Leg Ulcers

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Abbreviations

ABI or ABPI	Ankle-brachial pressure index
DVT	Venous thrombosis
ESWT	Extracorporeal shock wave therapy
MPFF	Micronised purified flavonoid fraction
NPWT	Negative-pressure wound therapy
PAOD	Peripheral arterial occlusive disease
PG	Pyoderma gangrenosum
VAC	Vacuum-assisted closure
VAD	Venoactive drugs
wIRA	Water-filtered infrared A

Key Points

- A leg ulcer is a wound located on the lower leg caused by different underlying diseases.
- Vascular diseases dominate the variety of pathologies, but also dermatological, metabolic, haematological, infectious or other disorders can be causative.
- Leg ulcers tend to evolve as chronic wounds, which have failed to heal within an expected time.
- Clinical knowledge and assessment is imperative for correct diagnosis.
- Treatment of leg ulcers encompasses the treatment of the underlying disease and local wound care.

Definition and Epidemiology

Leg ulcers can be defined as any wound located above the foot and under the knee (1). Ulcers on the foot and toes should better be denoted as foot ulcers although they are often numbered among leg ulcers. Leg ulcers – and foot ulcers – most often are chronic wounds. Such wounds have failed to proceed through an orderly and timely process to produce anatomic and functional integrity. The time frame in which a wound is expected to heal is variably estimated by different authors, ranging from 3 weeks up to 3 months. The delay of wound healing can be explained by different factors (e.g. lack of oxygen, bacterial toxins, increased proteinase levels), which are the consequence of a disease that in general is also the cause of the wound.

There are a large number of diseases that can induce a leg ulcer: Vascular, dermatological, metabolic, haematological or infectious diseases can be the cause but also neuropathies, malignancies

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A.D. Katsambas et al. (eds.), *European Handbook of Dermatological Treatments*,
DOI 10.1007/978-3-662-45139-7_49, © Springer-Verlag Berlin Heidelberg 2015

and chemical or physical exposure. An overview of underlying diseases is shown in Table 49.1. A chronic wound can only heal if the underlying disease is controlled; therefore it is mandatory to know the cause of a wound and treat it correctly!

Most studies have shown that a venous aetiology (varicose or postphlebitic) is most common in leg ulcers (70–90 %). However a pure venous aetiology should not be overestimated: An additional arterial component can be found in 10–20 % of venous leg ulcers. A recent population-based study among 250,000 people in London found only 43 % pure venous ulcers but a multifactorial aetiology in 35 % (Moffat et al. 2004).

The prevalence of leg and foot ulcers was investigated in large epidemiologic studies in the 1990s analysing more than 230,000 people. An overall prevalence was found in up to 0.3 %, with a prevalence of venous ulcers of 0.16 %. More recent data from Germany have confirmed these data, showing a prevalence of an active venous ulcer in 0.1 % of a general population (more that 3,000 subjects) (Rabe et al. 2003). In elderly people the prevalence is higher (up to 0.3 % in the cited Bonn vein study) with a predominance of females.

Leg ulcers are a major public health concern, representing about 2 % of the UK healthcare budget with costs of £400 million. In Germany annual costs of over two billion Euros were calculated.

Due to the fact that leg ulcer is caused by a huge number of different diseases involving different medical specialities, a multidisciplinary approach is important. A close collaboration of dermatologists, angiologists, vascular and plastic surgeons, internists, rheumatologist and others is a precondition when dealing with leg ulcers.

But also the interprofessional aspect is of relevance: Wound nurses today are experts for the treatment of leg ulcers. Their suggestions for a treatment plan should be taken into account.

Diagnosis

All diagnostic measures should first aim to find the cause of leg ulcer and to establish the diagnosis of the underlying disease!

As most leg ulcers have a venous or arterial aetiology, the first step should always be to *confirm a venous origin and rule out an arterial involvement*. For this purpose, clinical characteristics are important and most helpful.

If a venous and/or arterial origin is not obvious or another aetiology is clinically suspected, diagnostic procedures have to be performed that allow diagnosis of suspected diseases.

Diagnostic steps include the following.

Medical History

Basic information should comprise duration of ulceration, date and modalities of onset, change of shape, characteristics of pain, history of previous ulcers and recurrences and former treatments.

To confirm *venous origin*, personal and family history of venous disease is of interest, e.g. occurrence of varicose veins, earlier venous thrombosis (DVT), former treatments (surgical interventions) and forms of compressions therapy.

To rule out *peripheral arterial occlusive disease* (*PAOD*), one has to ask for intermittent claudication (occurrence of crampy pain in the calf or thigh during walking) or rest pain in the legs (improvement with walking). Risk factors for vascular disease have to be recorded, e.g. arterial hypertension, diabetes mellitus, hypercholesterolaemia and nicotine consumption.

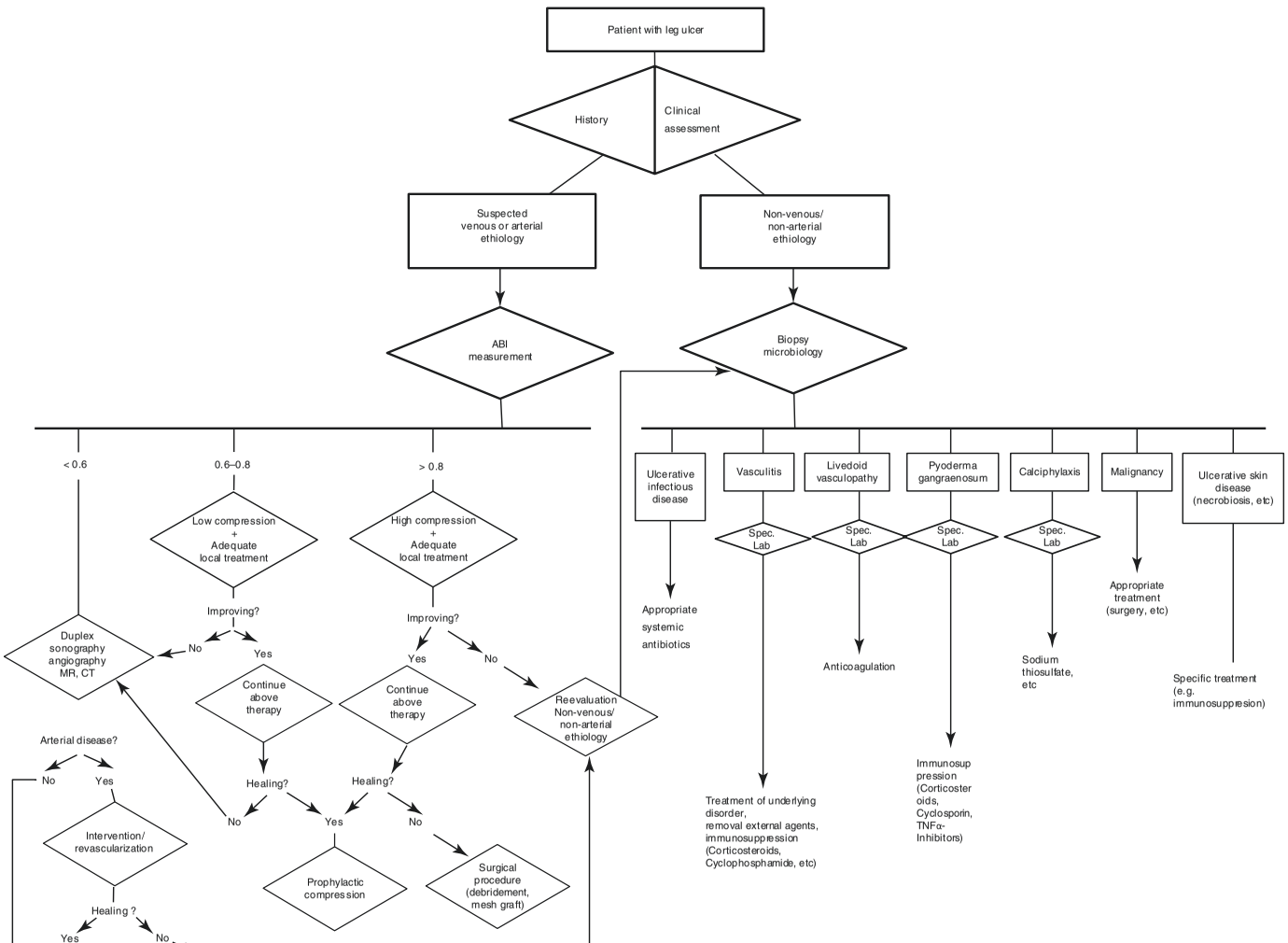
Recording of known diseases, allergies and drug intake is compulsory. Because patients with leg ulcers most often are elder people, information about life situation, impaired mobility and adequate nutrition is of great importance.

