Skin Necrosis

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Editors

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Part I

Definitions, Vascular and Imaging Investigations in Skin Necrosis

Dry Necrosis, Wet Necrosis: When to Debride, When Not to Debride

1

Luc Téot and S. Fluieraru

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1.1 Introduction

Skin necrosis is a result of several factors.

Ischaemia of a skin territory leads to venous congestion, which blocks microcirculation. The damage caused may remain reversible for a few hours, but 6 h or more of ischaemia lead to an irreversible situation and tissue loss. Several factors contribute to ischaemia. The most common is thrombosis of small arterioles, which progress, together with regional inflammatory processes, to devascularisation of a defined anatomical territory (angiosome). During the spreading of infections, necrosis is linked to the destructive effect of germs, which induce tissue damage by simple germ proliferation or induce vessel thrombosis. The germs may also secrete toxins, which are diffused inside the arteriolar and capillary vascular systems. This leads to rapid obstruction of the vessels by chemical intimal and subintimal lesions, causing necrosis of large territories involving not only the skin but also the underlying muscles, tendons and bones.

1.2 The Skin Necrotic Process

Subdermal necrosis may be induced by excessive pressure, leading to a mechanical crush. This is the most common factor in pressure ulcers and diabetic foot ulcers. In this situation, successive stages of skin necrosis can be observed—a situation reflected in the non-blanching stage 1

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pressure ulcer following the National Pressure Ulcer Advisory Panel (NPUAP) classification, which probably corresponds to a prenecrotic stage. This is also observed in extravasation injuries [1].

Epidermal-dermal necrosis may rapidly appear at the skin surface. However, in some areas, such as the foot or when the depth of keratinized epidermis is thick, the necrotic tissue may resemble a subepidermal collection. This is partly because of the Tyndall effect—a light scattering observed when particles are present in colloid suspension, with blue light being much more strongly affected than red light.

When mature, this subdermal necrosis is easily confused with a deep hematoma. This situation is often observed on the heel.

The time to complete the necrosis may vary from 6 h to 2–3 days, depending on the state of vascularisation of the limb. It may be more progressive, such as observed during terminal limb ischaemia or during angiodermatitis. Microvascular impairment, autoimmune vasculitis, macroangiopathy and venous blockade are the most frequent causes, together with infection and microarterial emboli.

Dermal necrosis may be accompanied by fasciitis, especially during a severe infection such as necrotising fasciitis, where the presence of germs secreting highly active toxins quickly involves all surrounding tissues and creates a regional progressive necrosis, a spreading infection rapidly leading to a septicaemic life-threatening shock. The proliferation of germs is facilitated at the level of fatty tissue, such as in Fournier gangrene involving the perineal area and progressing very quickly under the skin.

Others toxins and venoms may be secreted by a series of different animals (snails, mosquitoes) and may create an intense local inflammatory process leading to localised skin necrosis combined with an extensive subepidermal tissue degradation [2].

1.3 Wet Necrosis

Necrotic tissue and the normal skin with which it is in contact are both adherent to each other for a period of time of around 1 week. Separation starts with a fissure occurring between normal and necrotic tissues, initiated by a difference in mechanical resistance and elasticity. This dissociation creates the elimination fold, allowing the germs to penetrate deeply and to destroy the mechanical links between dead and living tissues. These germs proliferate in the subdermal fatty tissues. In large burns the dissemination of germs all over the involved area are the main cause of death.

In some situations the necrotic tissue presents as wet, usually when necrosis is covered with damp dressings, allowing anaerobes to develop. This wet necrosis is often seen on the heel or other parts of the foot, the perineum, places and where maceration usually occur. Wet skin necrosis is considered to be at high risk of local infection, and should be quickly removed.

1.4 Debridement

1. Evidence-based medicine
   When analysing the literature from an evidence-based point of view, the Cochrane review considers that debridement has not yet demonstrated its efficacy. Nevertheless, most of the practitioners and paramedics involved in wound healing recognise the beneficial effect of debridement.

   Skin necrosis is not infected for the first few days, but becomes heavily colonised when the edges are dissociated from the healthy skin. The time effect depends on a number of factors, grouped under the name of comorbidity markers. These markers may define the capacity of the patient to heal. Some of them, such as ankle brachial pressure index, albuminaemia, glycated haemoglobin and blood pressure measurement are easily collected. Others, such as inflammatory markers or evolution with time of the wound healing process (surrogate end point) should be accurately determined.
2. Indications and contra-indications of debridement
   Debridement is indicated when the limb is vascularised enough to prevent renecrosis on the edges of the wound. During the post

operative period, when the skin flap becomes necrotic, a surgical revision removing the necrotic areas is required. However, lower limbs presenting an ABPI (ankle brachial pressure index) lower than 0.5 should not be debrided. When the ABPI is over 0.5, the debridement should follow an algorithm depending on multiple factors such as accessibility to surgery, availability of expertise in the use of advanced dressings such as hydrogels, hydrobalance or new debriders. Wet to dry techniques are not recommended any more.

In the presence of spreading extended necrotic areas, an adapted debridement should be quickly proposed. In necrotising fasciitis, extravasation injuries, haematomas or Fournier gangrene, a large and extensive surgical debridement, including the edges of undermined cavities, is needed and should be considered as an emergency. The immediate post-debridement period should consider the need for repetitive debridement procedures when infection is still present. New debriders such as Versajet or Coblation WoundWand are useful in destroying local germs and preventing biofilm formation.

In the case of necrotising angiodermatitis, pain and skin necrosis may need surgical debridement and rapid skin grafting using pinch grafts to stop pain.

Pressure ulcers are common causes of necrosis, particularly in the perineal area and over the heel. On the perineal area, undermining is frequently observed, as a consequence of the shearing forces exerted on the skin. The skin is more mechanically resistant than the underlying structure, a relatively small opening covering a large undermined area being frequently observed. In this situation, all hidden cavities need to be opened to expose living edges. The granulation tissue and retraction is more rapidly obtained. Excision of the cover (decap surgery) by surgical means is an option, but simple incisions along the undermined area are more easily realised by non-surgeons (Figs. 1.1, 1.2 and 1.3). On the heel, a vascular assessment is mandatory (pedal pulse absence is the first sign, and should indicate ABPI and Doppler ultrasound, and in case of arteriopathy a vascular surgery consultation is needed) before any mechanical debridement to prevent renecrosis of the edges. An ABPI below 0.5 is a contraindication to debride. Poor vascularisation, end of life and palliative situations are contraindications to surgical debridement.

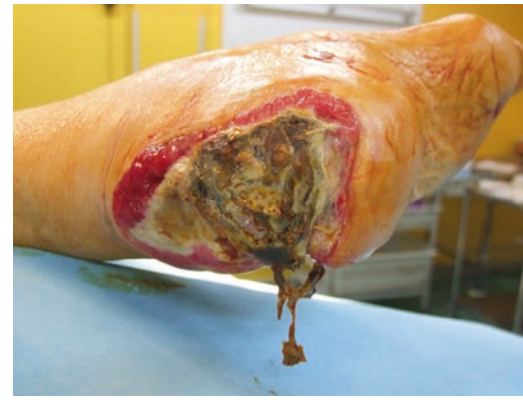

Fig. 1.1 Heel pressure ulcer: a spreading infection is observed some days after the necrotic tissue appeared

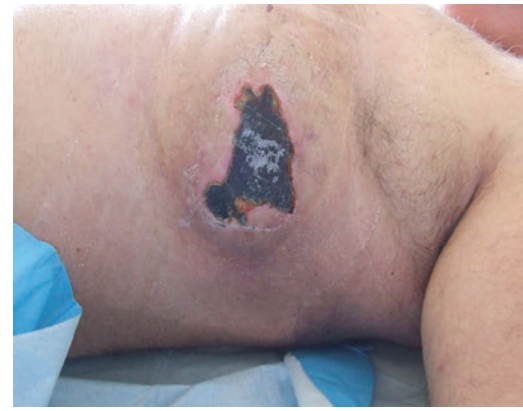

Fig. 1.2 A tigh haematoma presenting an "iceberg like" situation. The necrotic skin hides a large undermined zone of dissecting blood, source of potential infection

Diabetic foot ulcers may become necrotic at toe level, with a distal complete dry necrosis, and mummification can be expected (spontaneous evolution towards spontaneous amputation). In most cases skin necrosis is reduced to a small black spot with a large cavity hiding behind, the foot becoming oedematous and inflammatory. Pus will leak from different

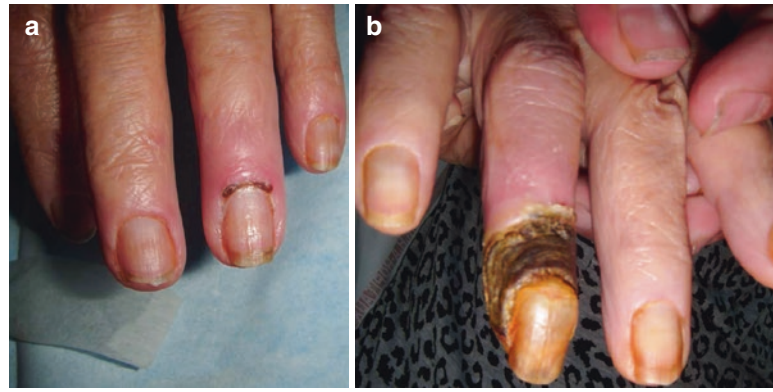

Fig. 1.3 (**a**, **b**) Progressive necrosis of the distal phalanx in a renal insufficient patient submitted to an arterial thief after arteriovenous fistula for hemodyalisis

zones on the foot, usually the dorsum and the interdigital spaces, proof of large infected soft tissues, osteoarthritis affecting joints of the foot. Large early debridement may prevent amputation if carried out rapidly, in close collaboration with the vascular surgery team in order to prevent renecrosis.

1.5 How to Manage Skin Necrosis

1. Wet to dry is a technique used in the past to eliminate debris on the wound
   Classically, the technique involves applying a wet gauze soaked in sterile water and waiting for its desiccation. When dry, it will be removed together with crusts, pus and debris. This technique is painful and will harm the granulation tissue, inducing local haemorrhage.
2. Progressive autolytic debridement
   Conservative solutions such as dressings providing moisture (autolytic debridement) will induce a progressive release and detachment of undesired tissues over the wound. Hydrogels are the most used dressing at home, the nurse moisturising the wound one day and gently removing the sloughy tissue the next. This less painful technique allows better psychological management, curettage of a leg ulcer every 2 days inducing a poor quality of life. Mechanical debridement remains extremely painful and should be reevaluated in the light of the new dressing performances, the capacity to remove metalloproteases from the wound surface, and using local antiseptics or irrigating fluid. Negative pressure wound therapy was proposed as a possible treatment for soft necrotic tissue [3], a promising strategy still under evaluation.
3. Preventing elimination folds around skin necrosis; playing the dry card
   Flammacerium, an antibacterial cream composed of silver sulfadiazine and 0.2 % cerium nitrate, offers a solution involving stopping all possibilities for germs to penetrate the edges of necrosis and stabilising the crust in order to transform it into a protective calcified armour against infection. The dry necrotic process is stuck in its evolution and no longer becomes infected (Fig. 1.4). Flammacerium was initially proposed as a barrier to germ penetration in third-degree burns [4], then proposed for arteriopathic necrotic wounds when revascularisation is not possible to limit or prevent amputations [5]. When applied onto extensive areas such as an 80 % third-degree burn surface, methemoglobinaemia may cause life-threatening damage [6]. Blood dosage of methemoglobinaemia is required in these specific situations, but this has not yet been described for wounds presenting small surfaces.

Conclusion

Necrosis may present either under a dry aspect, evolving spontaneously towards wet necrosis, depending on the local bacterial status. Each situation should be evaluated clinically in the context of the patient, taking care of the comorbidities, the vascularisation of the segment of limb and the availability of resources.

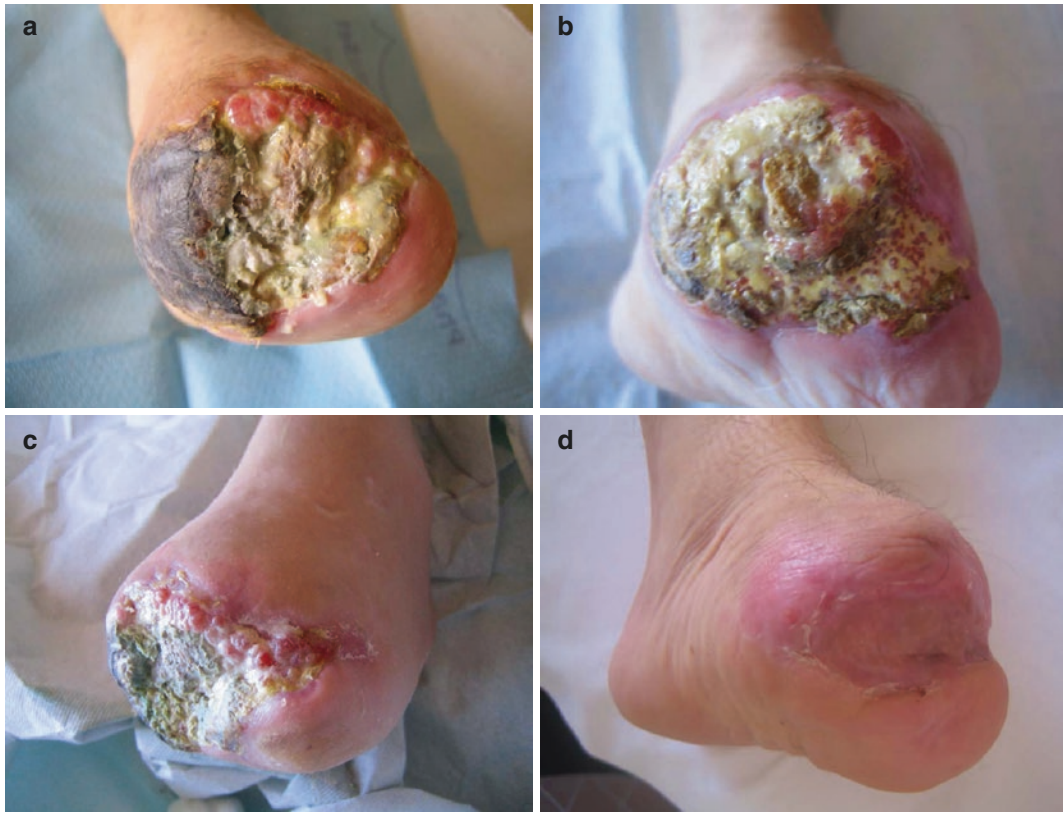

Fig. 1.4 (**a**, **b**, **c**, **d**) Midtarsal amputation after a failing flap in a young diabetis type 1 patient 42 years old; high level of comorbidities. Amputation could be prevented using local application of silver sulfadiazine plus cerium nitrate for 11 consecutive months

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Ischemia/Reperfusion: A Potential Cause for Tissue Necrosis

2

William J. Ennis, Timothy J. Koh, Norifumi Urao, Yih-Kuen Jan, Audrey Sui, Kate Brown, and Martin Borhani

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2.1 Circulatory Anatomy

A patient with a nonhealing wound requires a comprehensive work-up including a focus on six primary points of interest. These points include the status of tissue perfusion, role of bacterial contamination, pressure applied to the tissue, the immune status of the host, comorbid medical conditions including the patient's psychosocial status, and lastly, the status of the wound itself. Even after reestablishing macrovascular flow, many wounds either fail to improve or paradoxically worsen. Potential mechanisms for these unexpected findings include reperfusion injury, no-reflow, the presence of stunned/hibernating tissue, and occasionally tissue necrosis.

The circulatory system can be divided into two distinctive vascular beds. The macro-circulation refers to all vessels large enough to be seen by the unaided eye. Much clinical attention has been

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focused on the macro-vasculature because of the large number of innovative therapeutic procedures that have been developed to treat these vessels (balloon angioplasty, atherectomy, laser, etc.). The microcirculation refers to a "web" of tiny vessels located throughout the body. A superficial (subpapillary) plexus and deep horizontal plexus of arterioles and venules are present within the dermis. Most of the microcirculation is found 1–2 μm below the epidermal surface in the upper, papillary dermis. The deep plexus is formed from the perforating vessels of the underlying muscle and subcutaneous fat. The outer layer of nonviable keratin known as the stratum corneum has a depth between 10 and 20 μm, while the epidermis has a depth between 40 and 150 μm. The microcirculatory net therefore is located 100 μm from the upper level. The second layer of skin, the dermis, has a depth between 1,000 and 4,000 μm. It is the superficial plexus that gives rise to the "capillary loop" into the papillary system, which represents the source of nutrition for the skin and the surface area for the exchange of gases and molecules between the skin tissue and blood. Each papilla contains one to three terminal capillary loops innervated by sympathetic, parasympathetic, and sensory nerve endings. There are specialized arteriovenous shunts (glomus bodies), which allow blood to bypass the capillary bed. These shunts represent the thermoregulatory function of the skin. This system is dominant representing 85 % of the total blood flow, while the nutritive bed represents only 15 %. Therefore, initial ischemia can be mitigated by shunting more blood to the nutritive capillaries providing a natural protection. The nutritive capillaries are responsible for tissue viability by providing oxygen, nutrients, and fluid exchange. The capillary density determines the diffusion distance for gases and nutrients to dissolve through the tissues. The distinction between nutritive and nonnutritive flow is difficult to assess with indirect techniques. It is therefore critical to know the depth of penetration for any instrument when assessing the skin microcirculation. Instruments that sample at 500 μm or less are measuring the nutritive cutaneous flow, whereas studies beyond this mark are analyzing shunted (nonnutritive) flow.

