaneous oxygen pressure)[83]
Higher body mass index[83]
Poor vision[83]
Inadequate footwear[82]
Pressure ulcers
Advanced age[84]
Immobility[84,85]
Infrequent turning and repositioning[86,87]
Undernutrition/malnutrition[84]
Lack of usage of pressure-reducing devices[87,88]
Altered mental status[85,88]
Systemic illness such as respiratory disease[88] or anaemia[87,88]
Stool and urinary incontinence[85,87]
Smoking[87]
African American ethnicity[89]
Arterial ulcers
Advanced age[90]
Diabetes mellitus[90]
Smoking[90]
Hypertension[90]
Hyperlipidaemia[91]
Obesity[91]

Venous leg ulcers

Pathophysiology

Chronic venous insufficiency (CVI) is caused by calf-muscle pump failure, which propels venous blood flow, coupled with abnormal retrograde flow or reflux.[23] Most commonly, dilated veins or incompetent valves are at fault. CVI leads to development of sustained ambulatory venous pressure (venous hypertension), which results in distension of the capillary walls and leakage of macromolecules such as fibrinogen into the dermis and subcutaneous tissues of the calf. Fibrinogen then polymerizes to fibrin, which deposits in the form of pericapillary fibrin 'cuffs',[24,25] which have been hypothesized to compromise the diffusion of oxygen and nutrients to the tissues, resulting in hypoxia and formation of ulceration. However, interestingly these cuffs have been found to be discontinuous, and patients heal despite their presence.[11] Another hypothesis suggests that these cuffs trap essential growth factors, rendering them functionally inactive.[26] An additional hypothesis, the 'white cell trap hypothesis', suggests demargination of leucocytes in capillary walls, acting as a physical barrier and releasing proteolytic

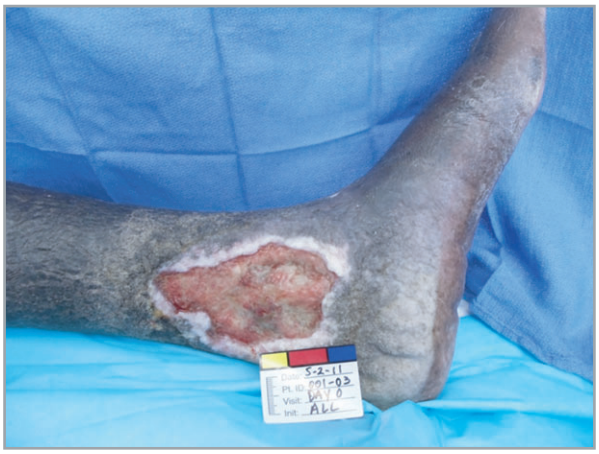

Fig 1. Venous leg ulcer located over the medial malleolus.

enzymes, cytokines, free radicals and chemotactic factors, which can cause further vascular permeability.[27,28]

Risk factors

In addition to the presence of venous reflux, deep obstruction, history of vein thrombosis and previous ulcer history, there are several other important risk factors, as outlined in Table 1.

Physical examination

VLUs usually present on the lower third of the leg ('gaiter area'), particularly on or above the medial malleolus (Fig. 1), but can also appear laterally or posteriorly; if large they can become circumferential. They are commonly superficial, thus rarely extending to bone or tendon, frequently exudative, and usually with fibrinous material referred to as slough. Patients often have evidence of venous disease such as spider or varicose veins, or dependent pitting oedema that resolves with leg elevation. Additionally, a red-to-brown discoloration of the skin around the wound can occur, representing haemosiderin and melanin deposition and (venous) dermatitis. Longer-standing disease can lead to fibrotic changes of the skin called lipodermatosclerosis, giving the characteristic 'inverted champagne-bottle' appearance of the leg. Another common feature is atrophie blanche, which is stellate porcelain white scarring with surrounding dyspigmentation and telangiectasias.[29] While patients are at high risk for developing cellulitis, the prevalence of osteomyelitis is low, as is the risk of amputation.

Diabetic foot ulcers

Pathophysiology

DFUs are caused primarily by diabetic neuropathy, and frequently occur in combination with peripheral arterial disease.[30] The presence of peripheral neuropathy is a major risk factor for DFU development.[31,32] Primarily DM causes a sensory neuropathy, but also motor and autonomic dysfunction. Sensory neuropathy reduces awareness of pressure, heat or injury, which would normally elicit pain or discomfort. Therefore repetitive unnoticed mechanical trauma to the skin may result in consequent ulceration. Motor neuropathy and nonenzymatic glycosylation of periarticular soft tissues lead to limitations in joint mobility, muscle atrophy, ligament stretching and concomitant foot deformities. This results in impairment of foot biomechanics, with gait change and uneven distribution of foot pressures.[33,34] Higher-pressure points, especially on bony prominences, and constant stress from ambulation along with neuropathy result in ulcer formation. Autonomic neuropathy results in dry skin[35] at increased risk of cracks and fissures, which further predisposes to infection and ulcer development.

Table 2 Wagner Ulcer Classification System for diabetic foot ulcers

Grade	Features
0	Absence of ulcer in a high-risk foot
1	Superficial ulcer
2	Deep ulcer, involving tendon and muscle, but not bone
3	Deep ulcer with infection (cellulitis, abscess or osteomyelitis)
4	Localized gangrene
5	Extensive gangrene of the foot

Risk factors and classification

In addition to neuropathy, vascular disease and a history of a prior foot ulcer, other risk factors for development of a DFU exist, as outlined in Table 1. The most practical and widely used classification system is the Wagner classification (Table 2),[36–38] but the University of Texas Diabetic Foot Risk Classification System is more comprehensive as it considers the presence of ischaemia in addition to depth and infection.[37] Patients with deeper ulcers who also have ischaemia and concomitant infection are at the highest risk for poor healing and

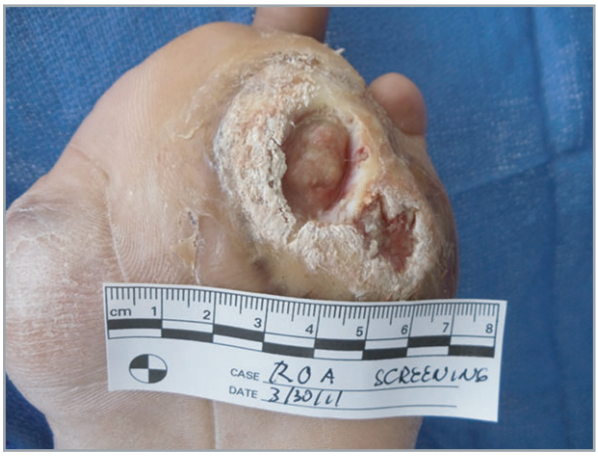

Fig 2. Diabetic foot ulcer surrounded by callus on a high-plantar-pressure point. Also multiple toe amputations.

amputation. Other more novel staging systems exist, for example the 'PEDIS' system proposed by the International Working Group on the Diabetic Foot, which grades the wound on the basis of perfusion, extent of wound, depth, infection and sensation.[39]

Physical examination

The feet of patients with DM should be examined daily by patients and routinely by clinicians for the presence of ulcerations. Patients should be tested for loss of peripheral sensation using a 10-g monofilament against intact, noncallus skin. Loss of peripheral sensation can also be assessed through vibration sensing using a tuning fork or biothesiometer.[40,41] Most commonly, DFUs present on the plantar surfaces of the feet over areas of increased pressure such as the heel, metatarsal heads and tips of distal phalanxes, as often noted by the presence of callus (Fig. 2). Ulcers tend to be deep and probe to underlying bone. Undermining of wound edges and periwound callus is common.