Clinical Assessment

The clinical aspect of a leg ulcer is often diagnostic for an underlying disease. Therefore it is crucial to be familiar with typical clinical signs:

- To confirm *venous origin* at a glance, localisation of ulcers is of primary interest: Venous ulcers are typically located around the medial ankle. Lateral or other localisation may occur, in particular in case of lesser saphenous vein insufficiency.
- Most helpful in diagnosing a venous origin of an ulcer are characteristic cutaneous signs of

Table 49.1 Algorithmic steps to achieve correct treatment of a leg ulcer. Rhomboid boxes: diagnostic step or intervention



chronic venous insufficiency, the underlying disease of venous ulcers. These skin changes on the lower leg were listed by Widmer in the 1970s in his classification of chronic venous insufficiency and define stages I and II of the disorder (Widmer and Wandeler 1978):

Look for ankle swelling, pretibial pitting edema and varicose veins, especially corona phlebectasia. Redness and dryness with scaling are signs of venous stasis eczema, small red and brownish spots are typical for purpura jaune d'ocre which can lead to hyperpigmentation. Diffuse redness resembling erysipela is indicative for hypodermitis. Dermatofibrosclerosis and atrophie blanche are typical for longstanding venous insufficiency. – The mentioned clinical signs also define clinical stages C1-4 of the CEAP classification that has been established in the nineties and is today widely accepted for the classification of chronic venous insufficiency (Ad hoc committee American Venous Forum. Classification and Grading of Chronic Venous Disease in the Lower Limbs: A Consensus Statement. Maui, Hawaii, 6th Annual Meeting February 22–25, 1994). (Eklof et al. 2004)

- Pathophysiologically chronic venous insufficiency results from venous hypertension induced by superficial and/or deep venous reflux. Both are mainly consecutive to valvular and/or perforator impairment (destruction in postphlebitic syndrome; incompetence due to venous dilatation) and dysfunction of muscular and articular pump (which supports recirculation of blood from foot to heart).
- Venous hypertension induces major microcirculatory disorders:
  - Dilatation, lengthening and microthrombosis of capillaries.
  - Distension of venular endothelial pores, allowing large plasmatic molecules to escape into the interstitial fluid and thereby inducing pericapillary deposits of fibrin. Increased oncotic pressure then favours the subsequent development of oedema, lymphatic overload and lymphangiopathy.
  - Accumulation and "trapping" of white blood cells in the distal medial part of the dependent legs of CVI patients, plugging of capillaries and releasing of cytokines as well as toxic metabolites.
  - Fibrosis and thickening of the fascia superficialis of the leg, histologically well demonstrated, altering calf muscle pump function.

Taken together, these alterations disturb oxygen diffusion and metabolic exchanges, inducing hypoxia, anoxia and leg ulcers.

- An *arterial involvement* has to be suspected when an ulcer is localised on the lateral aspect of the lower leg and when foot pulses are absent. Arterial ulcers are often more painful than venous ulcers.
- A very painful ulcer on the distal portion of the lower leg above the lateral malleolus with necrotic wound ground and livedoid borders is typical for *Martorell's ulcer* (*hypertensive leg ulcer*). Stenosing arteriolosclerosis is causative for the infarction of the skin that leads to ulceration; foot pulses may be palpable. Arterial hypertension and diabetes mellitus are underlying diseases.
- Ulcers with an atypical localisation, with rolled or everted wound edge, atypical granulation tissue (with hypertrophic, transparent aspect) and an increase of size despite adequate treatment are suggestive for *ulcerative malignancy*. Malignant neoplasias are the cause of a leg ulcer in up to 2.2 %. Basal cell carcinomas can be found most often. Squamous cell carcinoma can occur de novo or arise in long-standing chronic wounds due to "Marjolin transformation". In non-healing ulcers with no suspicious features, carcinoma can be found in 37.5 % (Miller et al. 2004).
- Disseminated necrotic lesions and ulcerations on both legs surrounded by flea bite-like, small red lesions are typical for *small vessel vasculitis*. The small red purple lesions that do not blanch when pressed are diagnostic: Such lesions (petechiae) are caused by extravasation of blood into the skin. This may result from hyper- and hypocoagulable states or vascular pathology. Petechiae that are palpable are indicative for vascular inflammation and therefore almost diagnostic for vasculitis afflicting small cutaneous vessels (palpable

purpura). Petechial lesions may become necrotic and ulcerate. Vasculitic ulcers usually are very painful.

- When ulcers are bizarrely shaped – often with a dendritic form – and surrounded by a purplish discoloration of the skin in a mottled reticulated pattern, *ulcerating livedo reticularis* can be diagnosed. The discoloration (reticular livedo) is caused by swelling of venules due to thrombotic obliteration of capillaries. A variety of diseases can lead to vasoocclusion of small vessels: haematological diseases (e.g. cryoglobulinaemia), autoimmune conditions with vasculitis (e.g. polyarteritis nodosa, systemic lupus erythematosus, etc.) and others.
- Reticular livedo together with atrophie blanche and episodic painful ulcers is diagnostic for *livedoid vasculopathy*. The disease is most often associated with coagulopathies.
- Livedo reticularis, painful panniculitis and large necrotic ulcers are the cardinal signs of *calciphylaxis*. In calciphylaxis pathological calcification of small arteries and fat tissue leads to thrombosis and skin necrosis. The disease most often occurs in patients on dialysis (stage 5 chronic kidney disease) and the term calcific uremic arteriolopathy (CUA) is equally used. However other risk factors have also been identified (elevated serum calcium and phosphate levels, hyperparathyroidism, obesity and type 2 diabetes mellitus, oral anticoagulation with coumarins, arterial hypertension and others). Calciphylaxis is extremely painful and necrosis and ulcerations can rapidly spread out.
- Another form of very painful ulcer that can occur on the lower leg shows undermined violaceous borders and a purulent, cleft wound ground, resembling dirty honeycombs. This corresponds to the classical picture of *pyoderma gangrenosum*, which typically has started with a small, red papule or pustule – looking like a bite reaction – changing into an ulcerative lesion with rapid centrifugal enlargement. Pyoderma gangrenosum is a non-infectious reactive neutrophilic dermatosis that is associated with inflammatory bowel disease, rheumatological and haematological disease and malignancy.
- Disseminated round, punched out lesions with a crusted necrotic surface are typical for *ecthyma gangrenosum*, an ulcerative infectious pyoderma of the skin caused by bacteria (*Pseudomonas*, *Streptococci*, *Staphylococci*). Patients often suffer from a haematological disease or receive immunosuppressive drugs. Diabetes and malnutrition may also favour occurrence of infection.
- Round ulcers with centrifugal enlargement over weeks and with a history of insect bite are suggestive for *leishmaniasis*. Infection is caused by protozoan parasites that are transmitted by the bite of sandflies.
- Round superficial ulcerations could be caused by bullous skin diseases even in the absence of visible blisters. *Bullous pemphigoid*, an autoimmunobullous disorder, can present solely on the legs. Autoantibodies against epidermal basal membrane induce bullous inflammation.
- Ulcerations occurring in well-circumscribed plaque-like areas on the shin with active, more indurated borders and waxy, strophic centres are typical for *necrobiosis lipoidica*. Initially, the underlying skin lesions are reddish brown but progressively become more yellow, shiny and atrophic in appearance. Necrobiosis lipoidica is a disorder of collagen degeneration.
- Ulcers on the feet and toes are typical for *diabetic foot syndrome*. As this article only deals with leg ulcers, the problem will not be discussed further.