2.2 Diagnostics

Methods for analyzing the macro-circulation include Doppler waveforms, duplex scans, contrast angiography, CT angiography, and MR angiography. There are numerous methods to assess the microcirculation; however, limitations include cost, operator-dependent variability, and non-familiarity among clinicians. Intravital capillaroscopy is a noninvasive technique used to identify nutrient capillaries. It consists of an optical microscope with epi-illumination, which is applied to the nail fold capillaries. The capillaries lie parallel to the skin surface in the nail fold. This anatomical distribution of the loop creates an ideal place to measure capillary blood flow velocity. Further advances to this technique have been introduced with orthogonal polarization spectral (OPS) imaging, which works without the fluorescent dye and gives more flexibility to the analyses. With this technology, it is possible to measure the capillary blood cell velocity (CBV), capillary density (capillaries/mm^2), and the diameter of the erythrocyte column. Laser Doppler perfusion imaging (LDPI) is a technique which utilizes a low-intensity laser (helium-neon) light. The device measures the backscattering created by moving red blood cells over a specific rectangular area analyzing up to 4,096 individual points. The wavelength of this monochromatic light is 670 nanometers (nm) with a maximum accessible power of 1 mW. Doppler shift results are accumulated and translated into numeric values expressed in volts and in an image-colored map. The penetration of the laser beam reaches 500 μm when applied to intact skin; however; penetration can reach 2.5 times greater in other non-skin tissues like granulation tissue. Laser Doppler flowmetry (LDF) has been used since the 1970s and is the basis for LDPI. LDF consist of a Ne-He low-intensity laser of 638 nm transmitted by a fiber optic to a terminal provided with a heater and thermistor to maintain a temperature constant. Measurements are done at a single point after a set temperature is achieved. Measuring only one site results in inconsistent results due

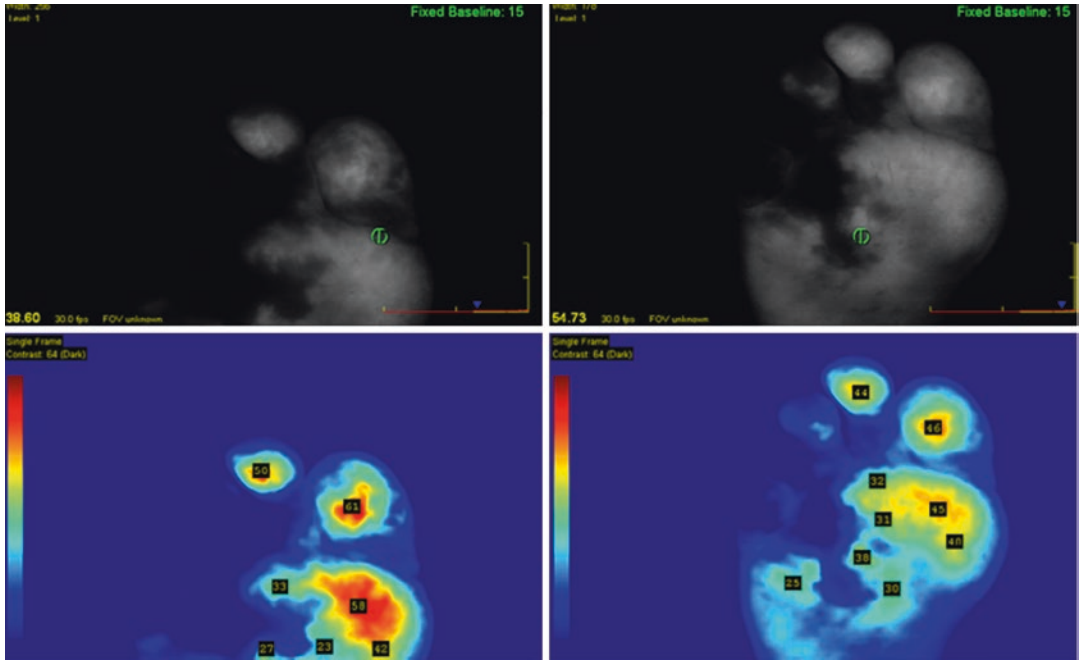

Fig. 2.1 First scans during surgery show reduced perfusion with manual graft compression at the medial portion covering three digits. Note the fourth digit and metatarsal head region which showed clinical signs of necrosis (Reprinted with permission from Perry et al. [1])

to the heterogeneity of microcirculation. TcPO_2, also called transcutaneous oximetry, is a technique widely used to detect the skin oxygen tension. A dime-sized Clarke-type solid-state polarographic electrode containing a platinum cathode with a reference electrode of silver chloride is housed in a probe tip along with a heater and thermistor. The reduction of oxygen at the cathode generates a current, which is then fed into the pO_2 channel of a monitor and converted into a voltage and digitized. The electrode is attached via a fixation device to the immediate periwound skin and heated to 43–45 °C, which induces hyperemia, and the dissolution of keratin lipids thereby increasing gas permeability. This procedure indirectly evaluates the microcirculation without an ability to differentiate nutritive from nonnutritive flow. More recently the use of indocyanine green dye has been employed to assess tissue perfusion at the microcirculatory level. This technique uses indocyanine green, a water soluble dye with a peak spectral absorption at 800–810 nm in blood. A laser light activates the dye and images are obtained from a charged coupled device camera. Unlike ultrasound images, these cutaneous angiographic images are intuitive to interpret, and due to rapid clearance, images can be repeated several times without accumulation of dye. This diagnostic technique might allow the bedside clinician to have a tool that allows for the assessment of tissue microcirculatory status and could be used in tandem with macrovascular studies for a complete picture of the perfusion of the skin. These images can be used to assess the efficacy of a revascularization procedure at the tissue level pre- and postoperatively [1] (Figs. 2.1 and 2.2).

2.3 Ischemia and Ischemia/Reperfusion Injury

Since the macro- and microvascular beds are connected in series, a reduction in macrovascular flow will lead to a decrease in microvascular flow unless compensatory mechanisms are stimulated. The

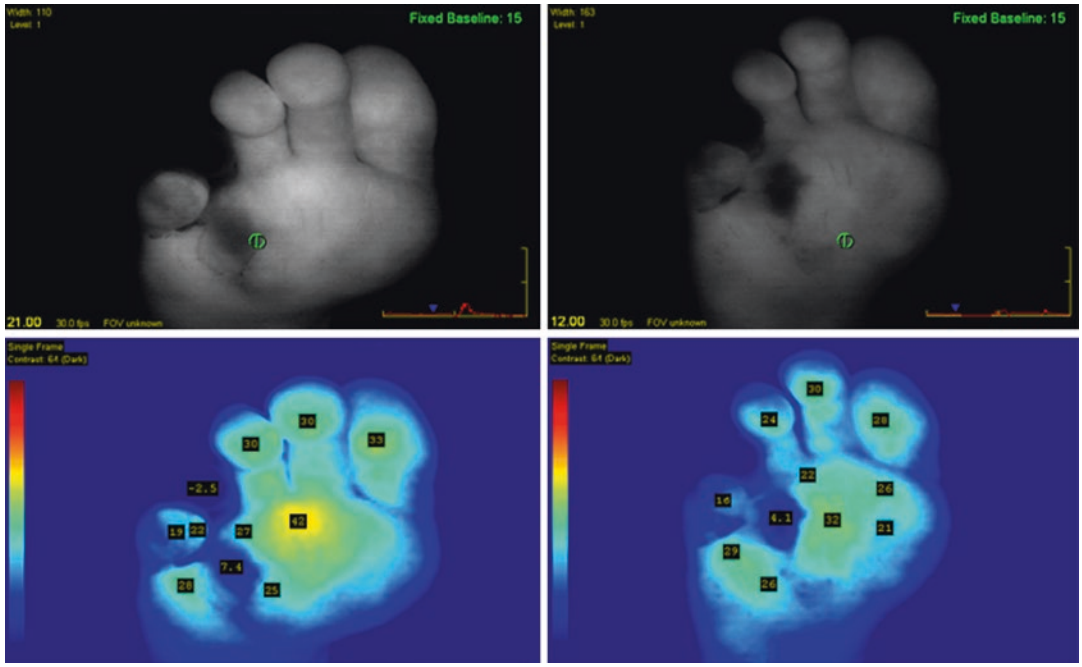

Fig. 2.2 Two follow-up SPY sequences following bypass procedure. Note that the fourth digit continues to demonstrate signs of necrosis and was eventually amputated (Reprinted with permission from Perry et al. [1])

term ischemia is used to denote reduced blood supply due to obstruction of the arterial inflow and was first used in the early nineteenth century. During prolonged ischemic periods, adenosine triphosphate (ATP) levels along with intracellular pH decrease as a result of anaerobic metabolism and lactate accumulation. Tissue injury and cell death are related to the duration and magnitude of the ischemia. The downstream biochemical effects include cellular swelling, increases in intracellular calcium levels, the generation of reactive oxygen species, and mitochondrial dysfunction [2] (Fig. 2.3). There are organ-specific differences that influence the extent, severity, and reversibility of organ damage after an ischemic event. Single-organ ischemia and reperfusion injury can occur in the heart, kidney, intestine, and brain. The brain, for example, is the most sensitive organ to reductions in blood supply due to its underlying high metabolic rate per unit weight. The brain also has an absolute requirement for glucose as an energy substrate and lower levels of protective antioxidants. As the largest organ in the body, the skin has not been studied as extensively as other organs in relation to ischemia and reperfusion injury. Ischemia reperfusion injury can have an effect on remote organs as well as the ischemic local organ. Multiple organs are injured in clinical conditions such as circulatory arrest, sickle cell anemia, sleep apnea, and during trauma and resuscitation. The mechanism of action for remote organ injury has been identified as the same factors implicated for local organ dysfunction such as reactive oxygen species formation, leukocyte activation, and inflammatory mediators. These circulating factors are responsible for the distant organ effects. The overall total organ injury sustained during prolonged ischemia followed by reperfusion is therefore attributable to an ischemic component, followed by a second component after reestablishing blood flow [2] (Fig. 2.4). Tissue-specific tolerances and confounding clinical conditions account for the variable responses noted in individual patients.

The skin and chronic wounds are dependent on the microcirculation for oxygen, nutrients, and the elimination of metabolic wastes. Decreased quantities of oxygen lead to decreased bacterial killing

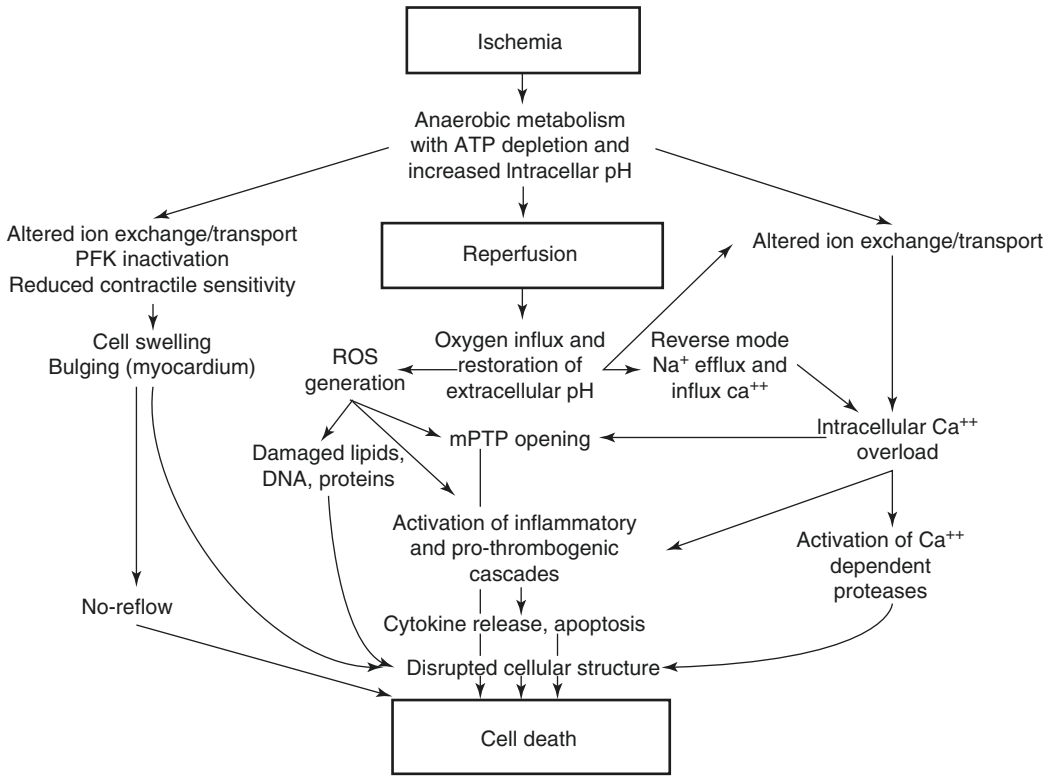

Fig. 2.3 Major pathologic events contributing to ischemic (*upper panel*) and reperfusion (*middle panel*) components of tissue injury, with overall integrated responses to I/R injury summarized in the *bottom panel* (Reprinted with permission from Kalogeris et al. [2])

by leukocytes, decreased collagen production, and decreased epithelialization. A patient may have compromised macroflow but, due to compensatory mechanisms such as the development of collateral flow, may be able to heal a wound. In a study of 111 patients with non-reconstructable vascular disease, the microcirculatory assessment was predictive of ultimate limb salvage [3]. The clinician can treat the microcirculation through the use of various energy-based modalities (i.e., ultrasound, electrical stimulation) that can increase angiogenesis and local blood flow to the wound bed [4]. A concept known as the push-pull theory has been presented by the authors as a working theoretical construct [5]. The push is achieved by the macrovascular-based arterial reconstruction. Other forms of "push" include increasing cardiac output, volume resuscitation, and the use of medications in the treatment of shock. Regardless of any potential negative side effects from revascularization, the first treatment option is to rapidly restore flow. The "pull" is essentially created by decreasing peripheral resistance and increasing the quantity of available capillaries, a process known as capillary recruitment. After the initial increase in microcirculatory flow, mediated by nitric oxide release from the endothelium within the microcirculation, a second phase of increased microcirculatory flow is achieved through the process of angiogenesis. Local microcirculatory perfusion can also be influenced by both vasoconstriction and adequate volume status. Noxious stimuli such as hypothermia, stress, pain, and depression can all lead to increased sympathetic tone and subsequent decreased tissue perfusion. Smoking, through the action of nicotine, can also result in decreased microcirculatory flow.

After a successful vascular intervention, the wound team needs to monitor the healing

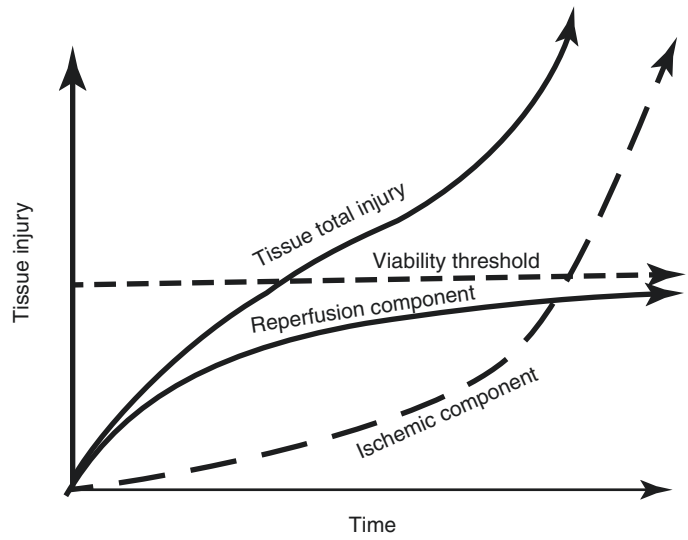

Fig. 2.4 Total injury sustained by a tissue subjected to prolonged ischemia followed by reperfusion (I/R) is attributable to an ischemic component and a component that is due to reestablishing the bold supply. At the onset of prolonged ischemia, two separate pathologic processes are initiated. The first are processes of tissue injury that are due to ischemia per se. The second are biochemical changes during ischemia that contribute to the surge in generation of reactive oxygen species and infiltration of proinflammatory neutrophils when molecular oxygen is reintroduced to the tissues during reperfusion particularly the initial phases. For a treatment to be effective when administered at the onset of reperfusion, reestablishing the blood supply must occur before damage attributable to ischemia per se represents a major component of total tissue injury. Therapeutic approaches that target pathologic events contributing to both the ischemic and reperfusion components of total tissue injury, such as ischemic or pharmacologic preconditioning, should be more effective than therapies administered when the blood supply is reestablished, which limit only the progression of reperfusion injury (Reprinted with permission from Kalogeris et al. [2])

trajectory and measure the microcirculatory status. The improvement in macro-level perfusion can be the result of bypass surgery, an interventional vascular procedure, medical management of fluid status or blood pressure, or improvement in cardiac function. The presence of chronic ischemia results in an adaptive peripheral arteriolar vasodilation in various organ systems and the lower extremity. In fact it has been demonstrated both in human and animal modeling that small episodes of ischemia can actually improve tissue tolerance to reperfusion, a concept known as ischemic preconditioning. The microcirculation can become both structurally and physiologically altered during the ischemic state. Reestablishing macroflow results in a large volume of blood entering a dysfunctional microcirculation with resulting problems such as "revascularization edema," which can further compromise tissue perfusion. Caselli demonstrated, for example, that transcutaneous oxygen levels increase over a 4-week period after successful revascularization but do not demonstrate consistent elevations except for a brief initial rise, when revascularization is unsuccessful [6].

The soft tissue and skin can suffer similar effects of reperfusion injury noted in other organ systems [7] (Fig. 2.5). How the skin responds to reperfusion will require further study. We need to be able to predict outcomes and therefore require surrogate markers that can be studied preoperatively to maximize outcomes. The production of oxygen free radicals and intracellular calcium overloading are two mechanisms of action reported for ischemic-reperfusion (IR) injury. Single episodes of IR can result in myocardial stunning. Stunning refers to the reversible mismatch of perfusion-contraction that occurs despite adequate macro-flow. Extended periods of ischemia can lead to an adaptive condition known as tissue hibernation. It is now appreciated that over time, cells exposed to chronic

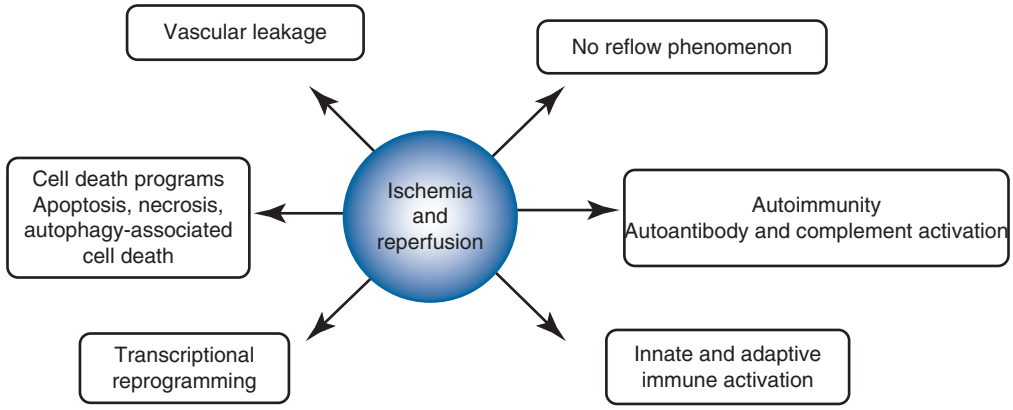

Fig. 2.5 Biological processes implicated in ischemia/reperfusion injury (Reprinted with permission from Eltzschig and Eckle [7])

ischemia will adapt by increasing the production of molecules known to produce an antiapoptotic effect. Another post-revascularization process reported in the cardiac literature is the concept of "no-reflow." The endothelium becomes dysfunctional during the revascularization period leading to subsequent cell swelling, leukocyte-induced inflammatory responses, in situ thrombosis, decreased nitric oxide production, vasoconstriction, and possibly distal embolization [8]. The reversibility of no-reflow is dependent on patient risk factors and the type of device used in the revascularization procedure. In lower extremity revascularization procedures with nonhealing wounds and, in particular, with open guillotine amputations, our team has observed progressive tissue necrosis and a heterogeneous pattern of granulation tissue formation that might be a result of the no-reflow process despite adequate revascularization. Even if tissue necrosis does not occur as a result of ischemia-reperfusion injury, we are uncertain that the quality of healing will be affected by the resulting biochemical changes. For example, changes might occur in tensile strength or the amount of scar formation, both of which ultimately may affect wound recidivism rates. The mechanism of cell death after IRI has many potential pathways [2] (Fig. 2.6). Extrinsic factors, such as depleted cellular energy stores, and the release of inflammatory mediators were thought to be responsible for the majority of tissue necrosis in IRI; however, it is now known that several additional mechanisms add to the overall process. Apoptosis (programmed cell death) is a regulated pathway that leads to cell shrinkage and condensation of the nucleus and cytosol. Autophagy is the cellular process of removing obsolete or dysfunctional cells. This process can generate much needed amino acids and fatty acids which can actually provide nutrition for the cell during times of sublethal stress situations. Uncontrolled autophagy, however, will ultimately lead to tissue necrosis. Programmed necrosis, also known as necroptosis, is thought to occur during IRI. This specific biochemical pathway is thought to occur in addition to the more random process of generalized tissue necrosis.