Pressure ulcers

Pathophysiology

PUs can start developing within 2–6 h of prolonged compression of soft tissues, most commonly between a surface and bony prominences, leading to local tissue damage. Four major mechanisms are involved: (i) sustained high-interphase pressure (the force directed perpendicular to the surface) and shear forces (the force directed tangential to the tissue surface); (ii) loss of elastin in aged skin, which allows for decreased resistance to pressure leading to hypoxia and necrosis of tissues;[42,43] (iii) frictional forces that can result in superficial erosions and blisters, which may further contribute to the formation of a PU; and (iv) excess skin moisture from prolonged exposure to sweat, urine, faecal matter or wound drainage, which can result in tissue maceration and breakdown. A reclassification of this latter group as 'moisture-associated skin disease' has been proposed.[44]

Interestingly, recent appreciation exists that ulcer development may occur in one of two scenarios. In one scenario, the injury initiates in the skin and progresses to deeper tissues, and in the other, deeper tissues such as the muscle are initially affected, from which the damage evolves to the skin. Muscle tissue has been described as being more sensitive to ischaemia than the overlying skin, resulting in earlier muscle damage.[45,46]

Risk factors and classification

Risk factors for PU development are outlined in Table 1. One of the most widely used classification systems for PUs is that created by the National Pressure Ulcer Advisory Panel (NPUAP) in the U.S.A. (Table 3).[47] However, recently the NPUAP staging has come under criticism, as later-stage ulcers may develop *de novo*, without going through earlier stages, presumably because of deep-tissue injury as discussed above.[44,45] Predicting and stratifying patients at risk can be accomplished using scales such as the Braden or Norton scales.

Physical examination

For patients at increased risk it is important to examine the prolonged-pressure areas and assess for skin disruption, temperature (warmth or coolness), tissue consistency (firm or boggy feel), sensation (pain or itching) and discoloration (redness or purple hues), which can all be initial signs of early PUs. PUs are commonly located on the sacrum, hips and heels.

Arterial 'ischaemic' ulcers

Pathophysiology

Arterial insufficiency is the most common form of ischaemia and most commonly results from occlusion of the arteries proximal to eventual ulcer formation. Progressive atherosclerosis is the most common aetiology, where the arteries become

Table 4 Rutherford classification of peripheral arterial disease

Stage	Features
0	Asymptomatic
1	Mild claudication
2	Moderate claudication
3	Severe claudication
4	Rest pain
5	Ischaemic ulceration not exceeding ulcer of the digits of the foot
6	Severe ischaemic ulcers or frank gangrene

Table 3 The National Pressure Ulcer Advisory Panel definition of pressure ulcers

Category: stage	Definition
I: Nonblanchable erythema	Intact skin with nonblanchable erythema. The area may be painful, firm, soft or warmer or cooler than adjacent skin
II: Partial-thickness ulcer	Partial-thickness loss of dermis presenting as a shallow open ulcer. May also present as an open/ruptured blister
III: Full-thickness ulcer	Full-thickness tissue loss. Subcutaneous fat may be visible but bone, tendon or muscle are not exposed
IV: Full-thickness ulcer	Full-thickness tissue loss with exposed bone, tendon, fascia or muscle. Osteomyelitis or osteitis is likely to occur

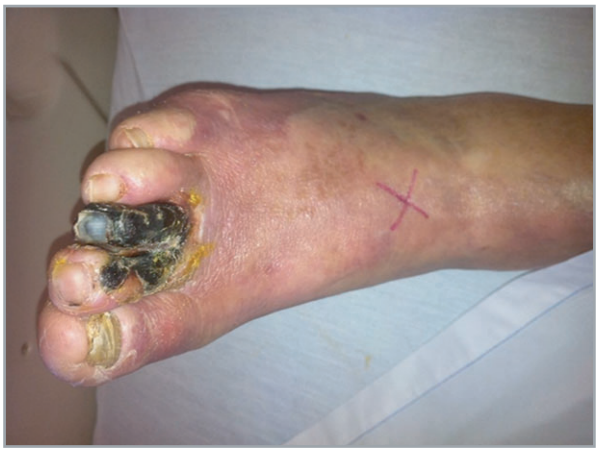

Fig 3. Typical arterial ulcer on toes with dry necrotic base and presence of gangrene.

stenotic as a result of lipid deposition in arterial vessel walls, often due to high levels of circulating cholesterol or triglycerides and aggravated by smoking, poorly controlled hypertension and DM, among other causes. The arteries fail to deliver oxygen and nutrients to the leg and foot, resulting in tissue breakdown. Any other process that obstructs the arterial flow (e.g. vasculitis, microthrombotic disease, sickle-cell disease) can result in an AU.

Risk factors and staging

Risk factors for the development of atherosclerosis and AU are outlined in Table 1. To assess and describe the severity of peripheral arterial disease, a commonly used clinical staging system is the Rutherford classification (Table 4).

Physical examination

AUs are most commonly located in the foot, especially distally on the toes, but may present on the heel, ankle or other parts of the leg, especially anteriorly where there is minimal collateral arterial circulation.[48] These ulcers tend to have a dry, pale base with poor granulation tissue, often with an eschar and on occasion, exposed tendons (Fig. 3).

Evaluation and helpful diagnostic tests

For all patients with leg and foot ulcers, thorough examination of arterial supply is essential.[49] Palpation of the dorsalis pedis and posterior tibialis pulses should be performed on physical examination, and, if nonpalpable or weak, further assessment should be performed with Doppler and/or more objective measurements such as ankle–brachial index (ABI). The Inter-Society Consensus for the Management of Peripheral Arterial Disease has defined a cut-off ABI value of $\leq 0{\cdot}9$ for diagnosing peripheral vascular disease at rest. In elderly or diabetic patients, falsely elevated ABI may require additional testing, such as transcutaneous oxygen measurements (< 40 mmHg considered abnormal) or toe–brachial index (< 6 considered abnormal).[50]

On evidence of abnormal initial testing, more complex and specific tests may be necessary such as Doppler arterial waveforms and pulse volume recordings. In all cases, but especially in patients with AU and DFU,[30] diagnosing both arterial disease and the severity of obstruction is important in order to establish whether there is a role for surgical intervention.[51]

Venous and arterial Doppler studies are typically performed on patients with a suspected VLU, to assess for the presence of venous reflux, vein thrombosis and superficial venous disease, and to assure adequate arterial circulation in order to institute appropriate compression therapy.[52,53]

Testing for infection with the swab culture technique in the absence of local signs of infection is discouraged, given the high likelihood of bacterial growth from contamination. Oral antibiotics should be instituted when there is evidence of infection as determined by host response (surrounding redness, oedema, increased pain, excess exudate, etc.).