Non-invasive Apparative Investigations

Ankle-Brachial Pressure index (ABI or ABPI)

In all leg ulcers at least this apparative investigation should be performed to exclude arterial disease. ABI stands for assessment of the ratio of blood pressure in the lower leg (ankle) to blood pressure in the arm (brachial): ABI = P leg/P arm.

It is a simple method that requires a Doppler ultrasound blood flow detector (Doppler probe) and a sphygmomanometer (blood pressure cuff). Ankle pressure is measured by slowly inflating

the blood pressure cuff around the distal lower leg and indicating at which pressure the pulse of distal pedal arteries ceases. For calculation of the ratio, the higher systolic reading of the left and right arm brachial arteries is generally used in the assessment and the higher of the two values of pressures measured in the posterior tibial artery and dorsalis pedis artery.

An ABI of less than 0.9 indicates an arterial disease. Of practical importance: Below a threshold of 0.8 compression therapy has to be performed with caution.

An ankle pressure of less than 50 mmHg demonstrates critical ischaemia. This is also the case with a toe systolic pressure below 30 mmHg.

Doppler and Duplex Investigation

Doppler probe offers a cheap and simple technique to diagnose alterations in the venous or arterial system; however sensitivity and specificity are low and therefore the Doppler is not advised any more in the diagnostic of leg ulcers for routine investigations (Guidelines for diagnostics and treatments of venous leg ulcers developed by the Guideline Subcommittee of the European Dermatology Forum 2013).

Duplex sonography (the combination of B-mode echography and Doppler sonography) in contrast has a high sensitivity and specificity in the diagnosis of venous or arterial thrombosis, arterial occlusion or stenosis and is most commonly used to visualise the superficial and deep venous system (e.g. venous directional flow, valve incompetence) of the leg. It is the preferred technique for patients with a vascular leg ulcer (Guidelines for diagnostics and treatments of venous leg ulcers developed by the Guideline Subcommittee of the European Dermatology Forum 2013).

A duplex sonography should be performed in all patients with venous or arterial ulcer when an intervention is a realistic option.

Pulse Volume Recording (PVR)

If arterial disease is suspected, this non-invasive diagnostic test can evaluate arterial circulation, which is measured at multiple sites of the leg according to the vascular segments. The test is based on pressure ratios and flow assessment and allows a more precise location of the arterial disease. The PVR may be non-diagnostic in patients with advanced vessel calcification as in diabetes or hypertension, due to atherosclerosis. In unclear cases, further tests like magnetic resonance imaging (MRI) are required.

Microbiology

All chronic wounds are contaminated or colonised by bacteria or yeasts. Therefore a routine swab from the wound ground for microbiological investigations is meaningless, if there is not a suspect of a critical colonisation that impairs wound healing or an obvious wound infection can be detected. In this case identification of microbes is important for the choice of antibiotics.

In countries with a high prevalence of methicillin-resistant *Staphylococcus aureus* (MRSA), routine swabs may be important to identify patients for hygienic reasons.

Histopathological Investigations

Ulcers with atypical appearance or inadequate response to treatment are suspicious for malignancy. A biopsy from the edge of the wound should be advocated for any ulcer that fails to respond to appropriate treatment to rule out malignancy.

A number of underlying diseases of leg ulcers can only be diagnosed histologically: This applies for all forms of vasculitis (especially small vessel vasculitis), calciphylaxis and ulcerating dermatoses (e.g. necrobiosis lipoidica, sarcoidosis). For other diseases like pyoderma gangrenosum, histopathological findings are important to support the clinical suspect.

Special investigations are required for some rare disorders: The diagnosis of leishmaniasis requires Giemsa's stain and/or polymerase chain reaction (PCR) assays from tissue; atypical mycobacteriosis can only be detected in Ziehl–Neelsen stain and by PCR. For the diagnosis of autoimmunobullous disorders, a direct immunofluorescence is mandatory.

These examples may underline the importance of clinical knowledge. Diagnostic investigations in the direction of rare diseases would not be performed without a corresponding clinical suspect.

Laboratory Investigations

It is debatable whether blood tests should be performed initially in all patients with leg ulcers.

It may be useful to have information from the beginning about a patient's blood count, C-reactive protein (CRP) levels, erythrocyte sedimentation rate (ESR), HBA1c, total protein and basic coagulation parameters.

In some cases laboratory findings however are imperative:

- In case of a wound infection (with erysipelas or phlegmon/cellulitis), differential blood count, CRP and ERS are relevant for diagnosis and monitoring of the course.
- In patients with PAOD, one should know the values of risk factors (cholesterol, glucose/HbA1c) and also values that are of interest for further interventions, e.g. angiography, angioplasty or surgery (creatinine and coagulation parameters/INR).
- When vasculitis is suspected, laboratory tests are important to diagnose the aetiology of vasculitis but also to assess acuteness and extent of the disease. Serological tests include titres of antinuclear antibodies (ANA), dsDNA, cANCA, pANCA and rheumatoid factor (RF); serology for hepatitis B and C; creatinine/urea, muscle enzymes (CK, aldolase), complement, evidence of cryoglobulins and antiphospholipid antibodies.
- If a vasoocclusive disease with hypercoagulable/hypocoagulable state is suspected (e.g. livedo vasculopathy), additional assessments are relevant to rule out coagulopathy (prothrombin time, partial thromboplastin time, proteins C and S, homocysteine, antithrombin III, APC resistance, lupus anticoagulant).
- Calciphylaxis requires special assessment of serum calcium and phosphate, parathormone, HbA1c and albumin.
- The diagnosis of pyoderma gangrenosum obliges to search for associated internal diseases.

Angiography: Arteriography and Phlebography

With angiography the inside of blood vessels can be visualised. This is performed by injecting a contrast agent into the blood vessel and imaging using X-ray–based techniques.

Phlebography is the technique in which contrast fluid is injected into the venous vascular system, either from distal (ascending phlebography) or from proximal by performing a Valsalva manoeuvre (descending phlebography). Phlebography has largely been replaced by duplex diagnostic and is not considered the diagnostic of first choice for venous leg ulcers. It should only be used for special indications (Guidelines for diagnostics and treatments of venous leg ulcers developed by the Guideline Subcommittee of the European Dermatology Forum 2013).