2.4 Clinical Case Example

Two patients with critical limb ischemia, diabetes, and hypertension were recently treated in our unit with very different outcomes. Patient number 1 was an African-American male, 68 years of age with distal foot necrosis and infra-popliteal arterial occlusions leading to a reconstituted posterior tibial vessel. A reverse saphenous graft bypass graft was performed from the popliteal artery to the posterior tibial artery, and an open guillotine transmetatarsal amputation was performed several days later. The patient was transferred to our subacute wound unit for postoperative management. Treatment included non-contact kilohertz

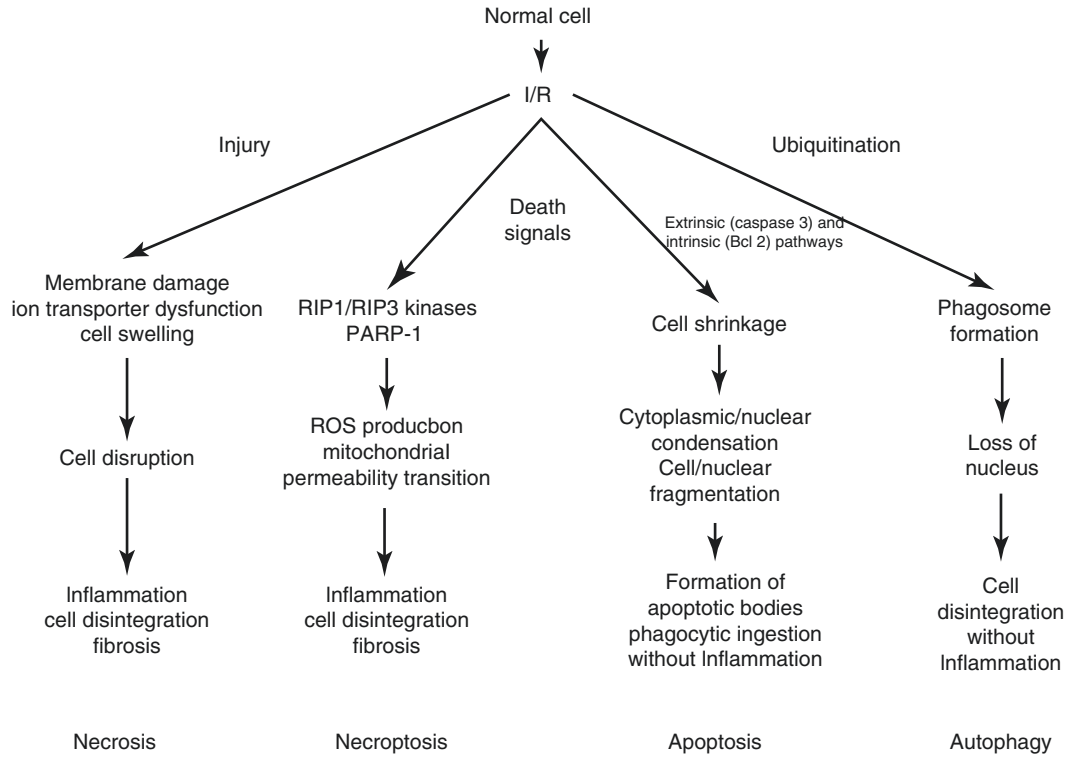

Fig. 2.6 Mechanisms of cell death in ischemia/reperfusion (I/R). I/R-induced necrosis generally occurs as a result of dysfunctional ion transport mechanisms, which causes cells to swell and eventually burst, effects that are exacerbated by plasma membrane damage. Release of proinflammatory mediators and damaged biomolecules initiates the influx of inflammatory cells such as neutrophils, which disrupt the extracellular matrix and cause damage to parenchymal cells by release of cytotoxic oxidants and hydrolytic enzymes. Apoptosis is a regulated form of cell death that causes cell shrinkage and condensation of the cytosol and nucleus (Reprinted with permission from Kalogeris et al. [2])

ultrasound therapy to enhance angiogenesis and capillary recruitment. Ultraviolet light was used to control wound bio-burden and dressings maintained a moist environment. Over two weeks, a homogeneous granular wound bed began to form, and negative-pressure wound therapy was implemented at 75 mmHg intermittent for an additional two weeks. Nasal oxygen was used to enhance tissue oxygenation, and edema was minimized through gentle compression and leg elevation. At the end of 4 weeks, an autologous split-thickness skin graft was used which resulted in 100 % take. An offloading orthotic shoe was created and the patient was discharged. Patient number 2 had identical vascular anatomy and tissue loss. The same bypass and open amputation was performed, and the patient was also discharged to the subacute unit. Within 2 days of arrival, the peripheral margins of the tissue began to show signs of necrosis. Only two to three small buds of granulation tissue developed, while implemented the same energy-based treatments as those used in patient # 1. Progressive peripheral necrosis expanded, and the fatty tissue became dusky and malodorous with a heavy exudate despite elevation and IV antibiotics. Due to continued soft tissue necrosis, the use of negative-pressure therapy was not started. The patient ultimately was readmitted and underwent a below-the-knee amputation. While there are always patient-specific difference that could account for such variation in clinical outcomes, the macrovascular pattern of disease and initial soft tissue loss were identical. We currently have no diagnostic methods to

predict these outcomes until they present themselves clinically. We are therefore always in a reactive mode and not a proactive or preventive mind set. There are a number of recently described potential therapeutic approaches that might improve our limb salvage rates in the future.

2.5 Treatment Options

Investigators are evaluating methods to enhance tissue tolerance to ischemia through preconditioning. Exposure to short, nonlethal episodes in ischemia can result in an attenuated tissue injury response following revascularization [7]. Through the use of animal modeling, investigators are trying to determine the biochemical steps responsible for the positive impact of preconditioning so that biological targeted therapy might be developed. Patients with long-standing lower limb ischemia and robust collateral formation have potentially already benefitted from these phenomena. Other investigators are approaching the problem via post-conditioning, remote conditioning, controlled reperfusion, and pharmacological manipulation of the perfusate [7]. Pharmacological therapy prior to revascularization has been evaluated with HMG-coA reductase inhibitors, immune suppressive therapy, and stem cells [9].

There is an opportunity for improving limb salvage rates, quality of life, and cost through an improved understanding of ischemia and reperfusion in the wound care community. Ischemia and reperfusion injury is considered important in venous ulcer pathology, sickle cell and vasculitic ulcers, and pressure ulcers. Variations in muscle and skin flow, for example, are critical when deciding on sitting protocols for paraplegic patients to prevent pressure ulcer formation [10]. Improved diagnostic and therapeutic options for this condition will allow us to strategize our treatment plan. Some patients may benefit for energy-based modalities and/or stem therapy in order to increase a low-resistance outflow bed prior to a revascularization. Others may benefit from controlled reperfusion and pharmacological interventions. Limb salvage rates continue to improve in many centers throughout the world, but with an aging population and an increased prevalence of diabetes, more and more patients will have concomitant soft tissue loss in combination with ischemia. Personalizing their therapy will be critical to achieve functional, successful, and cost-effective outcomes.

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3 Imaging, Vascular Assessment: Extension in Depth and Vascular Anomalies

Sadanori Akita, Seiji Houbara, and Mihoko Akatsuka

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3.1 Introduction

Vascular anomalies are composed of two distinguished main types. One is vascular tumors, which are most commonly infantile hemangioma and other related rare vascular tumors in children and in adults. The other is vascular malformation [1]. Vascular tumors are distinct from vascular malformations founded on clinical appearance, imaging, and pathologic characteristics [2]. Vascular tumors include infantile hemangioma, congenital hemangioma (rapidly involuting congenital hemangioma (RICH) or non-involuting congenital hemangioma (NICH)), kaposiform hemangioendothelioma, tufted angioma, pyogenic granuloma, and hemangiopericytoma. Various imaging methods are used in the diagnosis of vascular malformations. These techniques must be referred to their clinical findings and to the aim of imaging, which would be useful of diagnosis, pre- and intra-treatment assessment, or follow-up.

The majority of infantile hemangiomas (IHs) are small and not hazardous and may recede spontaneously with proliferation, involution, and involuted phases. IH can be alarming if found in life- and function-threatening locations such as the eyelid, orbit, or airway. Ulceration, continued infection, or hemorrhage requires treatment (Fig. 3.1). Ulceration is the most common complication of IH. The incidence in a referral population is generally reported to be about 16 %. In a prospective study of 1096

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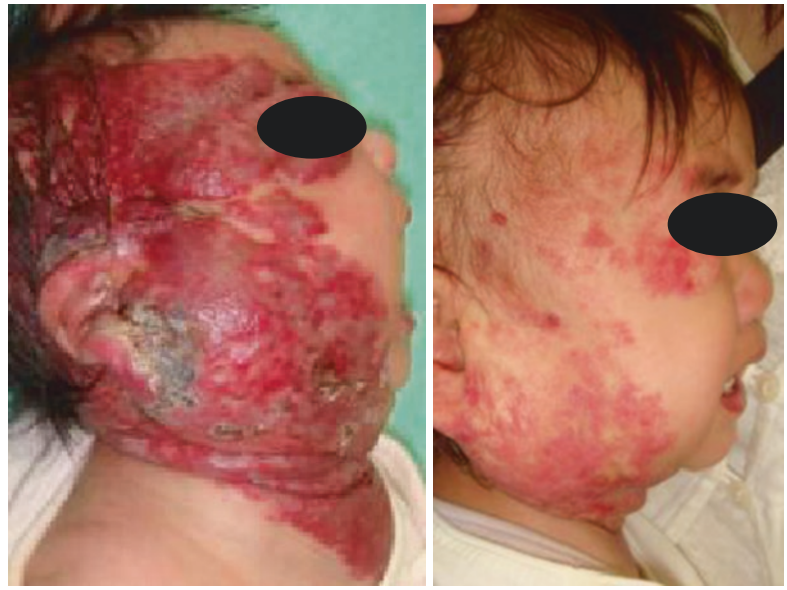

Fig. 3.1 Progression of infantile hemangioma on the right side of the face at 1 month in the first visit (*left*) and at 1.5 years (*right*). The ulcers in the preauricular, the cheek, and the submandibular areas are healed

patients, the median age at ulceration was 4.0 months, which correlates with the end of the proliferative phase [3]. Risk factors for ulceration include segmental morphologic characteristics, large size, and mixed superficial and deep subtype. Early white discoloration may suggest impending ulceration [4].

Vascular malformations consist of capillary malformation (CM), venous malformation (VM), lymphatic malformation (LM), and arteriovenous malformation (AVM). Some clinically combine more than one malformation and then categorize complex vascular malformation and complex syndromes such as Klippel-Trenaunay syndrome (CM + VM + LM) or Parkes Weber syndrome (AVM/or arteriovenous fistula (AVF) + skin pseudo-CM + lymphedema) as observed in more systemic signs and symptoms.

Skin necrosis often manifested in severe AVM and combined CM + LM as well as minority cases of IH.

3.2 Assessment and Imaging Tools

Many imaging tools are able to determine the diagnosis of vascular malformations.

3.2.1 Conventional X-Rays

These are usually of no or little value in most cases. Venous malformations (VMs) may be diagnosed if phleboliths (vascular stones) are observed on plain X-rays. Bone distortion is merely seen in large malformations with a soft tissue mass effect. Some diffuse and massive VMs cause osteolytic lesions and bring about a risk of pathologic fractures. AVMs involving the bone sometimes lead to osteolytic lesions due to intraosseous nidus or large draining venous channels after nidus.

3.2.2 Duplex Ultrasonography

This imaging is primarily used as a diagnostic tool [5] at the clinic in the first visit. It permits distinction between tumors and malformations. It also identifies a vascular malformation and pinpoints the type of lesion. It demonstrates either the lesion is cystic or tissular, clarifies either the presence or absence of flow, and thus distinguishes between fast-flow and slow-flow malformations (Fig. 3.2). Angiostructure and vessel density can be assessed; however, its reliability is most of the time poor. Peak flow velocities and arterial output may be measured in AVMs. In

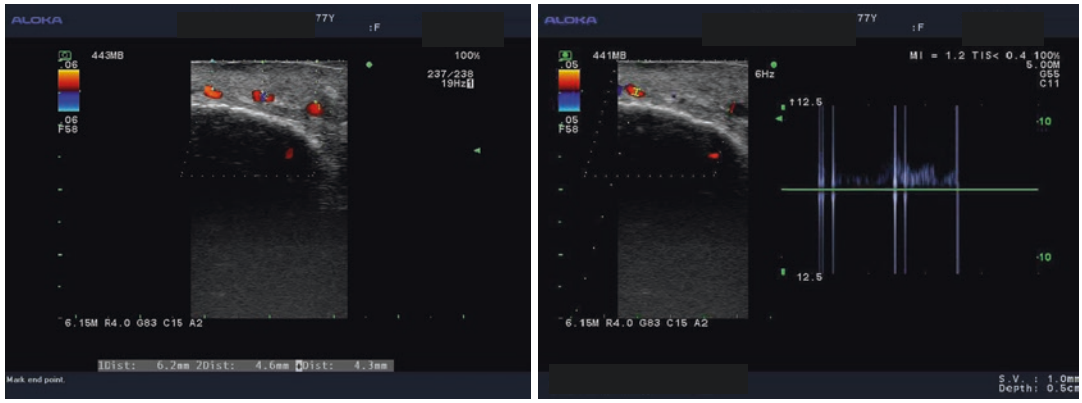

Fig. 3.2 Typical duplex ultrasonic examination. Flow patterns and localization of the lesions are depicted (*left*); flow intensity and pulse are demonstrated (*right*)

head and neck or extremity AVMs, comparing arterial output on the normal side and the abnormal contralateral side is crucial in prognosis, especially of possible cardiac failure, and thus useful for follow-up of AVMs.

3.2.3 Computed Tomography (CT)

This method is relatively of limited interest even with enhanced contrast, information of a lesion is merely whether highly vascularized or not. Precise delineation and diagnosis of soft tissue lesions remain frail with the exception of macrocystic LMs, where cysts are clearly depicted. The presence of phleboliths may lead to a diagnosis of venous malformation as distinctive calcifications develop on thrombosis and debris resulting from slow flow. Bony displacement or alteration can be seen due to chronic (long-term) compression seen in both VMs and LMs. Pathologic fractures and absorption may be seen in bone or bone-adjacent AVMs.

3.2.4 Magnetic Resonance Imaging (MRI)

This is the best diagnostic modality, giving optimal analysis of soft tissue masses and proper diagnosis, distinguishing tissular form cyst, and delineating fast or slow vessel flows. Venous and lymphatic malformations have each attribute pattern. They are hyperintense on spin echo T2-weighted sequences and optimally seen in fat-suppression sequences. T1-weighed and fat-suppression sequences with gadolinium injection demonstrate an intense enhancement in infantile hemangioma, while the enhancement is inconsistent and progressive on dynamic sequences in VMs. Gadolinium contrast allows differential diagnosis among VMs and LMs. LMs can be distinct from VMs as LMs indicate enhancement only at the margins of the cysts. By contrast, VMs are clearly and evenly stained. MRI is compulsory before treatment to make decisions of the extent of the lesion and the relationship among the vascular malformation, intact neighboring nerves, and vessels and for the identification and diagnosis of the lesions. In fast-flow vessels, they are identified as flow voids. MR angiography can confirm the diagnosis of fast-flow pathology; however, it remains insufficient for detecting accurate AVM's nidus and angiostructures.

3.2.5 Vascular Imaging

This procedure is mainly used for fast-flow vascular lesions. Angiography is a powerful pretreatment assessment method in AVM, of which early venous drainage is characteristic. Angiostructure of an AVM can be obtained by identifying its location, arterial suppliers,

draining veins, and relationship with normal neighboring arteries and veins. Angiography is used for diagnosis of quiescent AVMs, which simulates a capillary malformation.

3.3 Treatment

3.3.1 AVM

In vascular malformations, skin lesions are most frequently observed in AVMs, which demonstrate ulcers during the natural clinical course and post-therapeutic side effects following morbidity of embolization or sclerotherapy. In AVMs, a practical clinical staging system is proposed. This staging describes the progression of AVMs proposed by Schobinger. In the initial quiescent stage (stage I), the lesion presents as warm pink-blue macules. Then, it expands with pulsations, thrills, and bruits (stage II); subsequently it becomes destructive with pain, hemorrhage, or ulceration (stage III) and demonstrates decompensation and results in congestive heart failure (stage IV) [6]. It is ideal to treat at stage I and II, but often it will be unnoticeable until stage III, when the ulceration is observed as a clinical destructive sign. With mean follow-up of 4.6 years, the cure rate of AVMs was 75 % for stage I, 67 % for stage II, and 48 % for stage III [6]. AVMs are worsened after trauma, hormonal change, pregnancy, or puberty. Duplex ultrasonic examination as well as clinical signs and symptoms can assist the therapeutic decision making; however, a more precise and effective evaluation with MRI and angiography is necessary. While MRI can provide the spatial relationship between the lesion and the surrounding tissue and organ, angiography is most usefully applied in abnormal vascular assessment and therapeutic evaluation when embolization, which is often required for abolition of the nidus, flow, pooling, and drainage pattern around the lesion. When the AVM lesions are localized as often seen in stage II and for protection of vital organs, either surgical removal alone or combined therapy with precedent embolization within 24–48 h is of first choice. If the defect is large, reconstruction will be followed [7]. If the lesion is extensive and destructive (stage III) and the margin of the lesion unclear, controlled attenuation of the lesion should be considered. Embolization to control flow supply and drainage and subsequent percutaneous transcutaneous ultrasonic-guided sclerotherapy within 24–48 h may generate sufficient reconstruction of wound bed (Fig. 3.3).

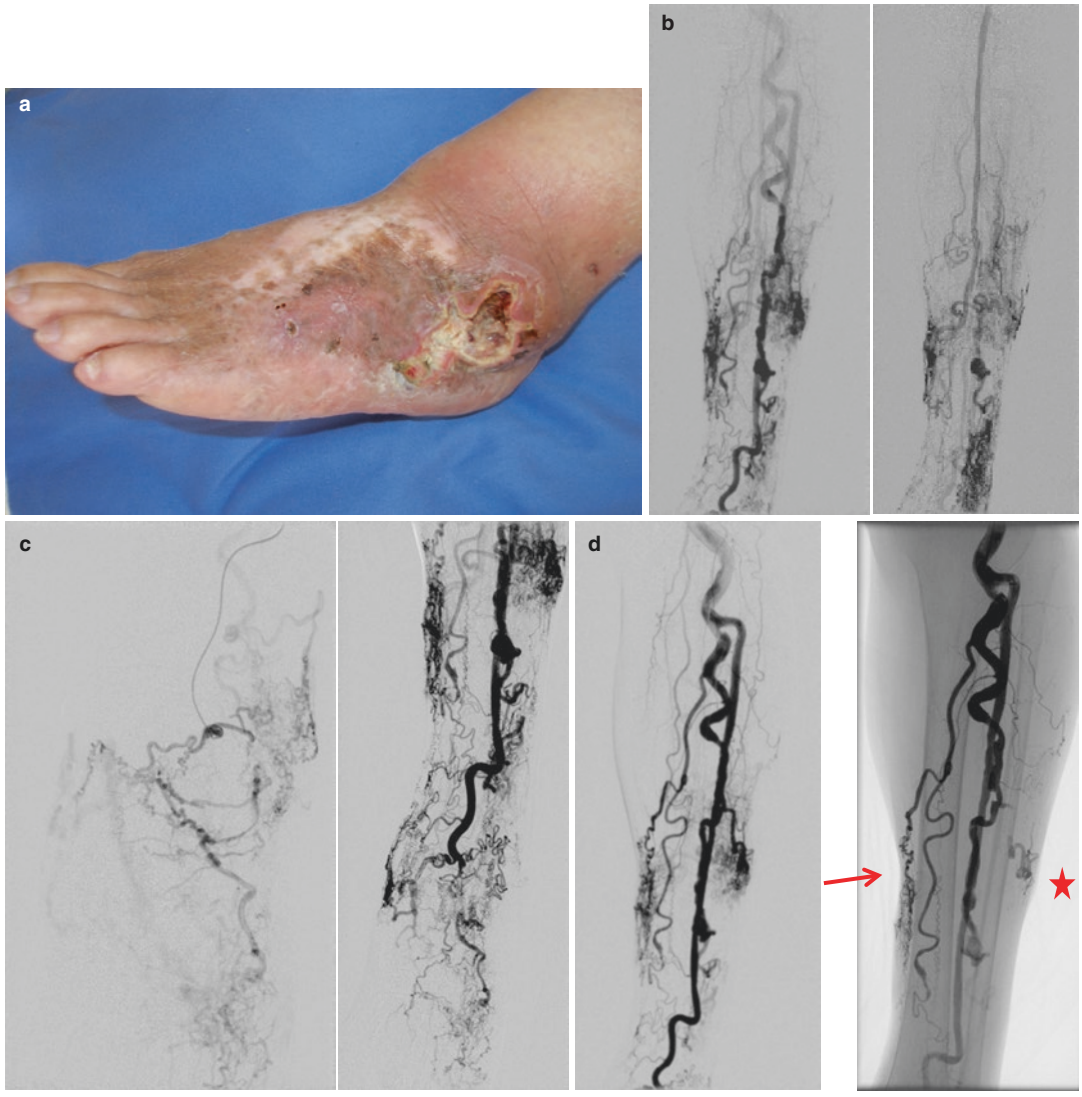

Fig. 3.3 (**a**) A 78-year-old female with arteriovenous malformation (AVM) in the entire calf after radiotherapy for tinea 40 years ago. Skin is hardened and discoloration is seen on the dorsum of the foot. (**b**) Angiograms depict AVMs in all three major branches of tibialis anterior, tibialis posterior, and peronealis in both early (*left*) and later (*right*) phases. (**c**) Selective angiogram in the tibialis anterior (*left*) demonstrates other two major branches. The angiogram in the tibialis anterior reveals the AVMs distal to the foot and toes in all three branches (*right*). (**d**) Pre-embolization angiogram in the tibialis anterior (*left*) and post-embolization angiogram (*right*). The flow rate in the tibialis anterior decreases; some AVMs in tibialis posterior (*arrow*) and peronealis (*asterisk*) are abolished. (**e**) Six years post-embolization, percutaneous ultrasonic-guided sclerotherapy (absolute ethanol) and skin grafting. There is still minor fistula seen (*arrow*). Even though local pain in the sole pad continues, dorsal flexion of the foot and walking are intact. (**f**) MRI findings demonstrate extensive nidus in the medial malleolus (*upper*), sole (*left*), and intermetatarsal spaces (*right*)