Imaging studies are useful when underlying osteomyelitis is suspected. Plain radiograph is an initial screening test in the presence of high clinical suspicion, but it is less sensitive during early phases of bone infection and less specific when other bone abnormalities are present. Magnetic resonance imaging is the most accurate (sensitive and specific) imaging test, but the gold standard is bone biopsy for culture and sensitivities.

A helpful algorithm for the evaluation and work-up of a chronic wound is shown in Figure 4.

Atypical wounds

If an ulcer is present in an atypical location, its clinical appearance or symptoms are uncommon and it does not respond to conventional therapy, then suspecting an atypical aetiology is warranted.[54]

For example, the thigh is an atypical location for a PU, VLU, AU or DFU and should raise the suspicion of an atypical cause. A wound on the medial aspect of the leg but extending deep to the tendon would be considered atypical despite being in a common location for VLU. Finally, any wound that is not healing after 3 months of appropriate treatment should raise the consideration of an atypical cause, even if the distribution and clinical appearance are classic for a common chronic wound.

For patients where the diagnosis seems unclear, tissue biopsy is often critical in narrowing the differential diagnosis. This can be done by performing a punch biopsy of the wound bed and edge to send for histology and culture. Histology can be helpful in determining ulcers of vasculitic or vasculopathic aetiologies, as well as infectious and malignant causes, but it is less specific in pyoderma gangrenosum. Depending on the biopsy result, further laboratory tests assessing for underlying and associated disease may be warranted (Table 5).

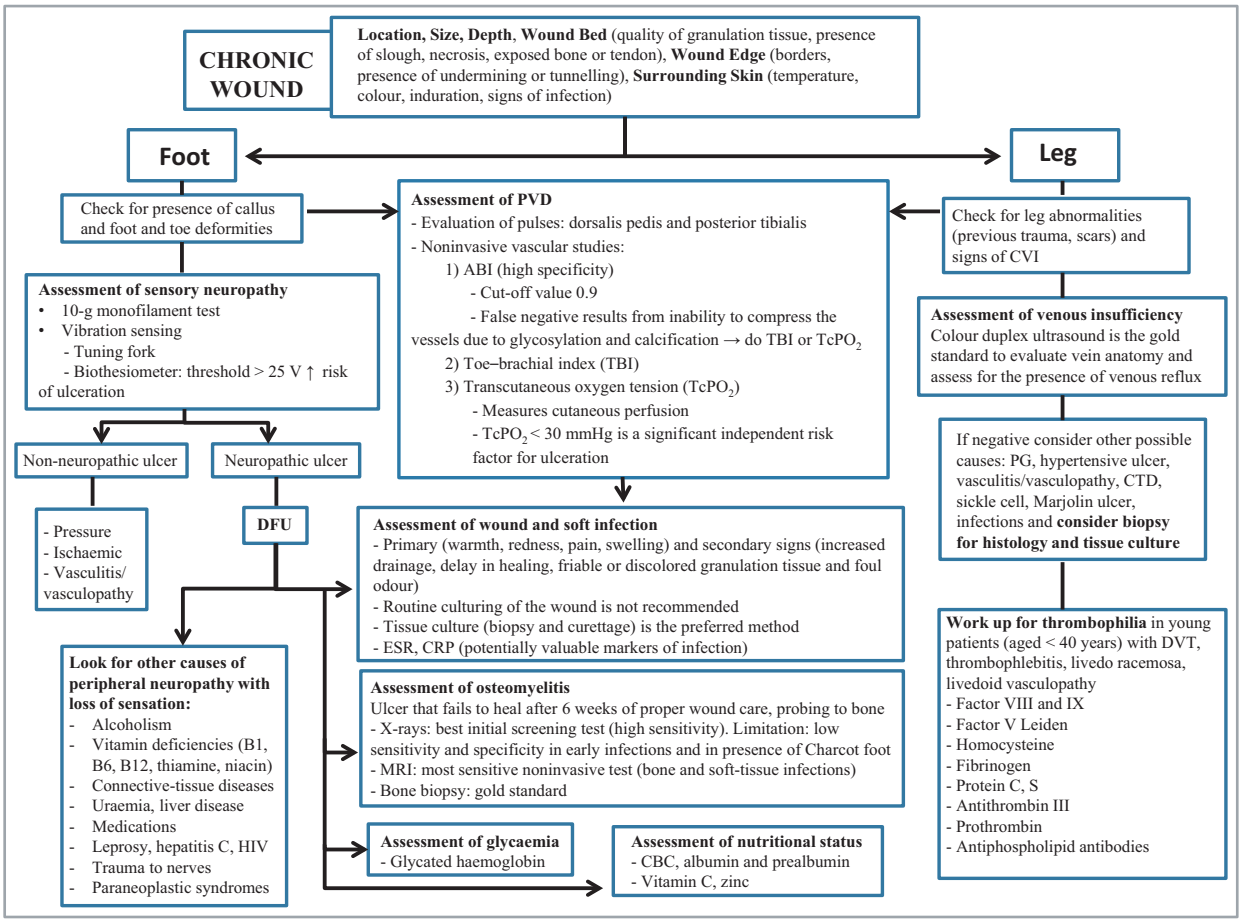

Fig 4. Evaluation of a chronic wound. ABI, ankle–brachial index; CBC, complete blood count; CRP, C-reactive protein; CTD, connective-tissue disease; CVI, chronic venous insufficiency; DFU, diabetic foot ulcer; DVT, deep-vein thrombosis; ESR, erythrocyte sedimentation rate; MRI, magnetic resonance imaging; PG, pyoderma gangrenosum; PVD, peripheral vascular disease.