Intra-arterial angiography refers to the visualisation of the arterial system with access gained through an artery, most commonly through the femoral artery. Angiography is performed to show stenosis of arteries in suspected peripheral arterial occlusive disease, which can be treated in the same session with angioplasty. For pure diagnostic measures, arterial duplex has become popular and also CT and MR angiography.

General Principles of Treatment

Treatment of leg ulcers is based on two pillars: The first comprises *treatment of underlying disease*, and the second encompasses *local wound care*.

The first step in the management of leg ulcers should always target at recognition and treatment of underlying diseases. As mentioned above, wound healing is only possible if the cause of the wound is sufficiently controlled. In the treatment of venous ulcers, in a Cochrane review, evidence for faster healing has been demonstrated for compression therapy (O'Meara et al. 2012), which is the treatment of underlying chronic venous insufficiency. In contrast the type of dressing applied beneath compression had not been shown to affect ulcer healing in another Cochrane review (Palfreyman et al. 2006).

Dealing mainly with elder patients that suffer from other diseases, one should not forget to look for concomitant diseases. These may have an influence on wound healing and should be treated: cardiac insufficiency, diabetes, obesity,

malnutrition, hypertension arthropathies, autoimmune disorders and others.

Treatment of Underlying Disease

Venous Ulcers: Treatment of Chronic Venous Insufficiency

The underlying disease of venous ulcer is chronic venous insufficiency, which can be treated noninterventionally or interventionally. Noninterventional treatments include compression therapy and medical treatments; interventional treatment encompasses all forms of invasive procedures from endovenous ablation techniques to surgery.

Compression Therapy

Compression therapy is an empirically originated treatment: Bandages are applied to exert pressure on tissue. Compression therapy is indicated in all forms of chronic venous insufficiency; it is and will remain the keystone of treatment for chronic venous insufficiency. Compression therapy reduces oedema, leads to constriction of venous lumina and thus reduces venous blood capacity. It enhances blood velocity in both superficial and deep venous compartments, improves pump function and reduces venous reflux. Reduction of capillary pressure corrects microcirculatory dysfunction and improves skin changes like dermatosclerosis.

Compression treatment may be performed with different forms of bandages:

- *Elastic long-stretch bandages* exert almost constant pressure due to their elasticity regardless whether a person is moving, standing or lying.
- *Short-stretch bandages* are less elastic and work on the principle of applying a low amount of pressure when the muscle is resting/not active. When the calf muscle is working, however, high resistance is applied to the muscle, which is known as working pressure.
- Nonelastic bandages like *multilayer bandages* or *Unna's boot* (gauze bandage containing zinc oxide paste) generate most working pressure and support optimally function of calf muscle pump. *Compression stockings* (*hosieries*) are manufactured with elastic materials and are worn knee-high, thigh-high or as pantyhose. They exert a graduated compression, which is strongest distally around the ankle. For elder people they may be difficult to apply by themselves. Compression stockings are mainly indicated for prophylaxis and in practice are generally recommended when an ulcer has healed. In the last ten years, however, special forms of high-compression stockings have been developed that are provided for ulcer treatment.

In a Cochrane systematic review, it could be demonstrated that compression increases ulcer healing rates compared with no compression. Multicomponent systems were more effective than single-component systems, and those multicomponent systems containing an elastic bandage appeared to be more effective than those composed mainly of inelastic constituents. Patients receiving a four-layer bandage healed faster than those with short-stretch bandage, and more patients heal on high-compression stocking systems compared to short-stretch bandage (O'Meara et al. 2012).

Compression therapy is safe; however there are some contraindications: Elastic bandages may not be used in stage III or IV of PAOD and/or below an ABI of <80 mmHg. Nonelastic bandages can still be applied because they do not exert pressure at rest. In case of heart failure, especially in the presence of right heart insufficiency, compression therapy has to be performed with care due to the shift of fluid into central compartments.

With bandage or stockings worn, regular exercise such as walking is imperative. Stimulation of ankle mobility to induce calf muscle pump is essential. Additional application of a bolster to the ulceration may selectively enhance compression.

Medical Treatment: Venoactive Drugs (VAD) and Others

Venoactive drugs (VAD) are a heterogeneous group of medicinal products of plant or synthetic origin, which have effects on oedema and on symptoms related to chronic venous disease. Synonymously used but better discarded are the terms oedema-protective agents, phlebotonics, venotonics, vasoprotectors, phlebotropics and venotropics. VAD include flavonoids (secondary metabolites of plants), e.g. benzopyrones like diosmin, hesperidin or coumarin; rutosides (rutin) and troxerutin; saponins like escin (from horse chestnut); calcium dobesilate; etc. The

main mechanisms of action of VAD is an increase of venous tone that results in restoration of normal blood flow, dispersion of red cell aggregates and better oxygenation. In the treatment of venous leg ulcers, VAD are used adjuvantly together with compression therapy which has to be the first-line treatment.

Micronised purified flavonoid fraction (MPFF) with diosmin and hesperidin has shown an adjuvant effect on healing of leg ulcers in double-blind studies (Guilhou et al. 1997; Roztocyl et al. 2003) and one meta-analysis (Coleridge-Smith et al. 2005), when ulcers were larger than 5 cm^2 and existing for more than 6 months. Pain was relieved in all treated patients.

Long-term administration of rutosides did not prevent leg ulcer relapses in one study (Wright et al. 1991).

Oral anticoagulants, heparin, aspirin, pentoxifylline and prostaglandins have been suggested to improve microcirculation and stanozolol to reduce dermatofibrosclerosis.

Interventional Therapy

Superficial venous insufficiency is a major cause of leg ulcers; up to 60 % of venous ulcers result from greater and/or lesser saphenous insufficiency, as could be demonstrated by duplex investigations in recent series. Superficial venous insufficiency can be treated and corrected by different forms of interventions:

- *Phlebectomy*, *sclerotherapy*, *echo-guided sclerotherapy or endovenous ablation techniques* (*radiofrequency or laser ablation*) of a feeding vein in the neighbourhood of the ulceration are simple and cost-effective treatment that can be performed in an outpatient setting.
- *Flush ligation and stripping* of insufficient greater and/or lesser saphenous veins suppresses reflux and venous hyperpressure. Photoplethysmography (1,2) is useful to determine the impact of venous reflux and can predict the improvement to be achieved with surgical removal of the incompetent vein(s).

The question whether compression and surgery are better treatments for venous ulcers has been answered by the ESCHAR study (Barwell et al. 2004) where the combination of surgery and compression was compared to compression alone in a randomised controlled trial with 40 patients. Healing rates after 6 months were similar in both groups (65 % vs 65 %), but 12-month ulcer recurrence rates were significantly reduced in the combined compression and surgery group (12 % vs 28 %). It could be concluded that most patients with chronic venous ulceration benefit from the addition of simple venous surgery regarding recurrence of ulcer but not concerning healing of the present ulcer.

Some surgical procedures may be indicated in cases of long-lasting venous ulcers with chronic skin changes.