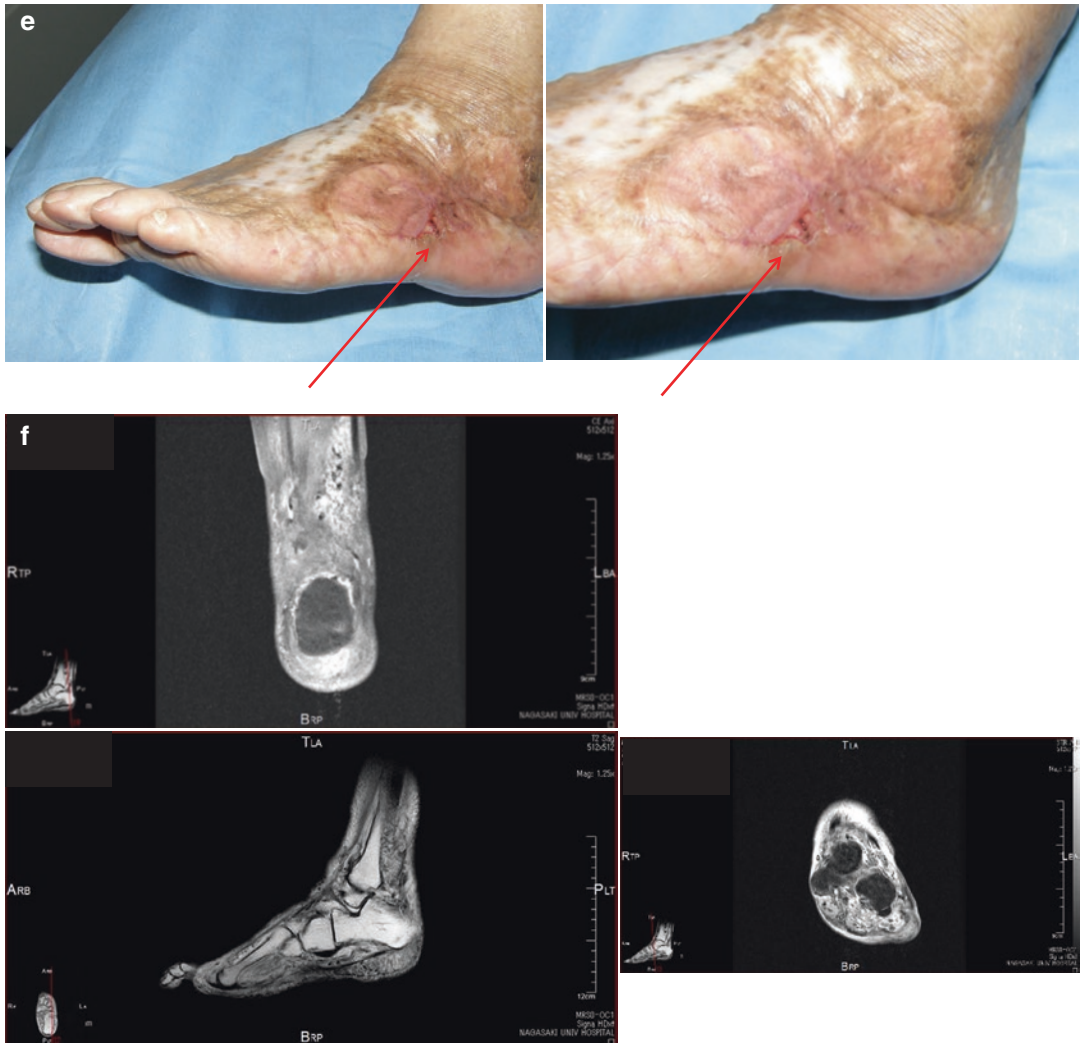

Fig. 3.3 (continued)

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Imaging of Hypodermal Fat Necrosis

4

Ximena Wortsman

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4.1 Introduction

Fat necrosis is a benign non-suppurative inflammatory entity of the adipose tissue that results from the aseptic saponification of lipids by enzymes. The reported causes include trauma, radiotherapy, anticoagulation, inflammatory diseases, surgery, percutaneous interventions, and perinatal asphyxia, hypoxemia, or hypothermia [1]. Imaging has been growingly used for studying fat necrosis due to the often variable history and clinical findings that can simulate other conditions which includes the differential diagnosis of palpable lumps and bumps when this entity affects the hypodermis. Additionally, patients may not spontaneously refer an inciting event such as trauma. Reports on imaging of fat necrosis started with the usage of X-rays, such as mammography, and have expanded to other imaging modalities such as ultrasound, MRI (magnetic resonance imaging), and most recently PET-CT (positron emission tomography-computed tomography). Besides the support to the clinical diagnosis, the usage of these imaging techniques may provide an anatomic perspective for evaluating the extent and characteristics of the structural changes in the tissues, as well as a support for assessing the differential diagnosis.

The aim of this chapter is to focus on the imaging characteristics of hypodermal fat necrosis with different imaging modalities and discuss some general principles, indications, advantages, and disadvantages for each method.

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4.2 Imaging Methods

4.2.1 X-Rays Mammography

X-rays are the most simple and accessible form of imaging study and involve the usage of low dose radiation for diagnostic purposes. Usually, this modality is not intended for particular study of fat necrosis; however, there are radiological signs suggestive of this condition that are frequently and incidentally found in the hypodermis, commonly during mammography screenings. The most frequent mammographic characteristic of fat necrosis is the presence of round- or oval-shaped hypodense structures, frequently showing a hyperdense calcified rim, also called "egg-shell"- or "rim-like"-type calcification that corresponds to calcified lipid cysts (Fig. 4.1). This sign is almost pathognomonic of fat necrosis; therefore, the patients presenting this feature may not need additional imaging studies and should continue with the recommended screening program according to their age and history. Less frequent forms of presentation of fat necrosis on mammography include focal asymmetries that may imply parenchymal edema. However, microcalcifications or spiculated dense masses can also be detected, the latter being related to a major presence of fibrosis or scarring [2, 3]. Since these occasionally seen mammographic signs may mimic a breast malignancy, more imaging studies are usually needed in these particular cases.

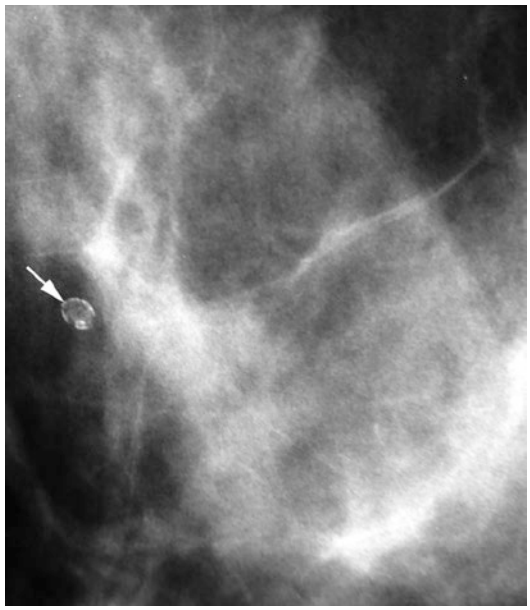


Fig. 4.1 *Fat necrosis on mammography* (lateral view) shows a "rim-like" or "egg-shell" type of calcification (*arrow*) within the fatty tissue of the breast

4.2.2 Ultrasound

Also called sonography, this widely available imaging method is based on the properties of sound waves and has been increasingly used for studying fat necrosis in soft tissues due to the high definition images of the superficial layers provided by the current machines. Besides its non-radiating nature and proved safety characteristics, there are several advantages of ultrasound such as its real time, 2D and 3D multiaxial and dynamic performance, as well as its reasonable balance between resolution and penetration that allow us to obtain a wide range of anatomical information that can reach from the skin layers to the bony margin. Also, ultrasound can show the vascularity of the tissues through its color or power Doppler capabilities which includes the detection of the type of vessel (arterial or venous) and the velocity of blood flow (cm/s) [4, 5]. This may avoid the adverse reactions due to the use of contrast media that have been widely reported with other imaging modalities such as CT or MRI. The current limitations of ultrasound are lesions that measure <0.1 mm, with only epidermal location, and the detection of pigments such as melanin [6]. These last two limitations are not relevant for the study of fat necrosis. In fact, the hypodermis seems to be a perfect target for ultrasound use, due to its anatomically superficial location in soft tissue that makes it easily accessible with most of the linear probes that work with frequencies ≥7.5 MHz. Nevertheless, probes working with higher frequencies (≥12 MHz) are most commonly recommended for studying the hypodermis due to their higher definition at this tissue depth. On ultrasound, the most common

sign of fat necrosis is the presence of well-defined round or oval-shaped anechoic pseudocystic structures, frequently with posterior acoustic enhancement, and sometimes surrounded by a hyperechoic calcified rim. These pseudocystic structures correspond to the oily cysts produced by the liquefaction of the fatty tissue. Internal echoes and a fluid–fluid level may sometimes be recognized in these pseudocysts, usually in cases with history of trauma where the serohematic material combines with the liquefied material of the fatty lobules. Also, increased echogenicity of the hypodermis and isoechoic pseudonodules, surrounded by an anechoic or hypoechoic halo, may be detected. These latter ultrasound features indicate the degree of hypodermal inflammation. Less frequent sonographic signs are anechoic masses with a posterior acoustic shadowing artifact due to gross calcification and well- or ill-defined hypoechoic solid pseudo-masses due to prominent fibrosis and scarring. All these characteristics may appear as single or combined features in the affected region (Figs. 4.2 and 4.3). Hypo- or hypervascularity in the hypodermis may be detected according to the level of inflammation present in the tissue, hypervascularity being the most commonly found in inflamed stages [1, 3, 7]. In cases presenting subcutaneous fat necrosis of the newborn, ultrasound has been reported to successfully support the diagnosis [8–10]. Thus, the main indications for ultrasound in fat necrosis are to support the early diagnosis and rule out solid tumors that may be hard to differentiate on a clinical basis only.

4.2.3 Magnetic Resonance Imaging

This is an imaging method based on the response of the body's hydrogen ions in a magnetic field. This technique has been widely used in the study of soft tissues, mainly in the musculoskeletal field, due to its high definition anatomical images. The main disadvantages of this method are its high cost and the potential adverse reactions to gadolinium, the usual contrast medium used in these examinations. Additionally, MRI has limited ability to show small calcifications, a common finding in fat necrosis which may be seen in this imaging technique as areas of signal void or may simply go undetected. On MRI, a wide spectrum of findings has been reported in fat necrosis and some of the findings may even mimic a malignant tumor such as a breast cancer. The most typical finding on MRI is a round or oval nodule or mass with hypointense T1-weighted signal on fat-saturated images that correspond to a lipid pseudocyst. Also, fat necrosis can show as well- or ill-defined isointense or hypointense areas or pseudonodules on T1-weighted images probably due to its inflammatory and hemorrhagic characteristics. In case with strong fibrosis, architectural distortion, with or without spiculated margins, and variable degrees of intensity (low, intermediate, or high signal) on T1-weighted images are reported. Fat suppression sequences may help to differentiate fat necrosis from malignant tumors. On T2-weighted sequences, isointense, hypointense, and hyperintense appearances have been described. Pseudonodular, globular, and laminated appearances have been additionally reported (Fig. 4.4). After the injection of gadolinium contrast medium, fat necrosis can show variable appearances that can range from no enhancement to irregular or peripheral enhancement and from thin to thick rims of enhancement [1–3, 7, 11, 12]. The most frequent indications for MRI regarding fat necrosis are to complete the imaging study in cases with mammographic abnormalities, especially the ones where a malignancy must be ruled out, and to assess the differential diagnosis in cases presenting palpable large lumps or extensive trauma.

4.2.4 Computed Tomography and Positron Emission Tomography

Computed tomography (CT) implies the cross-sectional usage of X-rays and has a broad range of applications, mainly in the neurological, cardiac, and abdominal fields. Thus, CT has been extensively used for staging malignant conditions. However, there are few reports in literature

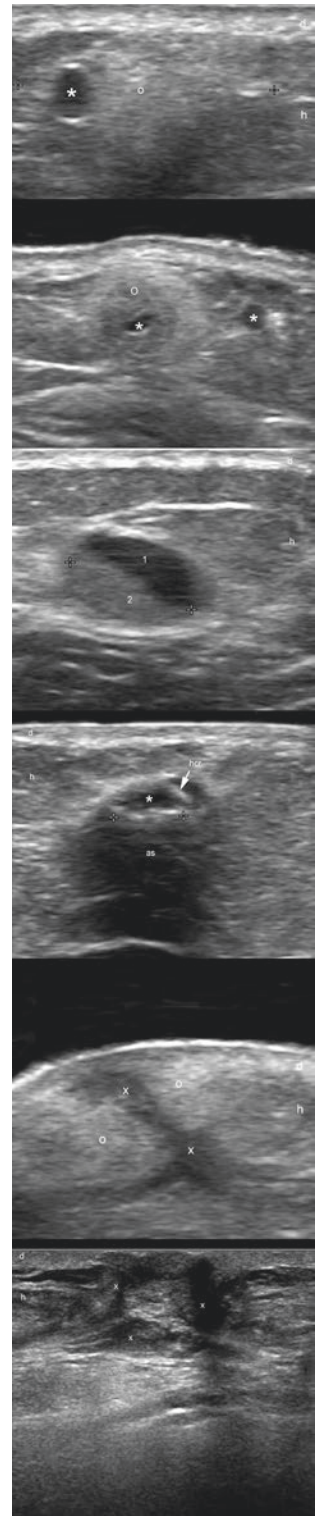
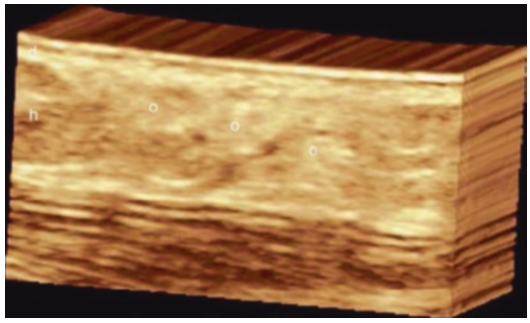
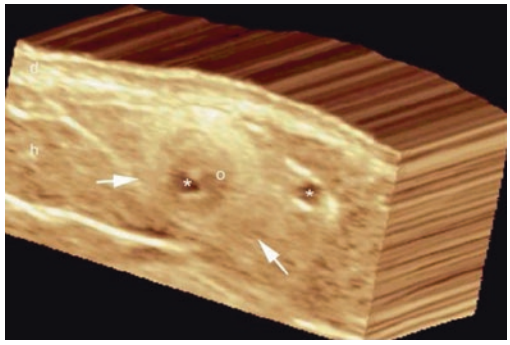


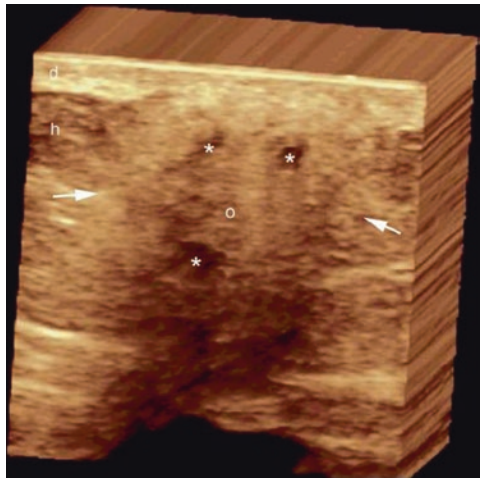
Fig. 4.2 *Fat necrosis on ultrasound* (gray scale, transverse views) demonstrates the wide range of appearance of this condition. Symbols: * pseudocyst, *o* pseudonodule, *x* fibrosis, *arrow* calcification, *1 and 2* fluid–fluid level. Abbreviations: *d* dermis, *h* hypodermis



Hyperechogenicity



Pseudocysts and pseudonodule



Pseudocysts, pseudonodule and distortion

Fig. 4.3 Fat necrosis on 3D ultrasound (gray scale, 5–8 s reconstruction, transverse views) shows variable forms of presentation. Symbols: * pseudocyst, *o* hyperechogenicity (*top*) and pseudonodule (*middle* and *bottom* location), *arrows* pointing out the lesional sites. Abbreviations: *d* dermis, *h* hypodermis

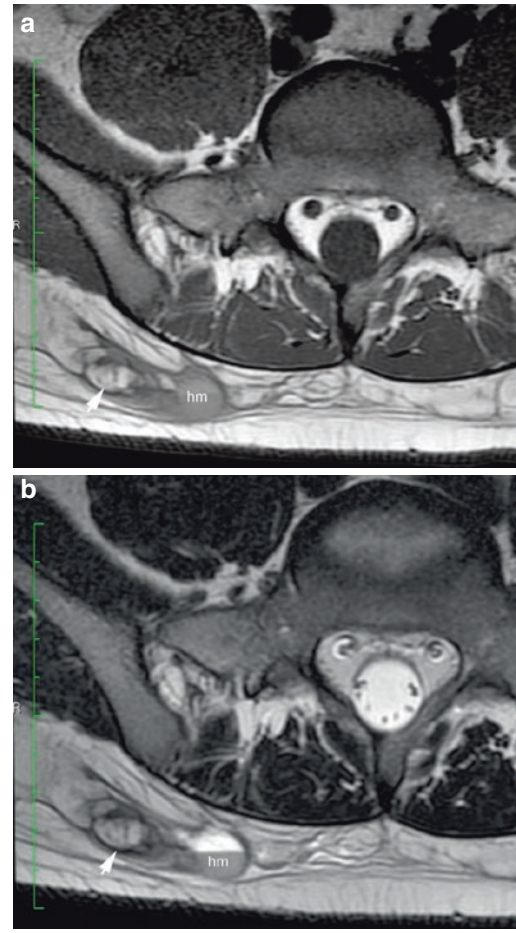


Fig. 4.4 (**a**, **b**). *Fat necrosis on MRI* (axial views). (**a**) T1-weighted sequence shows isointense pseudonodule with a hypointense rim located in the hypodermis of the right side of the lower back (*arrow*, fat necrosis area). In the vicinity, a hypointense oval-shaped hypodermal structure is detected that corresponds to a hematoma (*hm*). (**b**) T2-weighted image of the same case shows a change in the intensity of the hematoma (*hm*) with a fluid–fluid level (hyperintense/hypointense) and no change in the intensity of the pseudonodule (*arrow*, fat necrosis site) in comparison with the T1-weighted sequence (Courtesy of Drs. Raul Valenzuela and Herly Pulgar)

on the usage of CT for studying hypodermal fat necrosis, mostly showing isolated case reports. Advantages of CT are its wide availability and relatively short time of examination due to the new multi-slice machines that can acquire and process the images very rapidly. Disadvantages of CT are its high cost, its radiating nature, and the need for intravenous contrast media. On CT, fat necrosis has been reported as a well-defined hypodense mass with rim enhancement or a globular mass with central fat density [11].