Prognosis

Simplistically, two risk factors often associated with ulcer prognosis are wound size and wound duration.[55,56] A larger wound is less likely to heal than a smaller one, and a wound of longer duration is more likely to be refractory than one of shorter duration. For example, for a VLU, a wound < 5 cm^2 and of < 6 months' duration is more likely to heal with compression therapy than larger and more chronic wounds.[57] Compliance with appropriate therapy greatly affects the outcome in patients with lower-extremity ulcers. This can present as an issue particularly in patients with DFUs and VLUs, in which offloading devices and compression elastic systems are required, respectively, but compliance has been found to be poor.[58]

Education about the importance of good compliance and appropriate wound care is important for achieving successful outcomes. In patients with VLUs and DFUs, recurrence rates are high and patients should be educated on the importance of preventive measures. For patients with CVI, this includes rigorous use of compression stockings after complete healing of the VLU. For patients with DM, this includes regular podiatric examinations and self-foot examinations when possible.[59,60]

Treatment

Venous leg ulcers

The goal of treatment is to reverse the effects of sustained venous hypertension, and treatment comprises healing of the ulcer, reduction of oedema and pain, improvement of lipodermatosclerosis and prevention of recurrence.[53]

The simplest method is leg elevation above the heart level for 30 min several times per day, which reduces leg oedema and improves microcirculation. However, in advanced disease, compression therapy is required and is considered the mainstay of therapy. It improves venous flow and lymphatic drainage, and reduces the superficial venous pressure and reflux, while increasing the local hydrostatic pressure, resulting in reduction of volume overload in the venous system, reduction of oedema and decreased extravasation of macromolecules. Additionally, compression enhances fibrinolysis,[61] preventing trapping of important mediators for wound healing and decreasing the rate of ulcer recurrence.[62] The optimal pressure of the compression bandaging is 35–40 mmHg, and the bandage is typically changed weekly unless an excessive amount

Table 5 Atypical ulcers and associated conditions

Ulcer type	Clinical clues	Associated conditions
Connective-tissue ulcers	Unusual shapes, sharply marginated. Located on distal extremities. Common in digits	Rheumatoid arthritis; SLE; scleroderma, CREST and morphoea; Sjögren syndrome; dermatomyositis; mixed connective-tissue disease
Vasculitis-related ulcers	Wedge-shaped or irregular borders with necrosis. Usually bilateral on lower extremities. Presence of palpable purpura and livedo reticularis	Small-vessel vasculitis (leucocytoclastic vasculitis); medium-sized-vessel vasculitis (polyarteritis nodosa, microscopic polyangiitis, Wegener granulomatosis)
Microthrombi-related ulcers	Usually multiple, small, necrotic, painful punched-out ulcers. Commonly on dorsal lateral foot. Presence of livedo reticularis, splinter haemorrhages, superficial thrombophlebitis, cyanosis, gangrene	Primary hypercoagulable states; factor V Leiden; antithrombin III deficiency; prothrombin gene mutation; protein C/S deficiency; antiphospholipid antibody; cryoglobulinaemia/cryofibrinogenaemia; cholesterol emboli
Pyoderma gangrenosum	Small papule or pustule that evolves into an irregular, necrotic ulcer with violaceous, rolled-up and undermined borders. Cribriform scarring and pathergy (worsening of the ulcer in response to trauma)	Inflammatory bowel disease; connective-tissue disease; myeloproliferative diseases; monoclonal IgA gammopathy; rheumatoid arthritis
Marjolin ulcer (malignant ulcer)	Long-standing nonhealing ulcer on previously traumatized, chronically inflamed or scarred skin. Usually exophytic with exuberant granulation tissue and friable centre	Basal cell carcinoma; squamous cell carcinoma; melanoma; sarcoma; lymphoma
Hypertensive ulcer (Martorell ulcer)	Unilateral or bilateral rapidly progressive, extremely painful, shallow ulcer with purple edges and black eschar located on lateral–dorsal calf or Achilles tendon	Hypertension and diabetes (local subcutaneous atherosclerosis)
Sickle-cell ulcer	Shallow ulcer over medial malleolus. Similar to venous leg ulcer	Sickle-cell anaemia
Necrotizing fasciitis	Haemorrhagic bullae. Pain out of proportion to examination	Very ill patients; *Vibrio vulnificus* – increased in patients with liver disease
Calciphylaxis	Extensive irregular, necrotic and painful ulcers on fatty areas such as thighs, abdomen, breasts	End-stage chronic kidney disease
Necrobiosis lipoidica diabeticorum	Anterior shins. Plaque-like brownish-red areas that can ulcerate	Diabetes mellitus

SLE, systemic lupus erythematosus; CREST, calcinosis, Raynaud phenomenon, oesophageal dysfunction, sclerodactyly and telangiectasia.

of drainage requires more frequent changes. Multilayered bandage systems are the most useful as they provide sustained pressures when applied correctly and provide cushioning, have absorptive capacity and require less frequent dressing changes. However, this system requires trained personnel for adequate application.

Patients who are compliant with compression therapy have a significantly improved ulcer healing rate and a decreased rate of recurrence. Relative contraindications for compression include arterial insufficiency and uncompensated congestive heart failure.

In selected cases, the performance of superficial and perforator vein surgery, as well as minimally invasive procedures such as endovenous (laser or radiofrequency) ablation, may improve ulcer healing and decrease long-term recurrence rates.

Diabetic foot ulcers

Redistributing the pressure in the plantar aspect of the foot is critical in order to avoid repetitive trauma and achieve healing.[63] Pressure offloading can be approached with bed rest, wheelchairs, crutches, foot inserts, therapeutic shoes, casts or surgical procedures. The total-contact cast is considered the gold standard offloading device, as it has been associated with the highest healing rates.[64,65] However, its use is limited because it requires trained staff for application and removal, it can cause trauma to the foot if improperly applied, and it is contraindicated in infection, contralateral foot ulcer, significant arterial insufficiency and equilibrium problems. Therefore removable cast walkers have been increasingly used and can be equally effective. Successful offloading is frequently affected by poor patient compliance, given that these devices limit the performance of daily activities. Therefore, the best device is the one that best adapts to the patient and allows continuous use.[66]

Debridement, although limited by level II evidence, is considered part of the standard of care for DFU.[66] It allows removal of callus, abnormal edge tissue and necrotic tissue, and reduction of bacterial biofilms and excess matrix metalloproteinases.[67,68] Surgical debridement is preferred for DFUs as

it encourages healing by stimulation of the production of growth factors. The optimal frequency of debridement of DFUs is not clear, but it is often performed either weekly or as needed based on the formation of nonviable tissue.[69–71]

Pressure ulcers

Patients should be assessed for PU risk at the initial visit, after 48 h and thereafter at intervals based on the severity of illness. Constant turning and repositioning of these patients and optimizing their nutritional status are the mainstays of treatment. Also, pressure-redistributing support surfaces to decrease interphase pressure, such as foam or air-based, pressure-relieving mattresses, sheepskins and more high-technology dynamic mattresses or overlays, are effective and superior to standard hospital beds in treating PUs.[72]

Debridement should be performed to remove necrotic and devitalized tissue and to reduce bacterial bioburden, allowing healthy tissue to grow. Extensive grade III or IV PUs may require aggressive surgical debridement in the operating room and plastic surgical reconstruction. Oral or intravenous antibiotics may be required in the case of infection of the ulcer or in the presence of osteomyelitis.