- *Paratibial fasciotomy*, as described by Hach, yields excellent results in post-thrombotic syndromes or in painful atrophie blanche ulcers. It now usually completes perforator dissection and is performed through the same incision. The fascia is split down to the malleolus with long scissors or with a fasciotome. The mode of action is not clearly understood, but it certainly compensates a chronic compartment syndrome, by reequilibrating sub- and epifascial venous pressure. Fibrotic alteration of the fascia induces a fatty degeneration of the muscles and impedes its effect on the venous return. These changes are partially reversible after fasciotomy. Post-operative improvement of the microcirculation is immediate, as demonstrated by tcpO2 measures.
- *Large excision of the ulcer* and surrounding tissues, including the fascia, associated if necessary to endoscopical dissection of perforators, stripping and fasciotomy may be the single solution to definitively heal refractory long-lasting ulcers, which become "autonomous". Long-term results are excellent.
- *Shave excision and grafting* are indicated in circular superficial ulcers on dermatofibrosclerosis.

Arterial Leg Ulcers: Treatment of PAOD

If arterial perfusion is not sufficient for healing, revascularisation is mandatory. It could be demonstrated that wound healing is impaired high above the threshold of chronic critical limb ischaemia. Leg ulcers with an arterial involvement and an ankle pressure below 110 mmHg that do not heal under conservative measures will benefit from revascularisation.

Revascularisation requires angioplasty (PTA or percutaneous transluminal angioplasty, if necessary with stent placement), if solitary occlusions in large arteries are present. Often bypass surgery is needed for arterial reconstruction to circumvent a seriously occluded area of the arterial vasculature.

In leg ulcers meeting the criteria of critical ischaemia, where arterial reconstruction is not possible, intravenous prostacyclin (Ilomedin, Iloprost®) or prostaglandin E (Prostavasin, Alprostadil®) should be considered before amputation is executed.

PAOD requires general measurements: Activity should be recommended, e.g. walking to the point of pain and alternate with rest periods. Risk factors should be minimised: Smoking has be stopped, and arterial hypertension needs medical control, as well as hypercholesterolaemia if dietary measures are not sufficient. Reduction of overweight is another goal. Daily aspirin is recommended for overall cardiovascular care.

Martorell's Ulcer

The most important is to recognise the disorder which is often mistaken for pyoderma gangrenosum or calciphylaxis (which shares identical histological features, e.g. calcified vessels). Best treatment is surgical debridement and split-thickness skin grafting.

Ulcerative Malignancy

Most often basal cell carcinoma and squamous cell carcinoma are the cause of malignant ulceration on the leg. Both are best treated with surgical excision, which normally requires skin grafting of the excisional wound. Radiotherapy is an alternative option when surgical treatment is not possible or reasonable.

Vasculitis

Cutaneous small vessel vasculitis (leukocytoclastic or hypersensitivity vasculitis) is the most common vasculitis seen in clinical practice that leads to vasculitic ulcers. It can be caused by different diseases (autoimmune disorders, systemic vasculitis, Henoch-Schönlein, infection, etc.) but also by external agents (e.g. drug reaction). In most cases (up to 50 %), no cause is identified. Treatment of vasculitis requires treatment of underlying disorder (when identified) or removal of external agents (e.g. drugs). The mainstay of symptomatic treatment is the use of anti-inflammatory/immunosuppressant agents, first of all corticosteroids. In ulcerative and necrotic vasculitis, systemic treatment is the rule, in dosages up to 60–80 mg/day of prednisolone equivalent. An infectious aetiology should always be ruled out before the introduction of immunosuppressive therapy. In severe cases, a combination of corticosteroids and other immunosuppressants like cyclophosphamide may be needed. Mild manifestations of vasculitis with only palpable purpura can be treated locally with steroid ointments/cream. Additional measures like leg elevation and compression of leg lesions may also be helpful (See Chap. 17).

For underlying collagenoses or systemic vasculitis, treatment should be performed according to actual recommendations (Sunderkotter and de Groot 2008).

Livedoid Vasculopathy

As a result of recent research (Kerk and Goerge 2013), livedoid vasculopathy has been defined as a coagulation disorder classified as a vasculopathy different from inflammatory vasculitis. To improve rheology, aspirin and pentoxifylline have been recommended earlier. In view of the basic coagulation disorder, systemic anticoagulation is suggested in recent recommendations (Sunderkotter and de Groot 2008). Treatment experience exists for the use of low molecular weight heparin (e.g. enoxaparin in a daily dosage of 1 mg/kg s.c.).

Calciphylaxis

The appearance of wounds in calciphylaxis with widespread necrosis is seductive for wide surgical debridement. In one of the largest series ($n=64$) in a retrospective study, in fact, 1-year survival was better in patients that received surgical debridement (Weenig et al. 2007). These data should be handled with care. In our own experience and according to other recommendations, wound care should be atraumatic. Extensive wound debridement is strongly discouraged, as even the slightest trauma, such as taking a biopsy, can lead to massive, new ulcerations leading to

new septic foci. The use of antibiotics however is important to prevent sepsis, which is the most dreaded complication of calciphylaxis and the main cause of death.

Another aim is to minimise risk factors: Reduction of serum concentrations of calcium and phosphate is mandatory. The impact of parathyroidectomy is discussed controversially, as there are data that show a benefit (Duffy et al. 2006), whereas others do not (Weenig et al. 2007). Oral anticoagulants should be avoided.

Intravenously applied sodium thiosulphate has become the most favoured treatment in calciphylaxis with documented good outcome. Sodium thiosulphate acts as a calcium-chelating agent which allows for successful mobilisation and clearance of the vascular and soft tissue calcium deposits.

Cinacalcet, which inhibits the production of parathormone by negative feedback, is another therapeutic option, which is often used in combination with sodium thiosulphate.

Bisphosphonate is the third treatment option with documented therapeutic success in many reports.

Pyoderma Gangrenosum (PG)

In active PG – due to pathergy phenomenon – surgical interventions, including aggressive debridement, have to be avoided because of the likely occurrence of new lesions at surgical sites and worsening of the original lesions.

In almost all cases of PG, systemic treatment is indicated. In 2005, an evidence-based review of the literature based on more than 350 patients (Reichrath et al. 2005) recommended only three medical treatments as first-line therapies for PG: daily oral corticosteroids, medium- to high-dose (0.5–1 mg methylprednisolone/kg/day) and pulsed-dose methylprednisolone 1 g/day for 1–5 days and oral daily cyclosporine 5 mg/kg/day. All other medical treatments that are documented in literature for the treatment of PG were considered to be of "experimental" nature in this review: dapsone, cyclophosphamide, mycophenolate mofetil, methotrexate, azathioprine, clofazimine, thalidomide and intravenous immunoglobulins. One exception was infliximab (TNF-alpha inhibitor) that was evaluated as a first-line therapy but only in cases of PG associated with Crohn's disease. A placebo-controlled trial 1 year later demonstrated that infliximab was superior to placebo in all types of treated PG (Brooklyn et al. 2006). Its application however is in "off-label use".

In small and early lesions and also when systemic treatment is not possible, primary local treatment can be considered. First-line therapy is the use of potent topical or intralesional corticosteroids. Topical tacrolimus and pimecrolimus are other options.

In addition to systemic therapies, local wound care can be conducted with dressings appropriate to wound stage. Alternatively used for local treatment are – among others – benzoyl peroxide, 0.25 % acetic acid and polyhexanide-containing wound solutions that all have an antimicrobial effect and prevent from secondary infection.

Ecthyma Gangrenosum

Appropriate systemic antibiotic treatment should be initiated. It is crucial to have microbiological evidence of causative bacteria.

Bullous Pemphigoid (BP)

Autoimmune bullous dermatosis generally requires an immunosuppressant treatment, lasting for months. Oral steroids are considered the standard treatment. In bullous pemphigoid however potent topical steroids have also proven to be effective. For ulcerative BP on the lower leg, oral steroids can be recommended, starting at a daily dosage of 0.75 mg prednisolone equivalent. To minimise corticosteroid-related adverse effects, adjuvant immunosuppressive drugs may be used (see Chap. 11).