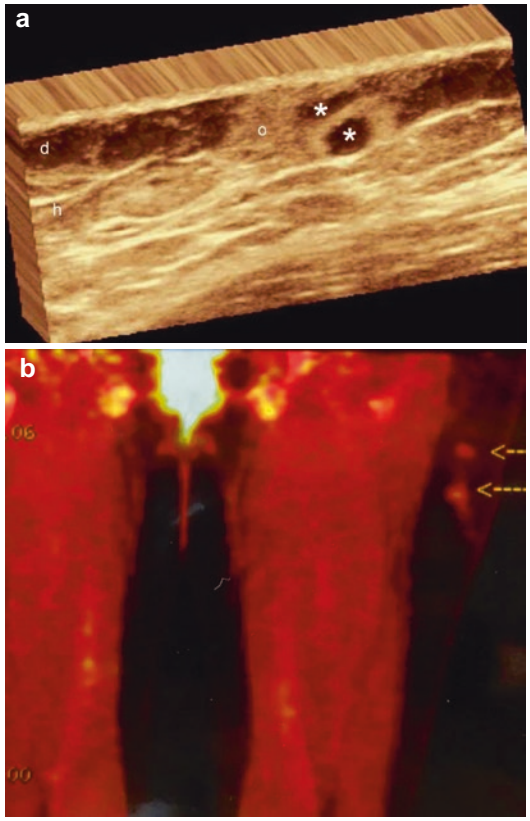


Fig. 4.5 (**a**, **b**) *Fat necrosis on 3D ultrasound and PET-CT*. Patient with history of removed in situ melanoma in the left leg. (**a**) 3D ultrasound (gray scale, 5–8 s reconstruction, longitudinal view) shows two anechoic pseudocysts (*) surrounded a hyperechoic pseudonodular structure (*o*) consistent with fat necrosis. (**b**) PET-CT (coronal view) demonstrates a false-positive uptake of FDG in the hypodermis of the left thigh with two hypermetabolic pseudonodules (*arrows*). Abbreviations: *d* dermis, *h* hypodermis (PET-CT image courtesy of Dr. Vicky Roizen)

Positron emission tomography (PET) is a nuclear imaging modality that registers the gamma rays emitted by a positron emitting radionuclide, also called tracer. The most commonly used tracer is fluorodeoxyglucose (FDG), an analog of glucose. However, this is a radiating modality that also requires injection of an agent.

In recent years the combination of these two modalities (PET-CT) has gained adepts due to the mix of the anatomical and biological images that have been widely used in the staging of cancerous lesions [13]. However, PET-CT has certain notable shortcomings, including the inability to perform simultaneous data acquisition and the significant radiation dose to the patient [14]. PET-CT is now used in the staging of melanoma, showing high sensitivity especially in advanced stages [15, 16]. Nevertheless, there are several reports of false positives of PET-CT due to the glycolytic activity present in inflammation that can easily mimic a malignancy in this modality [17–19]. These inflammatory features are common in fat necrosis; therefore, this condition seems to be one of the most common pitfalls for PET-CT. These reports mention pseudonodular solid images with hypermetabolic activity and increased uptake of FDG (Fig. 4.5). Besides fat necrosis, other causes of false positives of PET-CT have been reported. Among them are acute and chronic inflammation or infection, physiologic lactation, benign breast masses, including silicone granuloma, fibroadenoma, and postsurgical or radiotherapy changes. Therefore, the usage of PET-CT is not recommended as a first imaging modality in fat necrosis. Moreover, the usage of this imaging modality may cause diagnostic dilemmas in oncologic imaging [20].

Conclusion

There are several imaging methods that can reveal the anatomical characteristics of hypodermal fat necrosis. The usage of imaging in this condition is intended for the assessment of the differential diagnosis of lumps and bumps in the soft tissues, also to try to rule out malignant tumors. The advantages and disadvantages of each technique as well as the availability of these modalities in the medical institutions should be considered, when selecting the appropriate imaging modality for each case.

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Skin Necrosis and the Need for Vascular Assessments

5

T.L. Luk and Raj Mani

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5.1 Introduction

There are many causes of skin necrosis. The process resulting in skin necrosis begins with the sudden thrombotic occlusion of single or multiple blood vessels supplying the tissue. Compromised blood vessels leak red cells into the surrounding tissues where they become trapped within the ensuing tissue that is turning necrotic. The subsequent deoxygenation of haemoglobin in the red blood cells causes tissue hypoxia and renders it black in colour. While tissue is dying, cells release cytokines promoting inflammation. At the boundary of necrotic tissue, blood vessels dilate resulting in hyperaemia giving rise to the dusky grey-red colour of the surrounding skin. Thus, the successful diagnosis of skin necrosis depends upon the identification of the condition that causes vessel thrombosis.

Causes of vessel thrombosis is related to Virchow's triad which consists of the following:

- Alterations to blood flow (haemostasis)
- Injury to the vascular endothelium
- Alteration in blood constituents (hypercoagulability) [1]

Diseases that cause thrombosis typically fit into one or more of these groups: each group has a particular pattern of skin necrosis. By examining the pattern and distribution of skin necrosis and using Virchow's triad, a diagnosis is derived.

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Vascular assessment is therefore vital in assessing skin necrosis. Vascular assessment is based on good history taking and physical examination followed by the use of diagnostic tests to determine the blood supply.

1. History
   - Ask specifically on walking distance and claudication history.
   - Ask about medication, allergies, and specific symptoms of cold peripherals, rash, etc.
   - Identify any cardiovascular risk factors such as diabetes, obesity, ischaemic heart disease, hypertension, and smoking history.
2. Examination
   Examine for all peripheral pulses including pedal pulses like the dorsalis pedis and posterior tibial pulsation. Also examine capillary refill time and peripheral temperature.
3. Doppler examination
   Using handheld Doppler with 8 MHz probe, pick up the Doppler signals in specific arterial testing sites. A normal artery with good blood flow yields triphasic signals; when there is significant reduction of blood flow, Doppler signals are monophasic or even damped.

   The measurements of ankle-brachial pressure index (ABPI) and toe pressure index (TPI) give a reliable indication of blood supply in the lower limb. ABPI values below 0.9 are indicative of the presence of peripheral arterial disease. Values above 1.40 should always be confirmed with toe pressure or other techniques especially in diabetic patients. Diabetics and other patients with suspected calcified vessels should always be tested using Duplex ultrasound imaging or toe pressures. Toe pressures below 0.7 are abnormal (TASC II). Toe and ankle pressures, as well as calculations of toe/ankle-brachial index, are commonly used to assess vascular status in patients with suspected peripheral arterial disease (PAD). Toe pressures are particularly important in patients showing falsely high ankle pressures due to calcified vessels. However, as toe pressures can be difficult to measure, Duplex ultrasound imaging should be sought after. Duplex ultrasound scans permit images of the arterial tree as well as haemodynamic data and are accepted as a diagnostic tool. Duplex scanning may be achieved with portable, relatively inexpensive scanners though there is a need for experienced vascular laboratory support. Toe and ankle pressure measurements, including calculation of ankle/toe-brachial index (ABI/TBI), are well-established, objective tests for diagnosis and management of peripheral arterial disease (PAD) and critical limb ischaemia (CLI). These tests also give valuable clinical information for the evaluation and planning of revascularization procedures. Toe pressures are of particular importance in patients suffering from arterial calcification, a condition which often leads to falsely elevated ankle pressure values and a subsequent under-diagnosis of disease
4. Pulse Volume Recording (PVR)
   Based on air plethysmography, Pulse Volume Recording (PVR) measures changes in pressure reflecting arterial pulsatility. PVR can aid in localizing significant occlusive lesions in limbs (TASC II). PVR measurements are often combined with segmental pressure determinations.
5. Transcutaneous measurement of tissue oxygen ($TcPO_2$)
   $TcPO_2$ referred to as TCOM in US literature measures local O_2 released from heated skin through the capillaries, reflecting oxygen transported in nutritive flow. The technique relies on electrochemical sensing of oxygen

using a modified Clark electrode that was first described for neonatal use.

Only 5 % of the microcirculatory blood flow measured with laser Doppler originates from the capillaries. $TcPO_2$ is one of few techniques that can measure this flow selectively. It is gaining acceptance as a measure of tissue viability especially in the management of the diabetic foot even though it requires a side room on a ward to carry out. Values below 30 mmHg are considered critical (TASC II) [2]. Its use and applications have been well described in the literature (Dini et al. 2012).

Limitations of the $TcPO_2$ technique are (1) a need to vasodilate skin and (2) specialist support to run the test. To an extent, these limitations also promote use of the method and have provided us with better understanding of how to manage skin that is intrinsically incapable of sustaining itself.

6. Laser Doppler measurement of cutaneous blood flow

Controlled local heating combined with a laser Doppler flowmeter can be used to determine the viability of tissue and the degree of microcirculatory impairment. The increase in blood perfusion as a response to local heating indicates tissue reserve capacity and good endothelial function. These are important parameters for predicting healing and determining amputation level. Values above 20 perfusion units during heating and an increase greater than 150 % compared to the baseline value predict wound healing. This technique may also be used to identify microvascular reaction to iontophoresis using acetyl choline or sodium nitroprusside which permits discrimination between endothelium and nonendothelium-dependent responses.

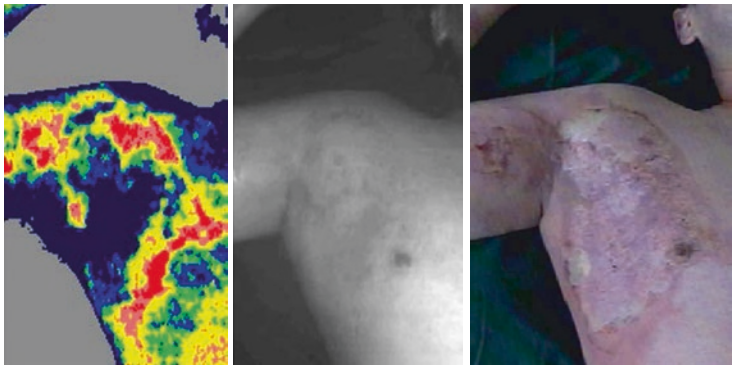
Laser Doppler has proven to be more sensitive than photoplethysmography in the low pressure range and does not require pulsatility [3]. The procedure involves placing an appropriate cuff on the toe/limb and a laser Doppler probe distal to the cuff. The cuff is first inflated to a pressure well above the systolic blood pressure and is then deflated linearly until the laser Doppler probe detects the return of blood perfusion. The pressure at the return of the blood perfusion is equivalent to the systolic toe or ankle pressure.

Laser Doppler imaging (LDI) is used to assess the depth of burns [4]. LDI is an advance of the laser Doppler flowmeter in that blood flow/perfusion over a preselected volume of tissue can be measured in the same scan. The method has been described (reference); in essence a laser beam of usually around 2 mW wavelength in the near infrared or infrared region is used to interrogate tissue. Using stepper motor control, this laser beam is moved over a preselected area that is scanned in raster fashion. Doppler shifted laser light is detected using optoelectronic devices to determine blood flow/perfusion data that are presented as colour maps.

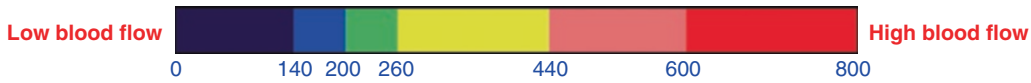
The best clinical use of this technique is to measure the invasion depth of burns [4]. Light cannot penetrate necrotic tissue as it is black. Assessments using this method can yield highly accurate blood flow/perfusion maps of areas surrounding the necrotic zone, thereby offering guidance to clinical management.

Healing Potential HP > 21: Case Study E

A 32-year-old male presented with 20 % TBSA scald burn to the chest, right arm, and left and right thighs. No details of first aid are available. MoorLDI imaging was performed on post-burn day 3.



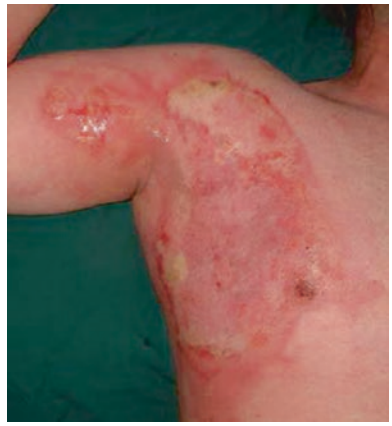
1 moorLDI flux image **2** moorLDI DC image **3** moorLDI CCD image



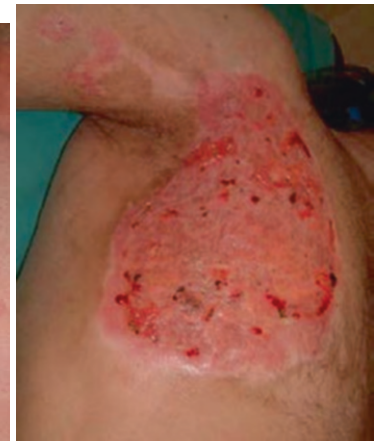
MoorLDI flux image (**1**) predicts the dark and light blue areas as HP>21. As shown in the clinical photographs, below, some healing occurred by post-burn day 20; these areas correspond to the areas of high flux on the moorLDI image (**1**). A biopsy was taken from the area indicated by moorLDI as HP>21, prior to surgery, on post-burn day 20 (clinical photograph **7**). The biopsy showed a third-degree burn wound.

Parts healed as predicted by HP type and the biopsy result was consistent with HP>21 criteria.

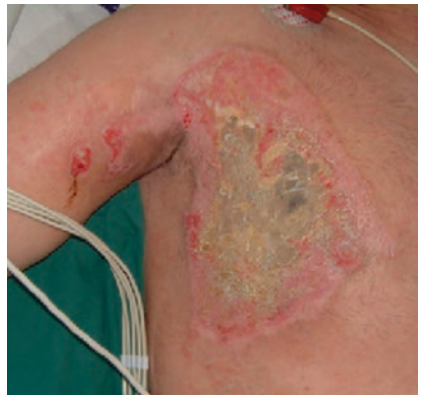
Clinical Photographs



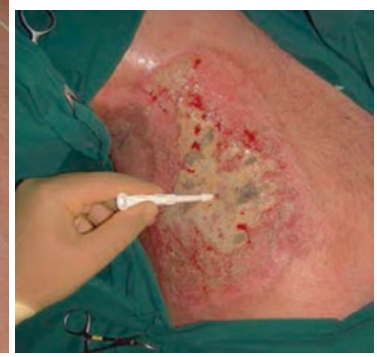
4 Scan day



5 Post-burn day 14



6 Post-burn day 20



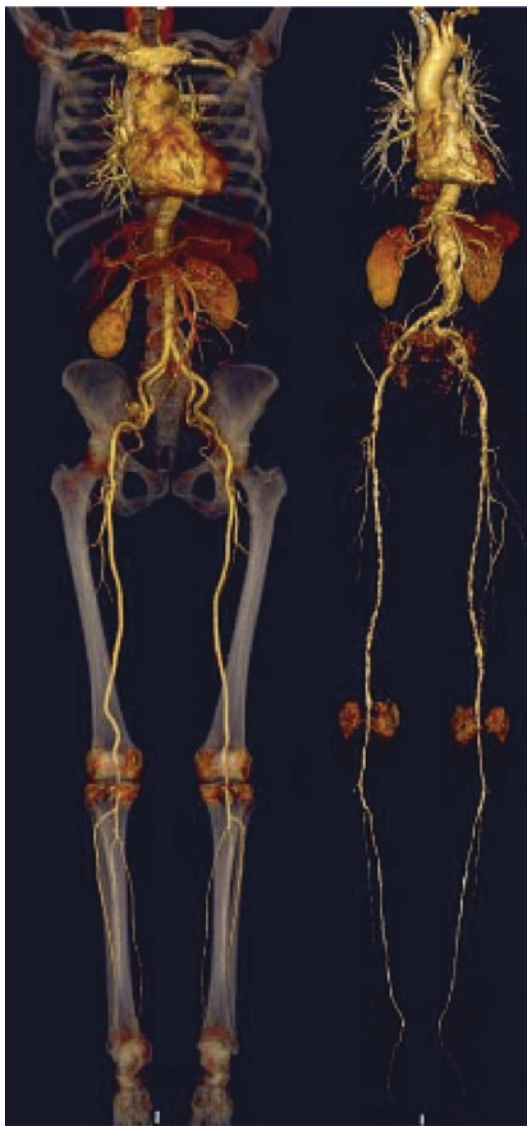
7 Biopsy position

NOTE: TAKE CARE COMPARING FLUX IMAGES WITH CLINICAL PHOTOGRAPHS: ORIENTATIONS MAY DIFFER

7. Duplex scan
   Duplex ultrasound is a special ultrasound technique that can assess how fast blood is flowing through a blood vessel. The test combines traditional ultrasound with Doppler ultrasound. Regular ultrasound uses sound waves that bounce off different structures of the body to create pictures. Doppler ultrasound records sound waves reflecting off moving objects, such as blood, to measure their speed and other aspects of how they flow. With addition of colour, the velocity can be measured. The accuracy and usefulness of Duplex ultrasound scanning in

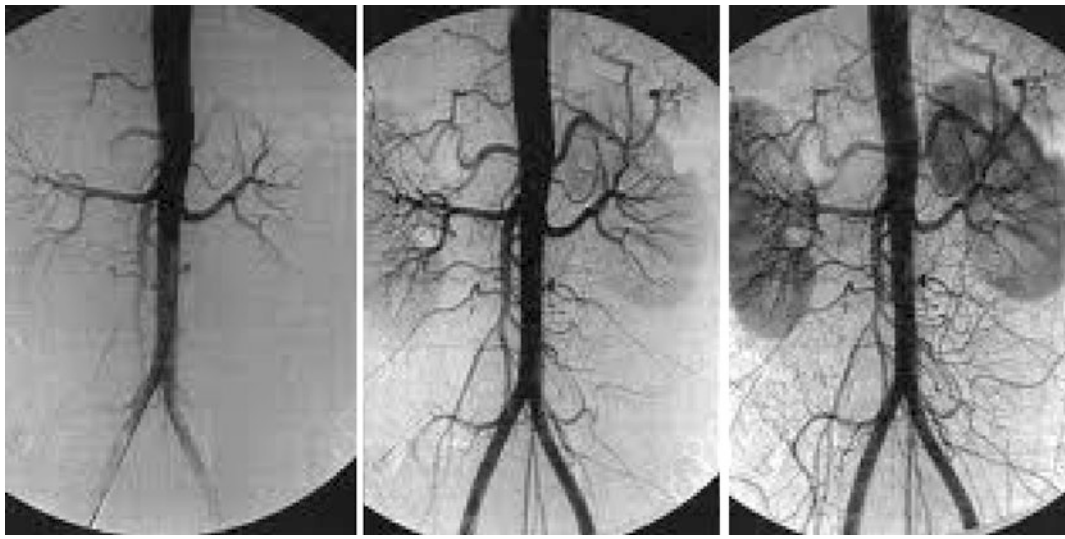
wound healing have been described in recent literature [5, 6].