Arterial ulcers

The goals in the treatment of AUs are to relieve pain, establish adequate circulation and prevent amputation.[73] The only effective way to heal these ulcers is to provide an increase in blood supply. Therefore, the presence of an AU is an indication for surgical intervention, thus prompt referral to vascular surgery or interventional radiology should be considered.[74] Percutaneous balloon angioplasty or stent placement and laser angioplasty are used in conjunction with surgical revascularization. In the event of failure of these methods or the presence of progressive gangrene or severe rest pain, amputation of the involved limb may be necessary. Preservation of maximal limb length depends on the promptness of diagnosis and intervention.

If the patient is not a candidate for revascularization, or if ischaemia is not causing severe pain or gangrene, AUs can be managed conservatively. Medical therapy with antithrombotic drugs and risk-factor reduction with statins and antihypertensive agents can be used, although they do not correct the underlying problem.[75] They also serve as adjunctive therapy to decrease perioperative cardiovascular complications and enhance arterial and graft patency after revascularization. Pen-

Table 6 Common chronic wounds, clinical presentation and standard-of-care options for treatment

Wound type and clinical presentation	Standard-of-care treatment
Venous leg ulcers	
Shallow, exudative with granulating base and slough	Leg elevation
	Compression therapy (35–40 mmHg)
Typically on medial malleolus	Debridement of devitalized tissue and bacterial biofilm (limited supportive evidence)
Other signs of venous insufficiency present	Use of antimicrobial dressings: (i) cadexomer iodine, (ii) silver dressings
	Moist wound environment (use of appropriate dressings)
	Fibrinolytic therapy (e.g. pentoxifylline)
	Use of antiseptic solutions (iodine, hydrogen peroxide, chlorhexidine) are not encouraged given their cellular toxicity
Diabetic foot ulcers	
Commonly deep, probing to bone, surrounded by callus	Frequent sharp debridement
Undermined edges	Offloading
Located on plantar feet over bony prominences	Moist wound healing (use of appropriate dressings)
Presence of neuropathy, foot deformities	Treatment of infection and osteomyelitis
Dry, cracked skin	Correction of coexistent peripheral vascular disease
Arterial ulcers	
Dry, pale, fibrous base, poor granulation tissue, often with an eschar and exposed tendons	Revascularization. The presence of an ischaemic ulcer is an indication for surgical intervention
Located on anterior leg, distal dorsal foot and toes	Medical therapy with antithrombotic drugs (pentoxifylline, cilostazol), statins and antihypertensive agents if surgery contraindicated or as adjunctive therapy to decrease perioperative complications
Nonpalpable or diminished distal pulses. Cold extremities	
Decreased ankle–brachial index	
Gangrene	
Pressure ulcers	
Area of erythema, erosion or ulceration	Regular relief from prolonged pressures by constantly repositioning patients
Necrosis is common	Debridement of necrotic tissue
Located over areas of bony prominences (sacrum, coccyx, heels, hips)	Optimizing nutritional status
In patients with limited mobility	Use of appropriate dressings to control moisture

Table 7 Evidence-based adjuvant therapies for chronic ulcers

Therapy	Details	References
Allogeneic bilayered cultured skin equivalent: Apligraf®, Organogenesis Inc., Canton, MA, U.S.A.	FDA approved for VLUs (1998) and DFU (2000) Human neonatal cultured living fibroblasts and keratinocytes in a bovine collagen type I matrix Fibroblasts producing matrix proteins, and growth factors allowing restoration and reversion of arrested cell cycle Leads to higher healing rates and incidence of complete wound closure	92, 93, 94, 95
Dermal skin substitute: Dermagraft®, Advanced Biohealing, La Jolla, CA, U.S.A.	FDA approved for the treatment of DFU (> 6 weeks' duration) in 2001 Human fibroblast-derived dermal substitute in a bioabsorbable and biodegradable polyglactin mesh scaffold Fibroblasts produce dermal collagen, matrix proteins, growth factors and cytokines, which help with tissue repair Leads to significantly faster time to complete healing compared with control groups	96, 97, 98
Becaplermin (Regranex®), Smith and Nephew, London, U.K.	FDA approved for full-thickness DFU with adequate arterial perfusion Recombinant platelet-derived growth factor Improves healing rates, time to complete closure and incidence of complete healing of DFU Favourable cost-effectiveness ratio	99, 100, 101
HP802-247, Healthpoint Biotherapeutics, Fort Worth, TX, U.S.A.	Cryopreserved allogeneic, growth-arrested fibroblasts and keratinocytes derived from neonatal foreskin and delivered through a fibrin spray Significantly greater mean reduction in wound area compared with vehicle, with the dose of $0{\cdot}5 \times 10^6$ cells mL^{-1} every 14 days showing the largest improvement Does not required a physical scaffold	102
Platelet-rich plasma	Portion of the plasma of autologous blood that has a platelet concentration above baseline Platelets initiate wound repair by releasing locally acting growth factors via α-granule degranulation, and suppress inflammatory cytokine release Increases migration and proliferation of endothelial and mesenchymal cells Accelerates epithelialization and promotes new capillary growth	103, 104, 105, 106
Hyperbaric oxygen	Stronger evidence for selected cases of DFU Proposed as an adjunctive treatment for chronic nonhealing DFU when basal $TcPO_2$ at the dorsum of the foot is > 25 mmHg Appears to improve health-related quality of life significantly vs. placebo Recently shown to downregulate genes involved in adhesion, inflammation and oxidative stress and promote angiogenesis and nitric oxide production	107, 108

FDA, US Food and Drug Administration; VLU, venous leg ulcer; DFU, diabetic foot ulcer; $TcPO_2$, transcutaneous oxygen pressure.

toxifylline, cilostazol and certain prostaglandins have been advocated in some patients but have limited evidence.[76]

A summary of the clinical presentation and initial standard of care for treatment of the most common types of ulcers is presented in Table 6. When these ulcers fail to heal with conventional modalities, implementing more advanced adjuvant therapies may be useful, such as bioengineered skin, platelet-derived growth factor, cryopreserved allogeneic skin, fibroblasts and keratinocytes, platelet-rich plasma and hyperbaric oxygen (Table 7).

Conclusions

Early recognition and understanding of the aetiology and complexity of the different types of common chronic leg ulcers is critical. Identifying patients at increased risk and implementing early prevention measures and standard-of-care treatment can potentially shorten the natural course of these wounds, improve outcomes, decrease complications and eventually reverse the growing incidence and prevalence of these wounds.

References

1 Sen CK, Gordillo GM, Roy S *et al.* Human skin wounds: a major and snowballing threat to public health and the economy. *Wound Repair Regen* 2009; **17**:763–71.
2 O'Meara S, Cullum N, Majid M, Sheldon T. Systematic reviews of wound care management: (3) antimicrobial agents for chronic wounds; (4) diabetic foot ulceration. *Health Technol Assess* 2000; **4**:1–237.