Necrobiosis Lipoidica

There is no standardised treatment for necrobiosis lipoidica. Ulcerative forms are generally difficult to treat.

Systemic corticosteroids are not an attractive option because most patients are diabetics.

Successful treatment has been documented in several case reports for the use of cyclosporine A and for TNF-alpha inhibitors. Topical calcineurin inhibitors are also promising.

Other treatment options are phototherapy (PUVA) and chloroquine.

Local Wound Treatment

In the last century, local wound treatment was performed for decades by applying dry gauze on the wound ground, allowing the wound to dry and to develop a hard crust.

In 1962, in an epochal article in *Nature*, Winter could demonstrate that epithelialisation is retarded by the dry scab which covers a superficial wound, and if the formation of the scab is prevented, the rate of epithelialisation is markedly increased.

Winter's change of paradigm that wound healing is accelerated in a moist wound environment led to the "golden age of moist wound treatment" which went along with the development of new dressings that were applied on the wound to keep it optimally moist: Hydrocolloids, hydrofibre, alginates, foams and many others have become standards in local wound care in the last 50 years.

Recent reviews however have disclosed that the effectiveness of these dressings might be overestimated and evidence for their efficacy is poor: In a systematic Cochrane review assessing the effectiveness of wound dressings for the treatment of venous leg ulcers, no evidence was found for a better efficacy of a special form of wound dressing nor that the type of dressing applied beneath compression did affect ulcer healing (Palfreyman et al. 2006).

In another critical review of the literature on the efficacy of modern dressings in healing chronic and acute wounds, no evidence was found that any of the modern dressings were better than another or better than saline or paraffin gauze (Chaby et al. 2007). And finally two very recent systematic reviews found no current evidence that either alginates or foam dressings were more effective than other wound dressings to treat venous leg ulcers (O'Meara and Martyn-St James 2013a, b).

Despite these findings, the impact of local wound care with regard to wound healing cannot be emphasised enough. Local wound care is more than just applying a wound dressing: Each wound is different and requires an individual approach to care.

For a structured approach to wounds, an international group of wound healing experts has provided a framework for a structured approach to wound bed preparation more than 10 years ago (Schultz et al. 2003); this approach represents a basis for optimising the management of open chronic wounds. The concept of wound bed preparation can be described by the acronym TIME, which stands in today's definition for Tissue management (T), Inflammation and infection control (I), Moisture balance (M) and Epithelial (edge) advancement (E) (European Wound Management Association (EWMA). Position Document. 2004).

TIME has become an internationally accepted approach to chronic wounds in the last 10 years and is also the topic of a position paper of the European Wound Management Association (EWMA) (2004).

TIME Framework: An Approach to Treat Chronic Wounds

T = Tissue Management

Tissue management means removal of non-viable tissue (debridement). The presence of necrotic or compromised tissue is common in chronic non-healing wounds, and its removal has many beneficial effects. It takes away non-vascularised tissue, bacteria and cells that impede the healing process. Unlike acute wounds, which usually only require debridement once, chronic wounds may require repeated debridement.

The balance of necrotic burden can be achieved with different forms of debridement:

- For *sharp superficial debridement*, curettes, scalpel or scissors are used. Local anaesthesia may be required. With a ring curette, it could be demonstrated that a single treatment accelerated healing of venous leg ulcers.
- *Surgical debridement* with removal of deep structures has to be executed in an operating theatre in general or regional anaesthesia.
- *Hydrosurgical debridement* with fluid jet technology is comparable to sharp and surgical debridement. Most often local anaesthesia is required.
- Other physical forms of debridement include *ultrasound* and *CO2 laser*.
- *Autolytic debridement* is performed with dressings with a high water content, such as hydrogels and hydrocolloids. Enzymatic activity in wound fluid leads to lysis of fibrin

or necrotic tissue. Autolytic debridement is slow and often not effective.

- *Enzymatic debridement* can be induced by proteolytic enzymes in ointments or solutions. Proteases are derived from animals, plants or bacteria. Clostridiopeptidase A, a bacterial collagenase, and streptokinase, an inducer of plasmin which degrades fibrin, are both commercially available.
- For *biosurgical debridement*, maggots (fly larvae of *Lucilia sericata*) are used that produce proteolytic enzymes. Maggots are raised in a sterile environment and are placed on the wound, under a loose bandage in a cagelike dressing, where they selectively degrade dead or dying tissue. To reduce pain, maggots can be placed in a bag or pouch on the wound to avoid direct contact to the wound ground. The efficacy of maggot debridement therapy has been demonstrated in leg ulcers (Dumville et al. 2009), pressure ulcers (Sherman 2002) and diabetic foot ulcers (Sherman 2003). The treatment is safe, but acceptance of patients may be problematic.

I = Inflammation and Infection Control

All chronic wounds are colonised by bacterial or fungal microorganisms. Bacteria may stimulate a persisting inflammation and lead to the production of inflammatory mediators and proteolytic enzymes, thus promoting chronicity of wounds. Evidence shows that a bacterial burden of 10^5 organisms or more per gram of tissue seriously impairs healing.

A bacterial overload with $>10^5$ microorganisms/gram tissue – in the absence of systemic signs of infections – is referred to as critical colonisation. As mentioned previously, microbiological investigations (swab) should be limited to situations where there is a clear indication that the bacterial load is implicated in delayed healing.

In all chronic wounds, non-specific antimicrobial measures are reasonable to restore bacterial balance: This includes removing of nonvital tissue, exudate control, regular cleansing with sterile saline and/or superficial debridement.

If a critical colonisation is suspected, specific antimicrobial treatment is indicated and is most often performed with antiseptics like polyhexanide, octenidine or silver-containing wound dressings, even if evidence from systematic reviews is low (Storm-Versloot et al. 2010).

Biguanide antiseptics polyhexanide and octenidine, both with bactericidal effect against gram-positive and gram-negative bacteria and also fungicidal properties, can be used as solution: When changing dressings, a moist compress is applied and kept on the wound for 3–5 (octenidine) or 10–15 min (polyhexanide). Both antiseptics can also be applied together with modern wound dressings (hydrofibres, alginates, foam substances).

Silver, which demonstrates good antimicrobial efficacy against gram-negative and gram-positive bacteria, can be applied on wounds as silver nitrate solution or silver sulphadiazine cream. Most frequently used today is silver incorporated in any form of wound dressing (e.g. foam, hydrofibre, hydrocolloid).

Antiseptic treatment can also be conducted with iodine-containing products (PVP-iodine/povidone-iodine as solution or as a hydrosomal wound gel or cadexomer-iodine), honey or honey-containing dressings or acetic acid solution (<1 % applied for 3–5 min).

Systemic antibiotics may occasionally be indicated in critical colonisation, when local antiseptic treatment is insufficient. An uncontrolled use increases bacterial resistance. Symptomatic infection with erysipelas, cellulitis, fever and systemic signs in laboratory investigation has to be treated with systemic antibiotics. For the selection of appropriate antibiotics, a microbiological diagnosis is relevant.

M = Moist Control

Dressing

In the course of normal healing, a wound goes through different phases (inflammation–proliferation–reparation/maturation/remodelling). In these phases a varying amount of exudate is produced, with the peak in the inflammatory phase. Chronic wounds – due to chronic inflammation – produce chronic exudate, which causes the breakdown of extracellular matrix proteins and growth factors, prolongs inflammation, inhibits cell proliferation and leads to the degradation of tissue matrix. Chronic exudate delays healing and causes

maceration of the surrounding skin. The management of exudate therefore is crucial.