8. Thermography, that is, an imaging modality based on sensing heat emitted by a body, has the potential to image insults to skin including necrosis. It has been used to detect damage due to burns though its availability and acceptance have possibly been limited by the expense of the equipment and the instructor required to conduct the scans.
9. CT angiogram/MR angiogram
   A CT angiogram is a diagnostic test that uses X-rays and an injected dye to produce three-dimensional images of the blood vessels and surrounding tissues. The test does not require entering the body (it is noninvasive). A CT can determine the location and severity of artery narrowing or blockages. MRA is similar to CTA but uses MR technology instead of X-ray.



10. Percutaneous angiogram/digital subtraction angiogram (DSA)
    In traditional angiography, we acquire images of blood vessels on films by exposing the area of interest with time-controlled X-ray energy while injecting contrast medium into the blood vessels. The images thus obtained would also record other structure besides blood vessels as the X-ray beam passes through the body. In order to remove these distracting structures to see the vessels better, we need to acquire a mask images for subtraction. The mask image is simply an image of the same area without contrast administration. So, using manual darkroom technique, clear pictures of blood vessels are obtained by taking away the overlying background.

    In DSA, the images are acquired in digital format through the computer. With the help of the computer, all images would be recorded into the computer and subtracted automatically. As a result, we can have a near-instantaneous film show of the blood vessels alone after X-ray.



5.2 Discussion

The aim of this short chapter is to briefly examine the need to assess skin necrosis and the techniques available. It is clear that following history taking and physical exam, a handful of techniques are available to determine clinical management.

Simple handheld Doppler exams and Duplex and contrast-based imaging have been discussed. Also discussed is the evaluation of the microcirculation which in the context of necrosis could be extremely valuable.

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Part II

Different Clinical Context of Skin Necrosis Physical Injuries

Electrical Burns

6

Christian Herlin

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6.1 Introduction

Electrical burns are rare but can be particularly severe or injuring and sometimes fatal. They represent approximately 5 % of burns [1]. In addition, it is estimated that 4,000 people every year undergo an electrocution in France.

This type of burn affects mainly *two categories of patients:*

- The young child exploring his environment
- The adult in his workplace

They are *two types:*

- Damage by direct contact with the electric current. The lesions spreading from an entry point to an exit point of the current (our focus of interest in this chapter).
- Injury by electric arcs in accidents at very high voltage. That is mainly thermal burns but at a very high temperature (>2,000 °C).

They can be divided into *two groups:*

- Low voltage injuries (<1,000 V) occurring mainly at home
- High voltage injuries (>1,000 V) occurring more often in the workplace

They mainly concern *two locations:*

- The upper limb
- The face

Mechanisms of tissular injury appear to be of *three different types:*

- The Joule effect: generating heat depending on tissue resistance – "$J = R\ I^2\ T$". The amount of the heat intensity generated (J depends indeed on voltage U because $U = RI$. T is the duration

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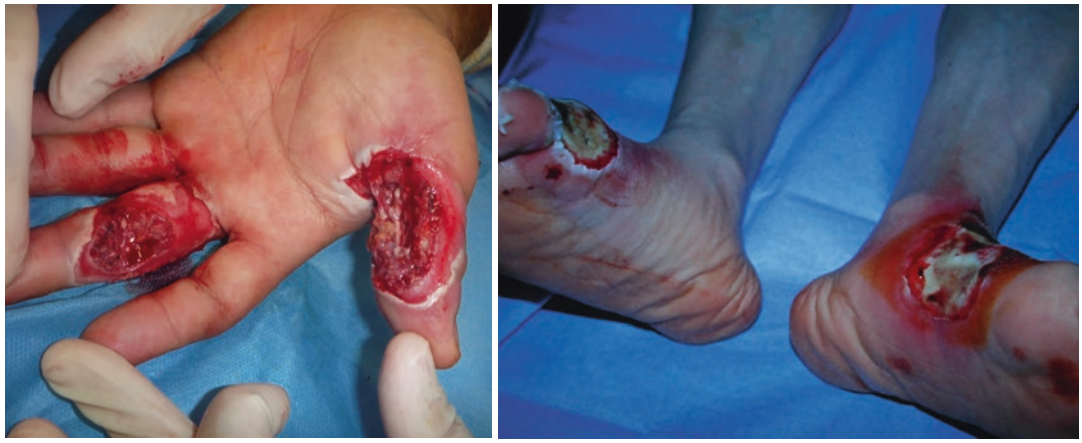

Fig. 6.1 Example of multiple points of entry and exits in the same patient

in seconds of the contact, R is the resistance in ohms, and I is the intensity in amperes).

- The higher the resistance, the greater the heat generated will be and the more serious the injuries are, but less current will travel through.
  Actually two parameters influence tissue resistance:
  - Its category (with decreasing resistance): Bone > fat > skin > muscle > mucosa > vessel > nerve
  - Its diameter: the smaller the diameter (wrist, elbow and ankle), the higher the resistance, and thus the damage related to the Joule effect is significant [2].
- Cell membrane destruction by electric shock (electroporation) [3] increasing tissue damage and promoting the release of myoglobin.
- Massive depolarisation, which will result in the damage of muscle, cardiac and nervous cells. The "shock" causes phenomena of tetanisation, which increase the contact time of the victim with the electric current source (cable grasps, feeling of being "stuck" to the source). Furthermore, tetanisation allows the joint's jump of current by hyperflexion of the joints [4].

6.2 Tissue Injury

1. *Entry and exit skin points*
   These points are most often located at the extremities. The entry point is centred by a sore indicating carbonisation. This area is surrounded by a burn of decreasing depth ("cockade aspect"). On the way to the exit point, an area of deep burn should be suspected, following theoretically the path of sensory and motor nerves (the superficial veins also).

   However, the current path remains unpredictable. Meanwhile, the exit point more often represents a whitish area. During the impact, it links the body to the ground or other external elements connected to it (Fig. 6.1).
2. *Muscle injury*
   It is always more severe than suggested by skin lesions and is due to the action of depolarisation and Joule effect. It represents the most important vital and functional prognosis factor in this type of burn. Muscles submitted to high voltage will undergo a very significant oedema, which can lead quickly to a compartment syndrome (>30 mmHg). This syndrome, if not managed by a fasciotomy, will significantly increase muscle, nerve and vascular damage, by direct compression, thrombosis [5] and necrosis leading to local acidosis. This vicious cycle is to be broken as soon as possible (Fig. 6.2).
3. *Myocardial damage*
   Except the acute cardiac fibrillation, approximately 10 % of patients admitted for electrical burn present electrocardiographic abnormality. This is most often represented by bundle branch block, supraventricular tachycardia or

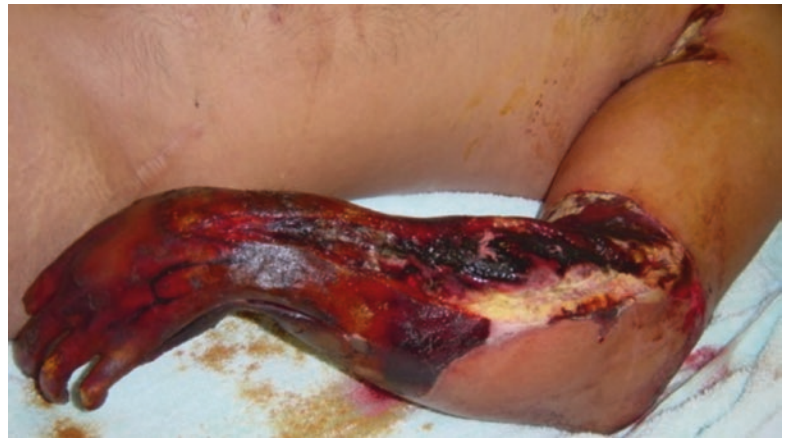

Fig. 6.2 Carbonisation of upper limb responsible for major and composite tissue lesions

nonspecific repolarisation disorder. To these mechanisms is added necrosis by coronary thrombosis according to the same mechanisms mentioned above.

4. *Buccal mucosa damage*
   It is typical of young children biting electric cables. The lesions are most often at the commissures, gums and tongue. Full necrosis occurs most often before the end of the second week. Spontaneous wound healing is often adequate but sometimes secondary interventions are required [6]. Their objective is in fact to reconstruct the anatomical subunits. The establishment of a shaper must be compulsory if there is a risk of microstomia.
5. *Nerve damage*
   It is most often a direct injury of axons by the current, causing paralysis or sensory disturbances more or less permanent. Indirect injury, often persistent, is caused by thrombosis or compression.
6. *Deep damage (except viscera)*
   They are the consequences of the Joule effect. With the bone and fascia being poor conductors, the heat effect is very significant, causing periosteal bone necrosis. In addition to that, fractures and serious sprains (typical posterior glenohumeral dislocation) are not uncommon due to tonic muscles tetanisation.
7. *Other damages*
   - Renal: damage by renal parenchymal necrosis, thrombosis or DIC (*disseminated intravascular coagulation*) and acute tubular necrosis by accumulation of myoglobin.
   - Visceral damage represented by gastrointestinal perforation, paralytic ileus, hepatorenal, liver injury or acute pancreatitis. Liver enzymes as well as amylase/lipase are to be obtained.

6.3 Medical Management

1. Monitoring
   The intensive care management (cardiovascular monitoring, rehydration, coagulation, CPK, K^+, etc.) must be rigorous and precautionary [7]. Compartment syndrome is to be ruled out (increased pressure of the compartments, hypoaesthesia, impaired distal perfusion, etc.).
2. Assessment of the lesions
   If entry and exit skin points are usually obvious, the path and the internal damages are sometimes more difficult to assess. Scintigraphy (99mTc; 133X) and MRI can provide important information on the condition about the deep integuments [8].

6.4 Surgical Management

1. First surgery
   It must be determined by the existence of a compartment syndrome, which must be

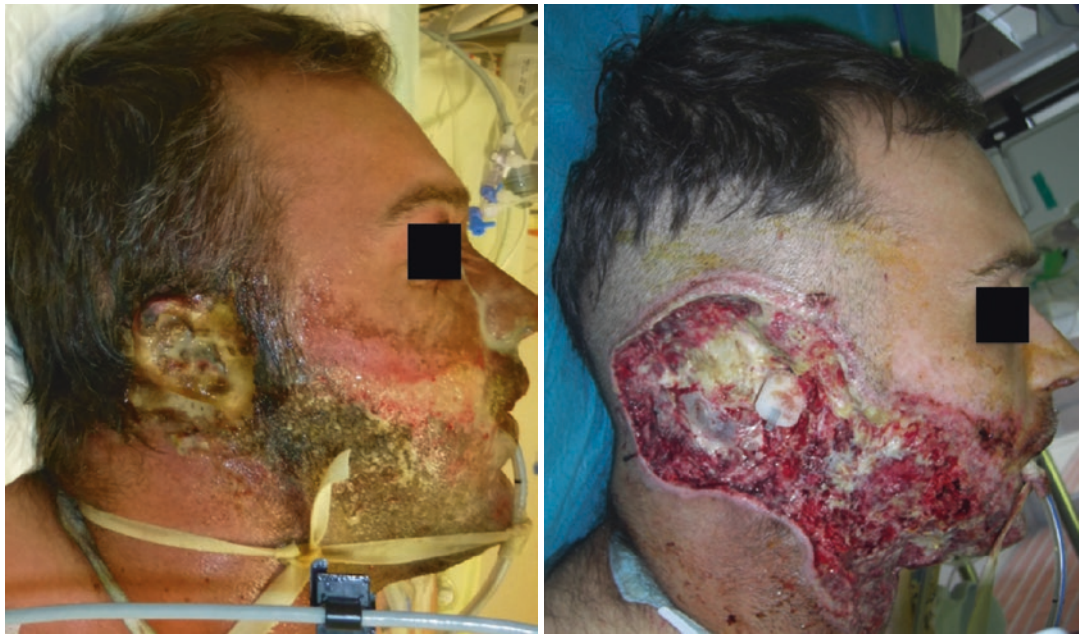

Fig. 6.3 Deep burn of the lateral side of the face due to a very high voltage electric arc

managed within 6 h of the injury [9]. Deep exploration is to be done while carrying out escharotomies and fasciotomies. Necrotic tissue should be removed; the damaged muscles and nerves have to be preserved if we consider a possible recovery especially after fasciotomy (Fig. 6.3).

Immediate flap coverage is recommended by many authors to limit devascularisation, but in emergency cases we think that it must be reserved for vital organs coverage [10]. Besides these situations, we believe that we must avoid to perform locoregional or free flaps before 3 weeks to allow time for oedema to decrease and promote drainage of all local toxins (free radicals, lactate) leached after the trauma. Immediate amputation is limited to extreme cases with anuria or shock; it will aim to keep a length always compatible with future equipment.

2. Second look
   It is carried out 2–3 days later. We have to spare the maximum of tissue (tendon, nerve, etc.) even if they fall in a grey zone. Skin coverage remains our priority; the damaged nerves will be repaired in a second time. Even if not widely practised, these interventions bring some interest as they will allow being less aggressive in the first surgery and opening a window for a new debridement of secondary necrotic tissue after the removal of the ischemia-reperfusion syndrome (when fasciotomy is performed). Ultimately, a third or a fourth revision is sometimes necessary to achieve complete debridement of large areas (Fig. 6.4).

   Furthermore, a polymicrobial infection of necrotic tissue can occur with plurimicrobiens processes often including anaerobes or *Pseudomonas aeruginosa*. Bacteriological samples are systematically taken and antibiotics are given as needed.

6.5 Global Management

This type of patients requires hospitalisation in specialised burn unit with experienced teams. Supervision by physiotherapists to limit retractions is necessary, but also the psychological side should not be neglected.

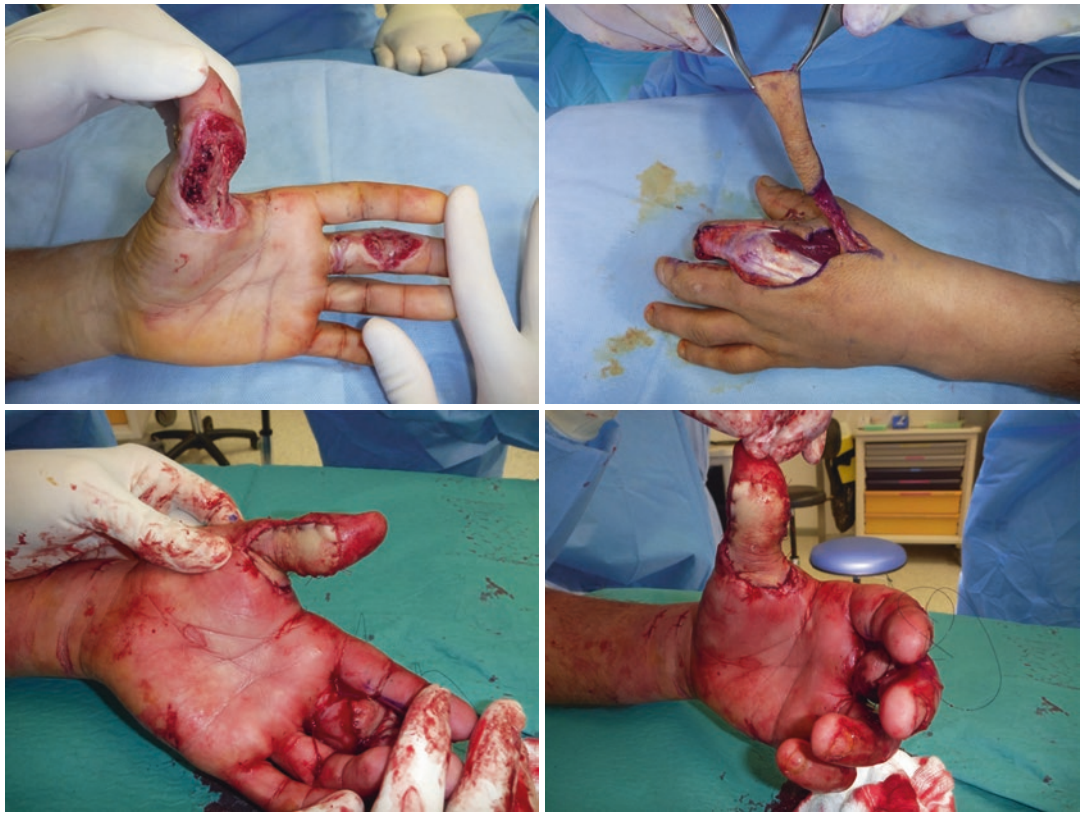

Fig. 6.4 Realisation of an island flap for the reconstruction of the proximal defect. Skin graft was used for the middle finger

It is indeed known that electrocution can have a psychological impact and even cause psychiatric diseases.

The final healing is often long and delayed. Thus, 3–4 weeks may be required to obtain granulation tissue after debridement and 2–3 months to hope for healing of the entry and exit skin points.

Conclusion

The electrical burns are rare but often severe. The initial management is dominated by the detection of deep lesions and the prevention of organ failure. Management of muscle injury is important for vital and functional outcomes; however, it remains very difficult to assess in the early days. Surgery is often delayed and should usually aim, after a second look, to restore the original anatomy and function. Cosmetic and functional sequelae will be supported later, usually at 18–24 months.

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Gunshot Wounds

7

Supaporn Opasanon and Apirag Chuangsuwanich

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7.1 Introduction

Gunshot wounds (GSWs) are one of the most fatal traumatic injuries. Bullets not only cause direct vital organ damage, but they can cause further problems from undermanagement of the wounds [1–3]. Soft tissue damage, foreign bodies, and bacterial contamination at GSW sites and along the wound tract are the factors that may cause infection and delay wound healing [4, 5]. After the Advanced Trauma Life Support (ATLS®) protocol [2] for life-threatening condition, GWSs should be managed thoroughly. In this chapter, we describe the updated knowledge and principle of GSW management.

7.2 Etiopathogeny

Gunshot causes tissue damages by disrupting the tissue, bleeding, and permitting entrance of infection [1–3, 6]. The mechanism of tissue injuries are mixed, blunt, and penetrating trauma injuries. For penetrating trauma, destruction of flesh tissue is due to passing of the bullet through it and the large amount of kinetic energy transferred to the tissue. Some blunt trauma is due to displacement of tissue adjacent to the track of the penetrating bullet. The bullet's shock wave may damage the adjacent structure. Severity of a bullet wound may be expressed by the formula $KE = \frac{1}{2}MV^2$. This formula expresses the amount of the energy transfer to the body by a bullet. Contusion and

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hemorrhage will occur. Increasing the velocity of the bullet will have more tissue destruction than increasing its mass. A bullet is not sterilized and may carry viable bacteria and clothing into a wound [4, 5].

7.3 Clinical Detailing

7.3.1 Characteristics of GSWs

Tissue destruction relies on the kinetic energy of the bullet. A high-velocity bullet causes more tissue damage than a low-velocity bullet. The anatomy of the wounds is also an important factor of severity:

1. *Cavity*
   Kinetic energy dissipates forward and laterally away from the bullet and pushes the surrounding tissue aside causing a cavity (Figs. 7.1 and 7.2). Entrance wound is round with abrasion ring and show soot deposition or blackening of the skin edge (Fig. 7.3). Stellate-shaped entrance wound may be found in near-contact shooting due to tearing of the skin from expanding gas (Fig. 7.4). Exit wound is typically larger and more irregular than the entry. If the path of the bullet is long, entrance and exit wounds may be small. Negative pressure may suck debris into the wound track.
2. *Abrasion ring (marginal abrasion, contusion ring)*
   Bullet indents the skin and abrades the margin of entrance wound.
3. *Crush and laceration*
   Direct laceration and disruption of the tissues occur along the track with any penetrating object and effects of gases.
4. *Secondary shock wave*
   Tissue damage may occur in the remote tissue caused by the kinetic energy of a high-velocity bullet which produces a shock wave.
5. *Skin burn*
   The bullet's kinetic energy is converted to heat. Heat is transmitted to the surrounding tissues.
6. *Bullet wipe*
   Lubricant and debris on bullet surface wiped off onto the wound edge.
7. *Smudging*
   Soot from partially burnt gases.
8. *Tattooing*
   Burning propulsive grains embedded in the skin.
9. *Retained foreign materials*
   GSWs penetrate the soiled clothing and introduce foreign bodies such as lubricant, debris, and bacteria into the wound track. They are the source of wound contamination. Retained wadding and bone fragment should be removed.