3 Grey JE, Enoch S, Harding KG. ABC of wound healing: wound assessment. *BMJ* 2006; **332**:285–8.
4 Wu SC, Driver VR, Wrobel JS, Armstrong DG. Foot ulcers in the diabetic patient, prevention and treatment. *Vasc Health Risk Manag* 2007; **3**:65–76.
5 Brem H, Maggi J, Nierman D *et al.* High cost of stage IV pressure ulcers. *Am J Surg* 2010; **200**:473–7.
6 Barron GS, Jacob SE, Kirsner RS. Dermatologic complications of chronic venous disease: medical management and beyond. *Ann Vasc Surg* 2007; **21**:652–62.
7 Jones JE, Robinson J, Barr W, Carlisle C. Impact of exudate and odour from chronic venous leg ulceration. *Nurs Stand* 2008; **22**:53–4, 56, 58 passim.
8 Situm M, Kolić M. Atypical wounds: definition and classification. *Acta Med Croatica* 2012; **66**(Suppl. 1):5–11.
9 Baker SR, Stacey MC, Singh G *et al.* Aetiology of chronic leg ulcers. *Eur J Vasc Surg* 1992; **6**:245–51.
10 de Araujo T, Valencia I, Federman DG, Kirsner RS. Managing the patient with venous ulcers. *Ann Intern Med* 2003; **138**:326–34.
11 Falanga V, Kirsner R, Katz MH *et al.* Pericapillary fibrin cuffs in venous ulceration. Persistence with treatment and during ulcer healing. *J Dermatol Surg Oncol* 1992; **18**:409–14.
12 Zaulyanov L, Kirsner RS. A review of a bi-layered living cell treatment (Apligraf) in the treatment of venous leg ulcers and diabetic foot ulcers. *Clin Interv Aging* 2007; **2**:93–8.
13 Reiber GE. The epidemiology of diabetic foot problems. *Diabet Med* 1996; **13**(Suppl. 1):S6–11.
14 Singh N, Armstrong DG, Lipsky BA. Preventing foot ulcers in patients with diabetes. *JAMA* 2005; **293**:217–28.
15 Reiber GE, Vilekyte L, Boyko EJ *et al.* Causal pathways for incident lower-extremity ulcers in patients with diabetes from two settings. *Diabetes Care* 1999; **22**:157–62.
16 Sarasúa JG, López SP, Viejo MA *et al.* Treatment of pressure ulcers with autologous bone marrow nuclear cells in patients with spinal cord injury. *J Spinal Cord Med* 2011; **34**:301–7.
17 Lyder C, Grady J, Mathur D *et al.* Preventing pressure ulcers in Connecticut hospitals using the plan-do-study-act model for quality improvement. *Jt Comm J Qual Patient Saf* 2004; **30**:205–14.
18 Gunningberg L, Lindholm C, Carlsson M, Sjödén PO. Reduced incidence of pressure ulcers in patients with hip fractures: a 2-year follow-up of quality indicators. *Int J Qual Health Care* 2001; **13**:399–407.
19 Baier RR, Gifford DR, Lyder CH *et al.* Quality improvement for pressure ulcer care in the nursing home setting: the northeast pressure ulcer project. *J Am Med Dir Assoc* 2003; **4**:291–301.
20 Shammas NW. Epidemiology, classification, and modifiable risk factors of peripheral arterial disease. *Vasc Health Risk Manag* 2007; **3**:229–34.
21 Hess CT. Arterial ulcer checklist. *Adv Skin Wound Care* 2010; **23**:432.
22 Hopf HW, Ueno C, Aslam R *et al.* Guidelines for the treatment of arterial insufficiency ulcers. *Wound Repair Regen* 2006; **14**:693–710.
23 Yim E, Richmond NA, Baquerizo K *et al.* The effect of ankle range of motion on venous ulcer healing rates. *Wound Repair Regen* 2014; **22**:492–6.
24 Browse NL, Burnand KG. The cause of venous ulceration. *Lancet* 1982; **2**:243–5.
25 Falanga V, Moosa HH, Nameth AF *et al.* Dermal pericapillary fibrin in venous disease and venous ulceration. *Arch Dermatol* 1987; **123**:620–3.
26 Falanga V, Eaglstein WH. The trap hypothesis of venous ulceration. *Lancet* 1993; **341**:1006–8.
27 Coleridge-Smith PD, Thomas P, Scurr JH, Dormandy JA. Causes of venous ulceration: a new hypothesis? *Br Med J (Clin Res Ed)* 1988; **296**:1726–7.
28 Thomas PR, Nash GB, Dormandy JA. White cell accumulation in dependent legs of patients with venous hypertension: a possible mechanism for trophic changes in the skin. *Br Med J (Clin Res Ed)* 1988; **296**:1693–5.
29 Maessen-Visch MB, Koedam MI, Hamulyák K, Neumann HA. Atrophie blanche. *Int J Dermatol* 1999; **38**:161–72.
30 Alavi A, Sibbald RG, Mayer D *et al.* Diabetic foot ulcers: part I. Pathophysiology and prevention. *J Am Acad Dermatol* 2014; **70**:1.e1–18.
31 Pecoraro RE, Reiber GE, Burgess EM. Pathways to diabetic limb amputation: basis for prevention. *Diabetes Care* 1990; **13**:513–21.
32 Adler AI, Boyko EJ, Ahroni JH, Smith DG. Lower-extremity amputation in diabetes. The independent effects of peripheral vascular disease, sensory neuropathy, and foot ulcers. *Diabetes Care* 1999; **22**:1029–35.
33 Fernando DJ, Masson EA, Veves A, Boulton AJ. Relationship of limited joint mobility to abnormal foot pressures and diabetic foot ulceration. *Diabetes Care* 1991; **14**:8–11.
34 Armstrong DG. Loss of protective sensation: a practical evidence-based definition. *J Foot Ankle Surg* 1999; **38**:79–80.
35 Ahmed ME, Delbridge L, Le Quesne LP. The role of autonomic neuropathy in diabetic foot ulceration. *J Neurol Neurosurg Psychiatry* 1986; **49**:1002–6.
36 Brodsky JW. Classification of foot lesions in diabetic patients. In: *Levin and O'Neal's The Diabetic Foot* (Bowker JS, Pfeifer M, eds). Philadelphia, PA: Mosby Elsevier, 2007; 227–39.
37 Calhoun JH, Cantrell J, Cobos J *et al.* Treatment of diabetic foot infections: Wagner classification, therapy, and outcome. *Foot Ankle* 1988; **9**:101–6.
38 Lavery LA, Armstrong DG, Harkless LB. Classification of diabetic foot wounds. *Ostomy Wound Manage* 1997; **43**:44–8, 50, 52–3.
39 Schaper NC. Diabetic foot ulcer classification system for research purposes: a progress report on criteria for including patients in research studies. *Diabetes Metab Res Rev* 2004; **20**(Suppl. 1):S90–5.
40 Perkins BA, Olaleye D, Zinman B, Bril V. Simple screening tests for peripheral neuropathy in the diabetes clinic. *Diabetes Care* 2001; **24**:250–6.
41 Young MJ, Breddy JL, Veves A, Boulton AJ. The prediction of diabetic neuropathic foot ulceration using vibration perception thresholds. A prospective study. *Diabetes Care* 1994; **17**:557–60.
42 Perier C, Granouillet R, Chamson A *et al.* Nutritional markers, acute phase reactants and tissue inhibitor of matrix metalloproteinase 1 in elderly patients with pressure sores. *Gerontology* 2002; **48**:298–301.
43 Dinsdale SM. Decubitus ulcers: role of pressure and friction in causation. *Arch Phys Med Rehabil* 1974; **55**:147–52.
44 Defloor T, Schoonhoven L, Fletcher J *et al.* Statement of the European Pressure Ulcer Advisory Panel – pressure ulcer classification: differentiation between pressure ulcers and moisture lesions. *J Wound Ostomy Continence Nurs* 2005; **32**:302–6.
45 Ankrom MA, Bennett RG, Sprigle S *et al.* Pressure-related deep tissue injury under intact skin and the current pressure ulcer staging systems. *Adv Skin Wound Care* 2005; **18**:35–42.
46 Paget J. In the wards. Clinical lecture on bed-sores. *Stud J Hosp Gaz* 1873; **10**:144–6.
47 National Pressure Ulcer Advisory Panel, European Pressure Ulcer Advisory Panel and Pan Pacific Pressure Injury Alliance. *Prevention and Treatment of Pressure Ulcers: Quick Reference Guide* (Haesler E, ed.). Perth, Australia: Cambridge Media, 2014.