Compression therapy is one important measure to reduce exudate, not only in venous ulcers, but in the treatment of all chronic wounds – if there is no relevant arterial involvement.

To control exudate, selection of an appropriate dressing is relevant. Modern dressings are all able to keep a wound moist, but they differ in the degree of absorbing exudate. As exudate production correlates with the wound stages, the aspect of the wound ground may be helpful to estimate exudate release: A yellow colour and a sloughy wound ground are typical for the inflammatory phase which may go together with heavy exudate production. Red colour means granulation tissue and less exudate, while pink is the colour of epithelialisation.

Wounds with high exudate production (early inflammatory phase) can be treated with foams, hydrofibre dressings and alginates. They all have a good capacity to absorb exudate.

- *Foam dressings* are sheets of foamed polyurethane or silicone. They have a variable thickness and structure and are highly absorbent but can transmit moisture vapour and oxygen. In many countries they have become most popular in modern wound care.
- *Hydrofibre* dressings are almost entirely composed of sodium carboxymethylcellulose fibres. They absorb exudate immediately and form a soft coherent gel. They retain exudate within their structure even under compression and do not allow horizontal spreading of fluid, thus protecting the surrounding skin from maceration.
- *Alginates* are biodegradable fibre products derived from brown seaweed. Alginates can absorb 15–20 times their weight of fluid. They partly dissolve on contact with wound fluid to form a hydrophilic gel.

If relevant bacterial load is suspected, silver-impregnated foam, hydrofibre or alginate dressings may be considered.

Wounds with less or little exudate can be treated with hydrocolloid dressings, low-adherent dressings or films:

- *Hydrocolloids* consist of a layer of hydrophilic colloidal gel-forming particles, made of sodium carboxymethylcellulose, gelatin, pectin, elastomers and adhesives that are bonded to a carrier of semipermeable film or a foam sheet. Hydrocolloids absorb liquid and form a gel on the wound surface that maintains an optimal moist environment. This promotes granulation, mediates local fibrinolysis, stimulates capillary proliferation, enhances the concentration of growth factors within the wound fluid and increases the rate of re-epithelialisation. Hydrocolloids should be left on the wound for at least 2–3 days. When dressings are changed, the gel in the dressing, which may be yellow and malodorous, may be mistaken for infection.
- *Low-adherent dressings* are designed to reduce adherence at the wound bed. They are manufactured in the form of tulles, which are open-weave cloth soaked in soft paraffin or chlorhexidine. They allow exudate to pass through into a secondary dressing.
- *Semipermeable films* consist of sterile plastic sheets of polyurethane coated with hypoallergenic acrylic adhesive and are used mainly as a transparent primary wound cover. Although they are impermeable to fluids and bacteria, they are permeable to air and water vapour.

Dressings have to be changed according to the stage of the wound. In exudative ulcers, they should be changed quite regularly, whereas in later healing stages, it is preferable to avoid frequent changes of dressing, as this interferes with healing and may compromise newly formed tissue, disturb the patient's life and enhance the costs of treatment.

Negative-Pressure Wound Therapy (NPWT) or Vacuum-Assisted Closure (VAC)

NPWT or VAC can be used on almost any wound and provides optimal exudate control and promotion of granulation. The primary intention is to remove chronic oedema and fluid from exudative wounds, stimulate granulation, increase local blood flow, impede nosocomial infection of the wound and isolate infected ulcers. A foam dressing under hermetical occlusion is applied on the ulcer and connected with an aspirating device assuring a controlled continuous or intermittent sub-atmospheric pressure (between 55 and 200 mmHg below ambient pressure). This technique may induce granulation in refractory

venous ulcers, decubitus, infected wounds or even in arterial ulceration.

Surrounding Tissues

When exudate is not sufficiently controlled, maceration may occur around the margins of the wound. It is manifested as white, soggy tissue. For protection, zinc paste may be used or liquid film-forming acrylate.

If contact dermatitis is observed, local corticosteroids are indicated for a short-term use. Patients with leg ulcers frequently acquire clinically relevant contact sensitisation. In patch testing, sensitisation can be found in up to two-thirds of patients. Sensitisations are often found for balsam of Peru, amechol, fragrance mix, wool wax alcohols and rosins but also to wound dressing materials.

E = Edge Effect

Effective healing requires the re-establishment of an intact epithelium. If the epidermal margin fails to migrate across the wound bed, there are many possible reasons, including hypoxia, infection, desiccation, dressing trauma, overgrowth of hyperkeratosis and callus at the wound margin. Careful clinical observation can help to determine the cause.

Surgical Local Wound Treatment

Skin grafting can dramatically shorten the time to complete healing. The wound has to be well conditioned, with a good granulation tissue in the wound ground.

Pinch grafting (or Reverdin graft) may be performed in outpatients. Small bits of partial- or full-thickness skin from a healthy area are obtained by elevating the skin with a needle and cutting across its base. The pinch is removed and seeded in the site to be covered.

Split-thickness and meshed grafts are indicated in large ulcers, where healing by secondary intention would last for months. Meshed grafts are also used to cover a wound after deep debridement or large excision of a fibrotic ulcer bed.

Advanced Wound Treatments

Besides conventional local wound treatment, a number of new therapeutic modalities exist that can be summarised as advanced treatments. Some of them have been used for years while others are still experimental. We will focus on treatments that have been established and are already widely used:

Growth Factors

Growth factors are of great importance in normal wound healing. They are produced by many cells involved in different wound phases. It is suggested that in chronic wounds, degradation of growth factors by up-regulated proteases is one factor that is responsible for the delay in healing.

In a number of experimental approaches, exogenous growth factors were supplied to the wound microenvironment to stimulate healing. An efficacy in wound healing could only be demonstrated for platelet-derived growth factor (Wieman et al. 1998). Until today a recombinant form of PDGF-BB (becaplermin) is the only growth factor that was licensed and distributed for topical application in diabetic ulcers.

Protease Inhibition

A new generation of wound dressings was developed to interact with the wound to stimulate healing. Examples are protease-modulating dressings, which stimulate healing by inactivating excess of proteases (Cullen et al. 2002).

Tissue-Engineered Skin Equivalents

For years wound research has tried to create "artificial" living skin substitutes. A number of epidermal, dermal or bi-layered skin equivalents have been developed. Most of them are meant for acute wounds, especially burn wounds. For the treatment of leg ulcers, two skin equivalents are commercially available:

- *Apligraf* is a living bilayered skin equivalent that consists of an epidermal layer derived from human keratinocytes and a dermal layer containing human fibroblasts and bovine collagen. It was demonstrated that the skin equivalent that can be easily applied on a conditioned wound improves wound healing in venous leg ulcers and diabetic foot ulcers (Falanga et al. 1998; Veves et al. 2001).
- EpiDex is an autologous epidermal equivalent containing keratinocytes from the patient's own outer root sheath (ORS). To cultivate epidermal

equivalents, the necessary cells are extracted by plucking the patient's anagen head hairs. The outer root sheath of isolated hair follicles contains precursor cells for epidermal keratinocytes. It could be shown that EpiDex was as effective as split-thickness skin autografting in the promotion of healing and complete closure of recalcitrant vascular leg ulcers (Tausche et al. 2003; Ortega-Zilic et al. 2010).