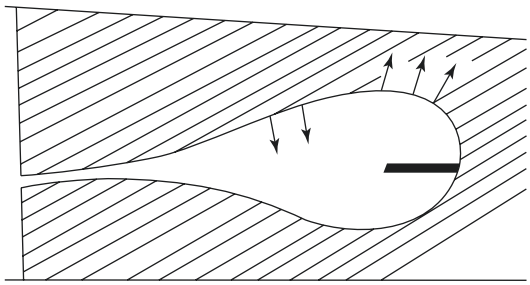

Fig. 7.1 Kinetic energy of the bullet dissipates in the wound track and another way, which causes damage outside the track

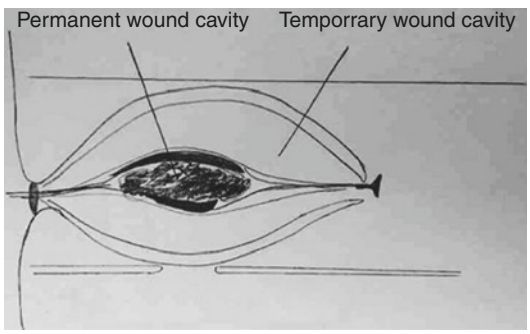

Fig. 7.2 The energy and heat expand explosively, causing a cavity in the tissue

7.4 General Principles of GSW Management

1. *Save life*
   - For initial management, ATLS protocol should be performed.

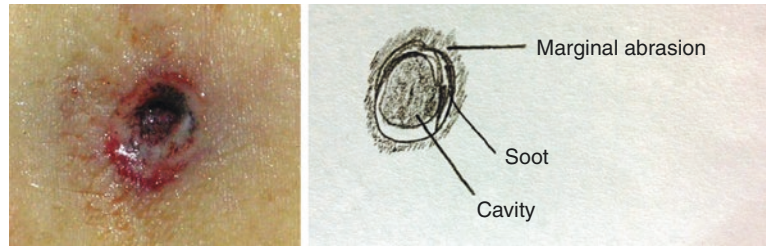

Fig. 7.3 Round entrance gunshot wound showing dark soot deposition with marginal abrasion

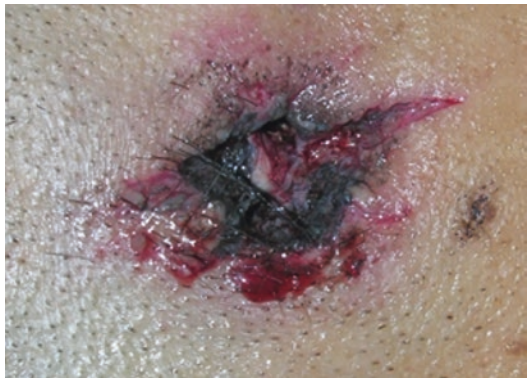

Fig. 7.4 Stellate-shaped entrance wound with soot

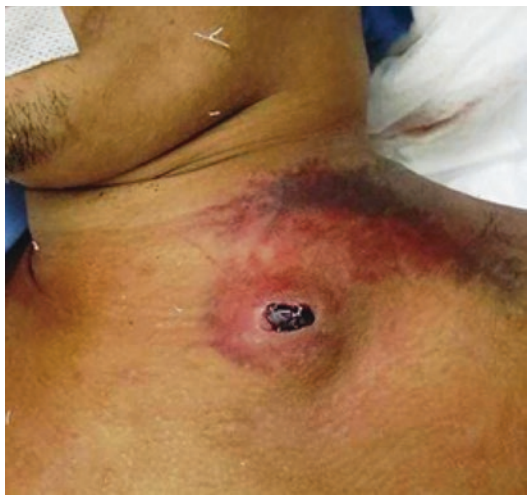

Fig. 7.5 Gunshot wound with hematoma

2. *Local wound care to prevent infection*
   - Control bleeding: Wound hematomas (Fig. 7.5) lead to infection [4].
   - Cleansing
   - Adequate debridement [4]: Debridement of all grossly nonviable tissues should be undertaken.
   - Remove foreign materials: soot, clothing, lubricant, and bone fragment.
   - Antibiotics [4]: Bullets are not sterile. Puncture wound is a risk factor for serious infection. Antibiotic prophylaxis is recommended in GSWs.
   - Tetanus immunization [4]: GSWs are at risk for tetanus, and the patient should receive tetanus prophylaxis.

7.5 Gunshot Wound Management

- *Initial dressing*
  Bleeding should be controlled with direct pressure. As always, GSWs should be treated as soon as possible in a hospital.
- *Wound surgery*
  "Treat the wound, not the weapon" is the key of GSWs management [7].
  – *Irrigation and debridement*
  Gunshot wounds are contaminated wounds and high risk of infection. Wound must be cleaned as much as possible. Wound irrigation with copious volumes of saline can reduce the number of bacteria in the wound. Soot and lubricant are removed. *High-pressure irrigation* may be as effective in removing contamination [4, 8].

  Adequate debridement is very important. Skin necrosis and damaged subcutaneous fat are removed by sharp debridement. *High-pressure hydrosurgery* [4] is one of the new debridement techniques. It is very effective to cut and debride the abrasion ring and laceration and clean bullet wipe. In addition, hydrosurgery is an easy method to clean the cavity wounds.

– *Dressing and closure*
Wound should be left open [4, 8]. Closing a contaminated wound can trap bacteria inside and lead to infection. Wide excision may be required to clear foreign materials. Moist saline gauze is inserted directly into the wound to allow drainage twice a day for the first few days or until there is no more fluid draining from it. Re-inspection at 72–96 h should be considered. After reevaluation, if there is no remaining fluid or other contaminants with no excessive loss of skin, delayed primary closure is accepted [4]. If the patient has deep cavity or large skin and soft tissue defect, flap reconstruction should be considered. The principle of wound management is to keep the wound environment moist [9]. *Hydrogel* supports autolytic debridement and provides a moist wound bed. It is a good choice for relatively desiccated wounds. Fluid in cavity wound can cause infection. Absorbent dressing is needed. *Calcium alginate* [9] and *hydrofiber* dressings are appropriate to control exudates. Alginates are available in rope form, which is very easy to apply in the cavity wound. An ionic-silver dressing is also a good choice for GSWs.
– *Instructions for special areas*
1. *A bullet wound to the head*
Bone fragment should be removed. It is easy to miss these in hairy parts of the body such as the scalp, axilla, and perineum, so careful examination is very important.
2. *A bullet wound to the face*
A good examination with attention to possible nerve damage and parotid gland and Stensen's duct injuries should be performed. The skin at the face is highly vascular and tends to heal better than other areas of the body. It can be sutured after good wound cleansing. In case of *through-and-through GSWs*, connecting between the skin and mucosa, such as the cheek and mouth, primary closure of mucosal wound must be done and thorough wound irrigation is recommended. Delayed primary closure of the skin may be considered.
3. *A bullet wound to the arm or leg* [8, 10]
Evaluation of injury to the neurovascular structures, muscle, and bone should be done. Massive debridement is required to clear the dead tissue, foreign material, and bone fragment. Close monitoring of compartment syndrome is mandatory. Hyperbaric oxygen therapy (HBO) [11] may help to reduce swelling and inflammation in pending case or use as adjunctive treatment. However complete fasciotomy is the primary treatment for compartment syndrome. Retained foreign material and inadequate debridement may lead to late infection.

Conclusion

GSWs can cause immediate life-threatening conditions that should be treated first followed by associated injuries. The severity of tissue damage depends on the bullet's kinetic energy and location of the wounds. Thorough wound evaluation, effective wound debridement, and prevention of infection are the principles of GSW management. Hydrosurgery with high pressure and hydrogel may be the tools for debridement with good outcome.

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Neonatal Pressure Ulcer

8

Christian Herlin

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8.1 Introduction

The structure of a premature newborn's skin is very different from that of the adult.

In the adult, the stratum corneum is composed of about 20 layers and has an important protective function. However, in the premature baby, this stratum is non-existent or minimal (0–3 layers). The thinness of these external layers is one of the principal sources of vulnerability (see Fig. 8.1).

The stratum corneum normally protects the body from toxins and infections, enables thermoregulation and controls transepidermal water loss.

In the premature newborn, in addition to the thinness of the external layers, there is also a lack of collagen and elastin in the superficial dermal layers. This considerably increases the risk of pressure ulcers, with spontaneous oedema increasing the cutaneous ischaemia.

In the hospital environment, the incidence of neonatal pressure ulcers (NPUs) is significant, affecting one in four babies in the neonatal intensive care unit (NICU) [1, 2].

Four per cent of babies who have been treated in a NICU are left with a scar [3]. In the majority of cases, these skin lesions are minor [4].

The significant incidence of NPUs in the NICU can be explained by the following risk factors [5]:

- The immaturity of the skin
- The restriction of the baby's voluntary movements (e.g. due to a central venous line, mechanical ventilation, etc.)

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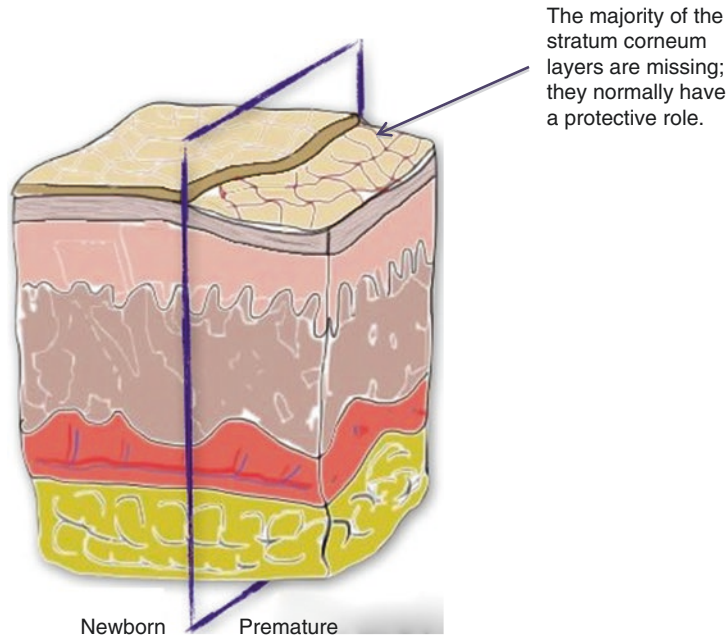


Fig. 8.1 Comparison of normal newborn and premature skin. The stratum corneum is absent or very underdeveloped in the premature skin

- The hot and humid environment
- The use or not of invasive ventilation

This chapter describes the main sources of pressure ulcers in the newborn and premature baby, their characteristic features, the therapeutic principles, and the potential sequelae.

8.2 Risk Assessment Scales

There are many different types of risk assessment scales, most of which have not been tested on a large scale. The Braden Q Scale [1] and the Neonatal Skin Risk Assessment Scale [6] seem to be reliable tools in terms of sensitivity and specificity.

8.3 Principles of Treatment

8.3.1 Topic Treatment

For Stage 2 pressure ulcers, the use of hydrocolloids seems to us to be appropriate in the majority of cases.

For Stage 3 and 4 pressure ulcers, treatment is very similar to that of the adult, but the possibilities available in terms of wound cleaning are often reduced as the baby cannot be moved.

Throughout the liquefactive necrotic stage, the use of silver sulphadiazine as an alternative to hydrogels seems to us to be a possibility. The dressings need to be substantial, thus allowing for additional discharge.

8.3.2 Surgical Treatment

It is reserved for severe cases. It uses the classic reconstruction ladder (skin graft, local and distant flaps). Taking account of the healing capacity of the newborn, the flap realization is often performed in a second step during infant growth.

8.4 Main Areas Affected

1. *The nose*

   The nose is the main area affected, representing half of all NPUs [5]. This has been seen since the 1980s, with the development of nasal continuous positive airway pressure (NCPAP).

   According to different studies, nasal lesion incidence is between 20 and 60 % in premature treated with NCPAP [7, 8]. The majority of occurrence is due to the technique being incorrectly used and/or poor monitoring of skin tolerance [9].

The pressure ulcer most often involves the philtrum, the tip of the nose, the soft triangle, or the nasal septum.

A deformation or a change in function results, which is usually temporary. However, cases have unfortunately been reported in which columellar necrosis has led to a significant disorder in growth.

Figure 8.2 shows a typical lesion due to excessive pressure from an endotracheal tube, which, in bending the soft triangle, has resulted in ischaemia.

Figures 8.3 and 8.4 show two similar cases of columellar necrosis, at different ages. In Fig. 8.4, note the asymmetrical character of the lesion and the consequences on the development of the tip of the nose.

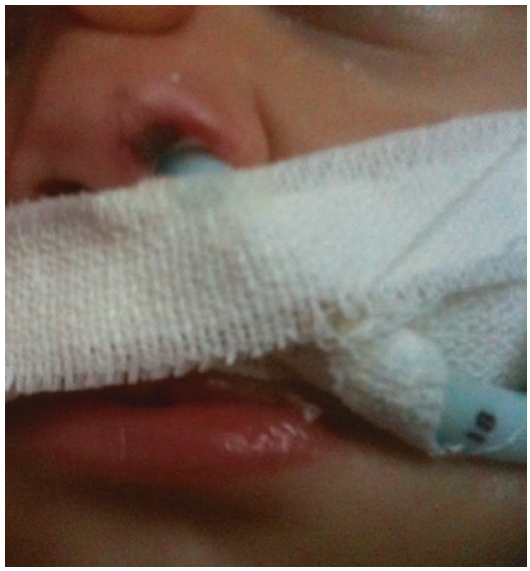


Fig. 8.2 Soft triangle pressure ulcer caused by excessive pressure from the endotracheal tube

2. *The foot and leg*

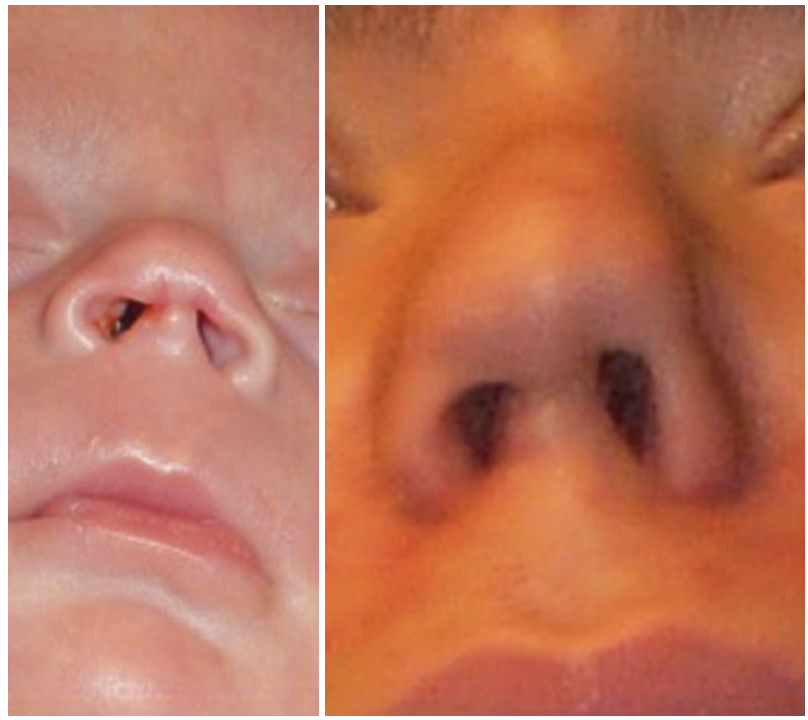
Here, the lesions are genuine pressure ulcers as seen in the bedridden or the paralysed. The main areas affected are the malleoli and the heels. Pressure ulcers have also been reported on the toes, due to the use of oximetry sensors. On the legs, they are often due to the premature use of postural splints.

These ulcers usually improve in a few days after removal of the pressure source and after mechanical or chemical debridement.

3. *The scalp and back*

The two main causes of scalp NPUs are birth trauma and excessive pressure on the occiput.

Scalp injuries are present in around 15 % of babies born using ventouse or forceps [7].



Figs. 8.3 and 8.4 Lesions linked to excessive pressure during NCPAP. The pressure ulcer especially affects the junction of the columella and the apex

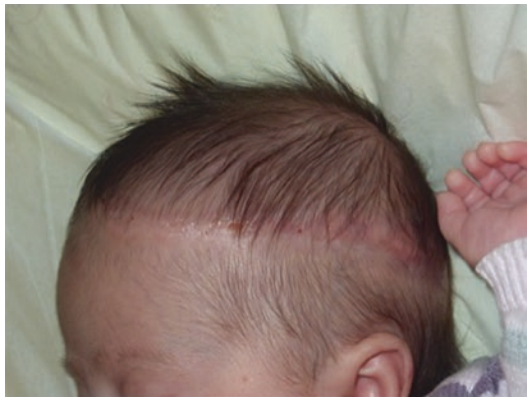


Fig. 8.5 Circular lesion caused by ventouse extraction

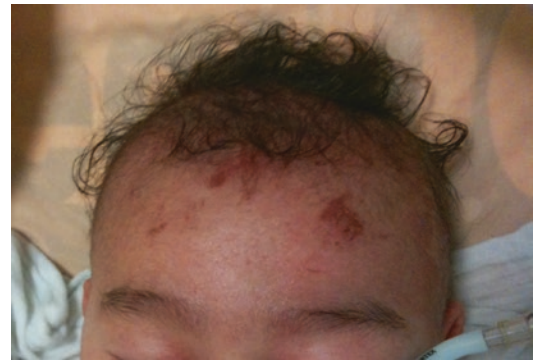


Fig. 8.6 Pressure ulcers on the forehead caused by EEG electrodes

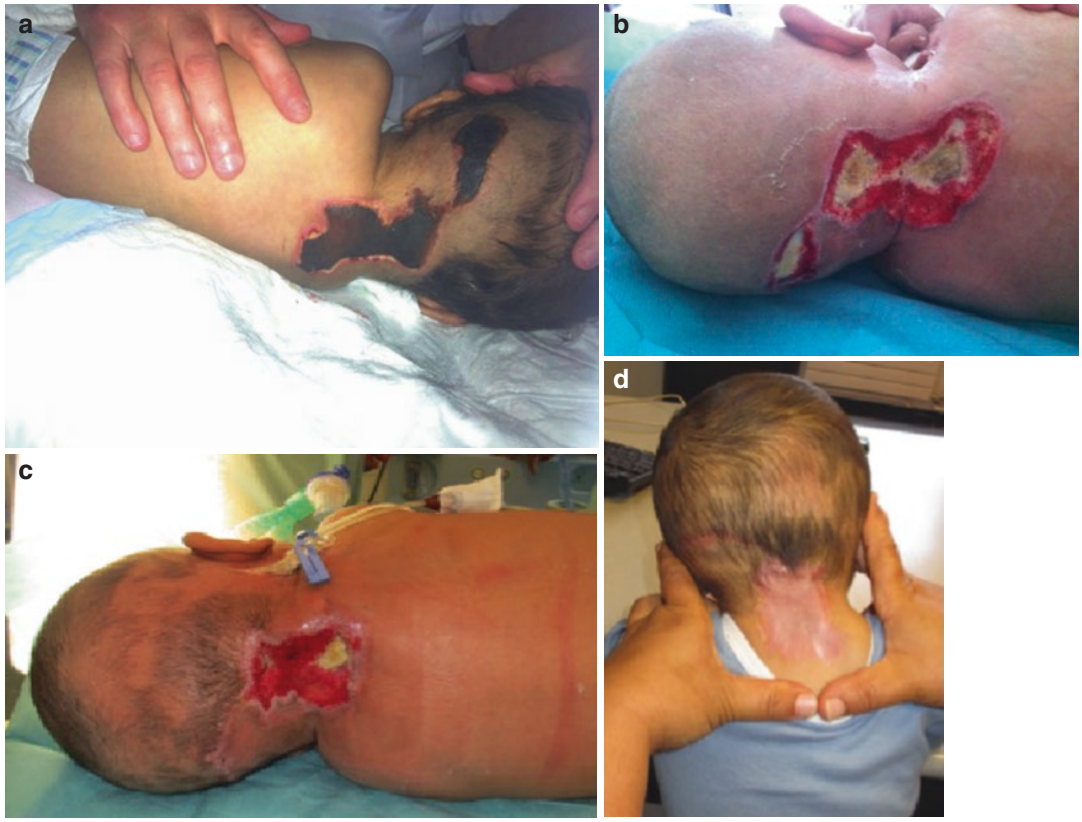


Fig. 8.7 (**a**) Extensive and deep pressure ulcer of the occipital and upper cervical region. (**b**) Result obtained after debridement and initiation of negative pressure therapy. The muscles and aponeurosis have been affected, with contact involving the cervical spine processes. (**c**) Closure of the superior area and repeated debridement (×5). (**d**) Results at 5 months after placement of artificial dermis and thin skin graft taken from the adjacent scalp

The lesions are often deep and semicircular, leaving a visible area of scarred alopecia.