48 Tam M, Moschella SL. Vascular skin ulcers of limbs. *Cardiol Clin* 1991; **9**:555–63.

49 Spentzouris G, Labropoulos N. The evaluation of lower-extremity ulcers. *Semin Intervent Radiol* 2009; **26**:286–95.

50 Venermo M, Vikatmaa P, Terasaki H, Sugano N. Vascular laboratory for critical limb ischaemia. *Scand J Surg* 2012; **101**:86–93.

51 Holloway GA Jr. Arterial ulcers: assessment and diagnosis. *Ostomy Wound Manage* 1996; **42**:46–8, 50–1.

52 Callam MJ, Ruckley CV, Dale JJ, Harper DR. Hazards of compression treatment of the leg: an estimate from Scottish surgeons. *Br Med J (Clin Res Ed)* 1987; **295**:1382.

53 Valencia IC, Falabella A, Kirsner RS, Eaglstein WH. Chronic venous insufficiency and venous leg ulceration. *J Am Acad Dermatol* 2001; **44**:401–21.

54 Hoffman MD. Atypical ulcers. *Dermatol Ther* 2013; **26**:222–35.

55 Margolis DJ, Allen-Taylor L, Hoffstad O, Berlin JA. Diabetic neuropathic foot ulcers: the association of wound size, wound duration, and wound grade on healing. *Diabetes Care* 2002; **25**:1835–9.

56 Margolis DJ, Allen-Taylor L, Hoffstad O, Berlin JA. The accuracy of venous leg ulcer prognostic models in a wound care system. *Wound Repair Regen* 2004; **12**:163–8.

57 Margolis DJ, Berlin JA, Strom BL. Which venous leg ulcers will heal with limb compression bandages? *Am J Med* 2000; **109**:15–19.

58 Crews RT, Sayeed F, Najafi B. Impact of strut height on offloading capacity of removable cast walkers. *Clin Biomech (Bristol, Avon)* 2012; **27**:725–30.

59 Lavery LA, La Fontaine J, Kim PJ. Preventing the first or recurrent ulcers. *Med Clin North Am* 2013; **97**:807–20.

60 Jeffcoate WJ, Harding KG. Diabetic foot ulcers. *Lancet* 2003; **361**:1545–51.

61 Comerota AJ, Chouhan V, Harada RN *et al.* The fibrinolytic effects of intermittent pneumatic compression: mechanism of enhanced fibrinolysis. *Ann Surg* 1997; **226**:306–13.

62 Trent JT, Falabella A, Eaglstein WH, Kirsner RS. Venous ulcers: pathophysiology and treatment options. *Ostomy Wound Manage* 2005; **51**:38–54.

63 Kato H, Takada T, Kawamura T *et al.* The reduction and redistribution of plantar pressures using foot orthoses in diabetic patients. *Diabetes Res Clin Pract* 1996; **31**:115–18.

64 Coleman WC, Brand PW, Birke JA. The total contact cast. A therapy for plantar ulceration on insensitive feet. *J Am Podiatry Assoc* 1984; **74**:548–52.

65 Walker SC, Helm PA, Pullium G. Total contact casting and chronic diabetic neuropathic foot ulcerations: healing rates by wound location. *Arch Phys Med Rehabil* 1987; **68**:217–21.

66 Braun LR, Fisk WA, Lev-Tov H *et al.* Diabetic foot ulcer: an evidence-based treatment update. *Am J Clin Dermatol* 2014; **15**:267–81.

67 Zhao G, Usui ML, Lippman SI *et al.* Biofilms and inflammation in chronic wounds. *Adv Wound Care (New Rochelle)* 2013; **2**:389–99.

68 International consensus. *The Role of Proteases in Wound Diagnostics. An Expert Working Group Review*. London: Wounds International, 2011.

69 Snyder RJ, Kirsner RS, Warriner RA 3rd *et al.* Consensus recommendations on advancing the standard of care for treating neuropathic foot ulcers in patients with diabetes. *Ostomy Wound Manage* 2010; **56**(4 Suppl.):S1–24.

70 Steed DL, Donohoe D, Webster MW, Lindsley L. Effect of extensive debridement and treatment on the healing of diabetic foot ulcers. *J Am Coll Surg* 1996; **183**:61–4.

71 Wilcox JR, Carter MJ, Covington S. Frequency of debridements and time to heal: a retrospective cohort study of 312 744 wounds. *JAMA Dermatol* 2013; **149**:1050–8.

72 McInnes E, Jammali-Blasi A, Bell-Syer S *et al.* Preventing pressure ulcers – are pressure-redistributing support surfaces effective? A Cochrane systematic review and meta-analysis. *Int J Nurs Stud* 2012; **49**:345–59.

73 Weir GR, Smart H, van Marle J *et al.* Arterial disease ulcers, part 2: treatment. *Adv Skin Wound Care* 2014; **27**:462–76.

74 Varela C, Acin F, De Haro J *et al.* Influence of surgical or endovascular distal revascularization of the lower limbs on ischemic ulcer healing. *J Cardiovasc Surg (Torino)* 2011; **52**:381–9.

75 Norgren L, Hiatt WR, Dormandy JA *et al.* Inter-Society Consensus for the Management of Peripheral Arterial Disease (TASC II). *J Vasc Surg* 2007; **45** (Suppl. S):S5–67.

76 Lee TM, Su SF, Tsai CH *et al.* Differential effects of cilostazol and pentoxifylline on vascular endothelial growth factor in patients with intermittent claudication. *Clin Sci (Lond)* 2001; **101**:305–11.