Water-Filtered Infrared A (wIRA)

Water-filtered infrared A (wIRA) radiation can improve the healing of acute and chronic wounds both by thermal and thermic as well as by non-thermal and nonthermic effects. wIRA increases tissue temperature, oxygen partial pressure and perfusion. Application of wIRA proved to be effective for the treatment of chronic venous stasis ulcers.

Extracorporeal Shock Waves

Extracorporeal shock waves are a sequence of sonic pulses characterised by high peak pressure over 100 MPa, fast pressure rise and short life-cycle. In urology, extracorporeal shock wave lithotripsy (ESWL) has been successfully used for years for the treatment of urolithiasis. Extracorporeal shock wave therapy (ESWT) can also be used for recalcitrant skin ulcers. Several studies in the last 10 years have shown that ESWT promotes angiogenesis, increases perfusion in ischaemic tissues, decreases inflammation, enhances cell differentiation and accelerates wound healing (Stieger et al. 2013).

Future

In adult organisms, stem cells that can divide and differentiate into specialised cell types act as a repair system for the body. It sounds promising to apply stem cells in a wound where they can differentiate into cells that are required for the respective wound stage. It was demonstrated that application of stem cells derived from bone marrow aspirate – delivered in a fibrin spray – was able to accelerate wound healing (Falanga et al. 2007). Another interesting approach is application of stem cells in a biomatrix to treat wounds (Vojtassák et al. 2006).

Finally there are high expectations in gene therapy: This treatment uses DNA that encodes a protein required for treatment of a disease. To get the DNA inside cells of the body, DNA is packed within a vector. Inside the cells, DNA becomes expressed and starts producing the therapeutic protein. To treat wounds, locally applied genes will induce production of growth factors and cytokines in cells of the wound. This has been demonstrated for PDGF-B, PDGF-A, VEGF and EGF (Eming et al. 2007).

The future of wound treatment looks promising (Figs. 49.1, 49.2, 49.3, 49.4, 49.5, and 49.6).

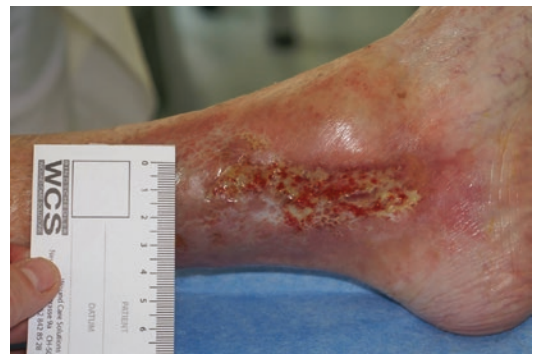


Fig. 49.1 Venous leg ulcer loco classico around the medial ankle

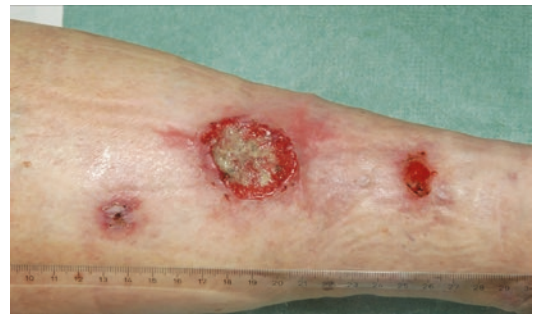


Fig. 49.2 Ulcerative basal cell carcinomas on the lower leg

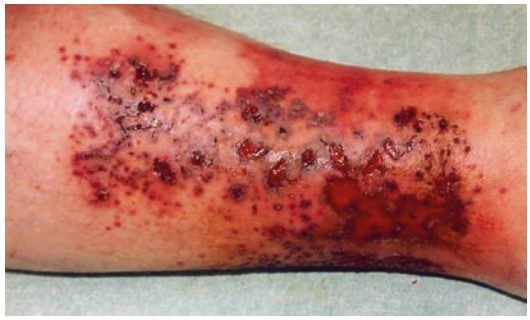


Fig. 49.3 Necrotic lesions and ulcerations due to small vessel vasculitis

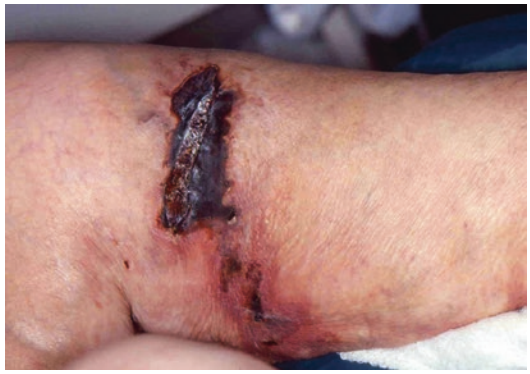


Fig. 49.4 Painful necrotic ulcer with livedoid extension caused by calciphylaxis

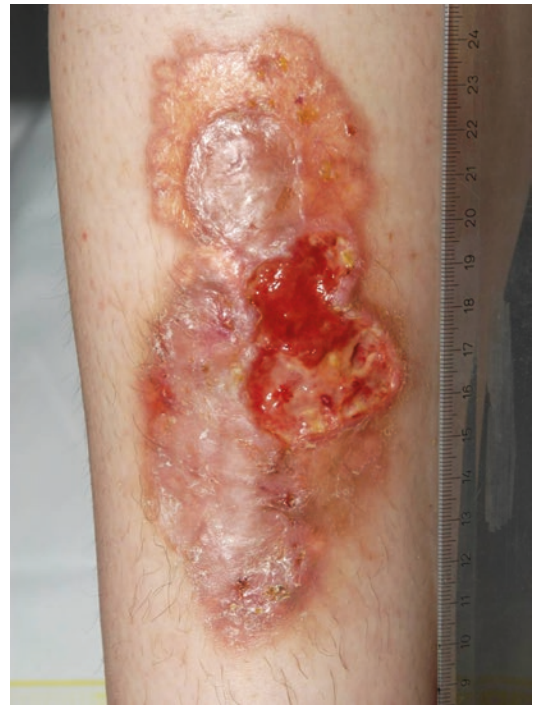


Fig. 49.6 Ulcerative necrobiosis lipoidica

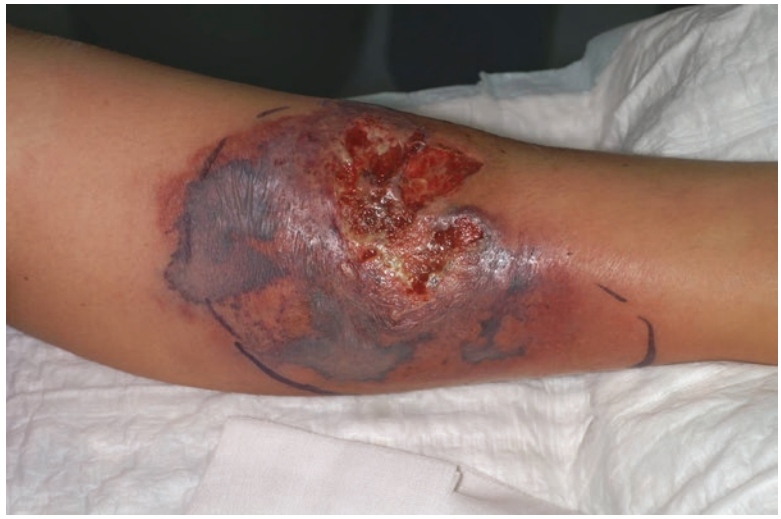


Fig. 49.5 Pyoderma gangrenosum

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