77 Vlajinac H, Marinkovic J, Maksimovic M, Radak D. Factors related to venous ulceration: a cross-sectional study. *Angiology* 2014; **65**:824–30.

78 Abbade LP, Lastória S, Rollo Hde A. Venous ulcer: clinical characteristics and risk factors. *Int J Dermatol* 2011; **50**:405–11.

79 Bérard A, Abenhaim L, Platt R *et al.* Risk factors for the first-time development of venous ulcers of the lower limbs: the influence of heredity and physical activity. *Angiology* 2002; **53**:647–57.

80 Hurley L, Kelly L, Garrow AP *et al.* Prospective study of risk factors for foot ulceration: the West of Ireland Diabetes Foot Study. *QJM* 2013; **106**:1103–10.

81 Ahmad W, Khan IA, Ghaffar S *et al.* Risk factors for diabetic foot ulcer. *J Ayub Med Coll Abbottabad* 2013; **25**:16–18.

82 Morbach S, Lutale JK, Viswanathan V *et al.* Regional differences in risk factors and clinical presentation of diabetic foot lesions. *Diabet Med* 2004; **21**:91–5.

83 Boyko EJ, Ahroni JH, Stensel V *et al.* A prospective study of risk factors for diabetic foot ulcer. The Seattle Diabetic Foot Study. *Diabetes Care* 1999; **22**:1036–42.

84 Campbell KE. A new model to identify shared risk factors for pressure ulcers and frailty in older adults. *Rehabil Nurs* 2009; **34**:242–7.

85 Michel JM, Willebois S, Ribinik P *et al.* As of 2012, what are the key predictive risk factors for pressure ulcers? Developing French guidelines for clinical practice. *Ann Phys Rehabil Med* 2012; **55**:454–65.

86 Kaitani T, Tokunaga K, Matsui N. Risk factors related to the development of pressure ulcers in the critical care setting. *J Clin Nurs* 2010; **19**:414–21.

87 Cakmak SK, Gül U, Ozer S *et al.* Risk factors for pressure ulcers. *Adv Skin Wound Care* 2009; **22**:412–15.

88 Campbell KE, Woodbury MG, Houghton PE. Heel pressure ulcers in orthopedic patients: a prospective study of incidence and risk factors in an acute care hospital. *Ostomy Wound Manage* 2010; **56**:44–54.

89 Fogerty MD, Abumrad NN, Nanney L. Risk factors for pressure ulcers in acute care hospitals. *Wound Repair Regen* 2008; **16**:11–18.

90 Weir GR, Smart H, van Marle J, Cronje FJ. Arterial disease ulcers, part 1: clinical diagnosis and investigation. *Adv Skin Wound Care* 2014; **27**:421–8.

91 Grey JE, Harding KG, Enoch S. Venous and arterial leg ulcers. *BMJ* 2006; **332**:347–50.

92 Falanga VJ. Tissue engineering in wound repair. *Adv Skin Wound Care* 2000; **13**(2 Suppl.):15–19.

93 Veves A, Falanga V, Armstrong DG, Sabolinski ML. Graftskin, a human skin equivalent, is effective in the management of noninfected neuropathic diabetic foot ulcers: a prospective

randomized multicenter clinical trial. *Diabetes Care* 2001; **24**:290–5.
94 Brem H, Balledux J, Sukkarieh T *et al.* Healing of venous ulcers of long duration with a bilayered living skin substitute: results from a general surgery and dermatology department. *Dermatol Surg* 2001; **27**:915–19.
95 Edmonds M. Apligraf in the treatment of neuropathic diabetic foot ulcers. *Int J Low Extrem Wounds* 2009; **8**:11–18.
96 Gentzkow GD, Iwasaki SD, Hershon KS *et al.* Use of Dermagraft, a cultured human dermis, to treat diabetic foot ulcers. *Diabetes Care* 1996; **19**:350–4.
97 Marston WA, Hanft J, Norwood P, Pollak R. The efficacy and safety of Dermagraft in improving the healing of chronic diabetic foot ulcers: results of a prospective randomized trial. *Diabetes Care* 2003; **26**:1701–5.
98 Hanft JR, Surprenant MS. Healing of chronic foot ulcers in diabetic patients treated with a human fibroblast-derived dermis. *J Foot Ankle Surg* 2002; **41**:291–9.
99 Smiell JM, Wieman TJ, Steed DL *et al.* Efficacy and safety of becaplermin (recombinant human platelet-derived growth factor-BB) in patients with nonhealing, lower extremity diabetic ulcers: a combined analysis of four randomized studies. *Wound Repair Regen* 1999; **7**:335–46.
100 Sibbald RG, Torrance G, Hux M *et al.* Cost-effectiveness of becaplermin for nonhealing neuropathic diabetic foot ulcers. *Ostomy Wound Manage* 2003; **49**:76–84.
101 Persson U, Willis M, Odegaard K, Apelqvist J. The cost–effectiveness of treating diabetic lower extremity ulcers with becaplermin (Regranex): a core model with an application using Swedish cost data. *Value Health* 2000; **3**(Suppl. 1):39–46.
102 Kirsner RS, Marston WA, Snyder RJ *et al.* Spray-applied cell therapy with human allogeneic fibroblasts and keratinocytes for the treatment of chronic venous leg ulcers: a phase 2, multicentre, double-blind, randomised, placebo-controlled trial. *Lancet* 2012; **380**:977–85.
103 Driver VR, Hanft J, Fylling CP, Beriou JM. A prospective, randomized, controlled trial of autologous platelet-rich plasma gel for the treatment of diabetic foot ulcers. *Ostomy Wound Manage* 2006; **52**:68–70, 72, 74 passim.
104 Yuan NB, Long Y, Zhang XX, Ran XW. Study on the mechanism of autologous platelet-rich gel to treat refractory diabetic dermal ulcers. *Sichuan Da Xue Xue Bao Yi Xue Ban* 2009; **40**:292–4. (in Chinese).
105 de Leon JM, Driver VR, Fylling CP *et al.* The clinical relevance of treating chronic wounds with an enhanced near-physiological concentration of platelet-rich plasma gel. *Adv Skin Wound Care* 2011; **24**:357–68.
106 Saad Setta H, Elshahat A, Elsherbiny K *et al.* Platelet-rich plasma versus platelet-poor plasma in the management of chronic diabetic foot ulcers: a comparative study. *Int Wound J* 2011; **8**:307–12.
107 Löndahl M, Katzman P, Hammarlund C *et al.* Relationship between ulcer healing after hyperbaric oxygen therapy and transcutaneous oximetry, toe blood pressure and ankle-brachial index in patients with diabetes and chronic foot ulcers. *Diabetologia* 2011; **54**:65–8.
108 Löndahl M, Landin-Olsson M, Katzman P. Hyperbaric oxygen therapy improves health-related quality of life in patients with diabetes and chronic foot ulcer. *Diabet Med* 2011; **28**:186–90.

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