Figure 8.5 shows a case of scalp lesion secondary to ventouse extraction, which affected a ¾-circular area. Wound healing was obtained after 3 weeks of closely supervised healing by secondary intention and involved additional surgical intervention.

Wound healing is usually attained in a few weeks under such supervision. Dressings need to be changed daily and use silver sulphadiazine or hydrogel.

There are other rare locations, which are nevertheless worth mentioning. The use of EEG monitoring equipment can cause pressure on the forehead; this can be a source of ulcers, which are sometimes deep. Figure 8.6 shows an example of lesions seen in intensive care which caused visible scarring.

In a recent study [5], pressure ulcers on the back of the head were found to represent 14 % of all NPUs.

Excessive pressure can cause occipital ulcers, which are sometimes extensive. They affect children in intensive care or recovery. Catastrophic situations can result from the combined risk factors of mechanical ventilation, sedation, a central venous line, humidity, the warmth of the incubator, and the baby's state of shock (see Fig. 8.7).

In the baby seen in Fig. 8.7, the pressure ulcer was due to prolonged excessive pressure in the context of major cardiac surgery, with prolonged low cardiac output. The child had not been turned because of its haemodynamic instability. Healing was obtained after surgical debridement in the intensive care bed, dressings using negative pressure therapy, followed by skin graft on a thin one-layer artificial dermis (Matriderm®). One part was closed without tension.

The result was not perfect (see Fig. 8.7d), but it enabled rapid coverage, without adhesion.

Conclusion

Neonatal pressure ulcers are specific entities which require special attention from neonatal care teams. The thinness of the stratum corneum makes the skin of the premature and nursing baby particularly vulnerable to pressure. During the critical maturation phase, care teams must remain alert to the possibility of pressure ulcer formation, especially in an environment which can encourage such ulcer development.

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Frostbite

9

Marc-James Hallam, S. Lo, and C. Imray

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Frostbite is defined as the injury sustained by tissues subjected to temperatures below their physiological freezing point (−0.55 C). The severity of a frostbite injury is related to the temperature, wind chill and the duration of exposure to that temperature, as well as the volume of tissue subjected to cooling. As a result a description of a frostbite injury is somewhat of an umbrella term used to describe wounds ranging from those with minimal tissue damage over small areas to substantial necrosis of entire limbs, necessitating amputation. Advances in frostbite management have improved the potential outcome in frozen injuries, and thus it is important that front-line medical staff can recognise and treat frostbite effectively [1].

9.1 Aetiology

Frostbite typically affects the extremities with 90 % of injuries affecting the fingers and toes although the nose, ears and external genitalia are

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Table 9.1 Aetiological factors predisposing to frostbite injury

Extrinsic factors	• Extreme cold exposure • Innapropriate clothing • Homelessness • Smoking
Systemic pathology	• Vascular/raynauds disease • Diabetes • Psychiatric illness • Previous frostbite injury
Pharmacologic	• β-blockers • Sedatives • Anxiolytics • Illicit drugs
Injury	• Head injury • Spinal cord injury • Multi-trauma • Injuries compromising circulation

also commonly affected [2]. Although historically it was most frequently observed in military personnel, there has been a shift over the last few decades with increasing numbers of civilians being affected. Modern epidemiological evidence suggests that high-risk groups still include those in military organisations but also the homeless, extreme sports enthusiasts, those in poor health, individuals intoxicated through drink or drug use and genetic susceptibility, e.g. people from warm climates (see Table 9.1) [1, 2].

9.2 Classification of Frostbite

There are a number of ways one can classify frostbite injuries, and the most commonly utilised classification is simply one of mild or severe injury, but the first predictive outcome classification was suggested by Cauchy et al. 2001 [3]. Cauchy's classification is based on anatomical location, radiotracer uptake on technetium scanning and skin blistering. This was based on a retrospective study of 70 frostbite patients presenting to the Department of Mountain Medicine in Chamonix, France (Table 9.2).

9.3 Pathology

A frostbite injury results both from the direct and indirect effects of freezing and pathologically is characterised by a continuum of overlapping pathological phases that ultimately cumulate in cellular ischaemia and necrosis of the affected tissues. These phases can be broadly divided into the following:

- Pre-freeze phase
- Freeze-thaw phase
- Vascular stasis phase
- Late ischaemic phase

9.3.1 Intracellular Effects

The direct effects of freezing are principally due to the formation of ice crystals within the tissues themselves. These crystals increase the oncotic pressure within the extracellular space, dehydrating cells via the osmotic movement of water out of the cellular membranes and disturb the intracellular homeostasis. With the rewarming of tissues, the crystals melt producing interstitial tissue oedema. Indirectly the freezing injury stimulates

Table 9.2 Predictive classification of frostbite injuries affecting the limb extremities

Severity grade	Lesion location (day 0)	Radioactive tracer uptake on bone scan (day 2)	Character of blistering (day 2)	Likely outcome
1.	Not visible	N/A	None	No tissue loss or long-term sequelae
2.	Distal phalanx	Hypo-fixation	Clear	Soft tissue loss with nail changes
3.	Mid-phalanx	Absence of uptake at phalanx	Haemorrhagic	Amputation of digit. Functional sequelae
4.	Carpus/tarsus	Absence of uptake at carpus/tarsus	Haemorrhagic	Extensive amputation with likely sepsis or thrombosis. Functional sequelae

Adapted from Grieve et al. [2]

the release of a variety of pro-inflammatory cytokines.

9.3.2 Extracellular Effects: The Freeze-Thaw-Refreeze Injury

Initial exposure to cold temperatures results in an immediate, localised vasoconstriction. This may sometimes be followed by a transient vasodilatory reflex known as the "hunting response", or cold-induced vasodilatation. This physiological reflex results in a redistribution of flow from the core and is thought to be a primitive reflex to protect the extremities from freezing. Ultimately this results in a drop in core body temperature and furthermore is ineffective in protecting the peripheries against extreme cold stress. The reduced blood flow secondary to vasoconstriction in turn further exacerbates localised cooling producing a vicious cycle of ever-increasing vasoconstriction and tissue cooling. An oedematous state results through a combination of increased plasma viscosity, microvascular damage and fluid migration. The microvascular (endothelial) damage produces a pro-thrombotic environment through activation of the clotting cascade in which microthrombi form, occluding the capillaries, resulting in ischaemia. When such a time as tissue rewarming occurs, further microvascular clot occlusion occurs due to the promotion of a pro-thrombotic state through the lysis of frozen cells. Local mast cells degranulate in response to the lytic cell membranes, releasing histamine which further increases vascular permeability and oedema. The end point of all of these processes is potentially devastating local tissue ischaemia, and as first noted by Baron Larrey, Surgeon General to Napoleon, the most significant ischaemia, and therefore tissue necrosis, is seen in injuries that freeze, thaw and are then frozen again.

9.3.3 Long-Term Sequelae

It should also be appreciated that aside from these immediate-type effects seen following a freezing injury, there is also long-term pathological damage sustained by tissues which may result in chronic dysfunction or impact upon the patient many years post-injury. Although rare, one of the most serious observed syndromes is probably related to chronic vasomotor dysfunction, manifesting clinically as chronic pain affecting the previously frostbitten area that is often unresponsive to conventional analgesia and requires anaesthetic or pain specialist input. Those that develop these complex regionalised pain syndromes frequently also suffer with associated problems such as paraesthesia and cold intolerance. It should also be noted that all patients who have experienced frostbite are at increased risk of further

future episodes (presumably again secondary to vasomotor dysfunction) and all patients must be warned of this and given appropriate preventive advice. More serious long-term sequelae of frostbite that have been reported include the malignant transformation of frostbitten tissues and bone and joint pathologies including osteoporosis and arthritic changes [1].

9.4 Clinical Evaluation of Frostbitten Patients

9.4.1 History

Critical details of the patient history include the likely temperature, duration and timing of exposure, as this will help predict the severity of injury and may affect subsequent management. It is also important to obtain information relating to the patient's premorbid state such as peripheral vascular disease and pertinent risk factors such as smoking or the use of β-blockers.

9.4.2 Examination

In rare cases frostbite injuries may present as a purely uniform frozen injury, but more frequently there is a mixed clinical picture with overlapping areas between deeper frozen tissues and more superficial nonfrozen tissues. Even in the case of a purely frozen injury, there is much variation in severity from the lesser affected forms (frostnip) to large areas of frozen tissues or indeed whole limbs.

It can be seen that frostbite presents in variable fashions and the injury evolves with time, and thus one is often unable to determine the full or likely extent of injury for some time after the injurious cooling from clinical examination alone, illustrating the importance of a thorough history. Nonfreezing injuries may be managed locally without the need for specialist intervention, and they typically follow a short exposure to (relatively) warmer temperatures and involve the feet most commonly with patients complaining initially of localised numbness and or paraesthesia. As the tissues rewarm severe pain is experienced with the rapid onset of a reactive hyperaemia and tissue oedema. The pain is usually transient but may become chronic with patients suffering long after tissues have recovered. Actual tissue loss is uncommon in these cases with most injuries only exhibiting mild discolouration, and very occasionally small areas of watery blisters may develop.

Any potentially serious frostbite injury however must be discussed with a suitably experienced unit for consideration of patient transfer, especially if the patient has presented less than 24 h post-injury as they may be a candidate for thrombolytic therapy.

9.4.3 Radiological Investigations in Frostbite

Due to some of the difficulties outlined in accurately assessing the initial severity of tissue devitalisation in frostbite injuries (hence avoiding early surgical debridement), a variety of radiological investigations have been suggested as clinical assessment adages. It is important to appreciate however that no radiological investigation is currently predictive in isolation and these studies are designed only to augment clinical opinion in cases that may be unclear.

Many investigations have been suggested over the years to image frostbite injuries, but the most clinically useful appear to be technetium 99 (Tc-99) triple phase scanning and magnetic resonance angiography. There is convincing evidence from a large retrospective review of 92 patients with severe frostbite injuries that Tc-99 scanning in the first few days can predict the subsequent level of amputation in up to 84 % of cases [4]. However further large-scale studies are required in this area, and currently there is little role for complex imaging in routine and less severe frostbite cases. Possible exceptions to this include severe injury with early presentation and no associated traumatic injuries, those rare cases where early surgery is being undertaken, or if thrombolytic therapy is being considered.

9.5 Acute Frostbite Management

9.5.1 Prioritisation of Life-Threatening Injuries and Specialist Referral

It is vital to appreciate that patients presenting with frostbite frequently present with coexisting severe and life-threatening emergent conditions such as hypothermia or significant traumatic injury. In line with the management of any emergency situation, such coexisting morbidities must be treated and stabilised before commencing treatment or transferring a patient to an expert centre for localised frostbitten tissue(s). Hypothermia should be corrected and core temperature should be raised to 34° [2] In any case, frostbite injuries often occur in remote regions where transfer or access to expert centres is not immediately possible and immediate management must be commenced locally. In today's technologically advanced age, those treating frostbitten patients can seek expert advice through the use of satellite phones and the Internet; indeed, many remote facilities rely on such technology.

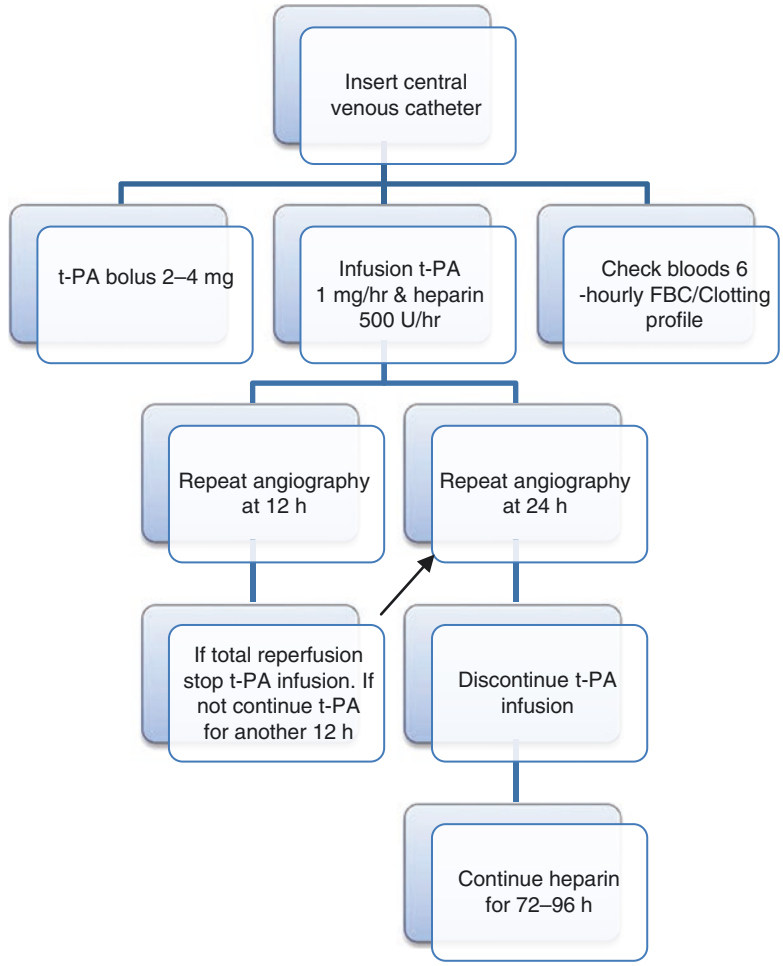
9.5.2 Prevention of Refreezing and Differential Approach to Rewarming

It is also imperative that rewarming of the locally frostbitten tissues must only be commenced once there is absolutely no risk of refreezing as this will result in further tissue damage; similarly it is advised that frostbitten tissues should not be rubbed or massaged for similar reasons. Once a patient with a frozen injury has been secured in a safe environment and any emergent conditions stabilised, directed therapy can be commenced. In such injuries (be they minor areas of freezing or more extensive), the principal goal of treatment is to rapidly rewarm the affected area in a water bath with an antiseptic agent such as chlorhexidine in an attempt to preserve the dermal circulation. State of Alaska guidelines suggest a warming bath of 37–39 °C, whilst others suggest 40–41 °C [1, 5]; in practice, especially if in the field, it is nearly impossible to maintain exact water temperatures and the critical factor is that the water should be warm, not hot, as the tissue will be neuropathic and one must avoid scalding. The rewarming should continue for a minimum of 30 min or as long as necessary for all affected tissues to be defrosted, thoroughly rewarmed and pliable exhibiting a deep-red or purple colour, carefully monitoring the water temperature throughout. This 30 min regime of rewarming should be repeated at twice-daily intervals until such a time that there is either evidence of tissue regeneration or clear demarcation of necrotic tissues, and the tissues should be kept warm and dry during in-between periods. There are a variety of commercial whirlpool or foot spa devices suitable for this purpose. It should be noted that a differential approach to rewarming is used in true frozen injuries in comparison to milder, nonfrozen cases. Milder cases should be warmed more slowly at normal room temperature, as rapid rewarming may exacerbate injury.

9.5.3 Pharmacological Support During Rewarming

Patients with frostbite require pharmacological support with respect to analgesia, vasodilatation and antibiosis, but certain caveats apply to the drugs that should be used and those that should be avoided. The rewarming of frozen tissues is frequently accompanied with severe pain and all patients must therefore be provided with judicious amounts of analgesia. Analgesia should always, where possible, include ibuprofen due to its selective anti-prostaglandin activity which may improve tissue perfusion in addition to providing analgesia. Some authors have recommended avoiding aspirin-based analgesia as it irreversibly blocks prostaglandin function and some vasodilatory prostacyclins, which may be beneficial in the healing wound [6]. Regarding vasodilators, surgical sympathectomy used to be used routinely but has now been superseded by vasodilatory drugs such as iloprost. Iloprost should be infused over a 5-day period in an appropriate high-care facility that is capable of performing regular (at least every 30 min) patient observations. Most units have locally approved infusion protocols for

Table 9.3 Treatment algorithm for t-PA infusion



Adapted from Bruen et al. [7]

iloprost but a suggested regime is to commence a 10 ml/h infusion of 100 mcg iloprost in 500 mls 0.9 % saline. The dose can then be titrated up incrementally to a maximum of 50 mls/h or until there are observed side effects and should be run over a period of 6 h in any one day. Necrotic or devitalised tissues are at risk of infection which may secondarily worsen tissue damage, and prophylactic broad-spectrum antibiotics, such as co-amoxiclav, should be administered together with tetanus vaccination where appropriate.

Thrombolytic therapy (see Table 9.3) with tissue plasminogen activator (t-PA) aims to lyse the multiple small intravascular thromboses that occur during the vascular stasis phase of frostbite and restore perfusion to the affected area, improving tissue survival. The use of t-PA reduced amputation rates from 41 to 10 % in a study when administered within the first 24 h of injury [7]. Treatment with thrombolytic agents is not without risk (severe haemorrhage) and thrombolysis should only be reserved for patients presenting with severe frostbite within 24 h of injury and without any contraindications to treatment such as concurrent traumatic injuries. This form of treatment should only be considered in

facilities that are equipped with high-dependency care facilities and are familiar with caring for patients undergoing thrombolytic therapy. Aside from the risk of associated major haemorrhage, the restoration of perfusion following thrombolysis to a limb may cause a compartment syndrome (secondary to oedema from damaged capillaries), and the requirement for prophylactic fasciotomies must always be considered. The vasodilatory agent iloprost has been shown to be a suitable alternative to t-PA in a randomised controlled trial [8]. Cauchy et al. randomised 47 patients with frostbitten digits to receive either buflomedil, iloprost or iloprost + t-PA treatments following rewarming and antiplatelet therapy. Results showed that the risk of amputation was significantly lower in the iloprost and the iloprost + t-PA groups compared with the group that received buflomedil alone. No evidence was gained to suggest superiority of either treatment, and the study recommends that prostacyclin (iloprost) be used in patients with severe (grade 3) frostbite and the addition of t-PA be reserved for severe (grade 4) frostbite [8].

9.6 Post-thaw Frostbite Care

9.6.1 Management of Blisters

Areas subject to a freezing insult will frequently exhibit blistering, and a clinical decision must be taken as to the management of such areas. Generally speaking small blistered areas that are not tense with clear fluid should be left intact as de-roofing these blisters may increase susceptibility to opportunistic infection. Blisters are sterile until they burst, and immunoglobulins have been shown to be present in blister fluid [9]. However in most circumstances, more extensive areas of tense blistering or haemorrhagic blisters should be carefully de-roofed in aseptic conditions by a specialist. In rare cases where the patient is at particular risk of opportunistic infection, such as in dirty wounds, or if the patient is known to be colonised with as resistant organism, then it may be appropriate to leave all blistered areas intact to reduce the risk of a potentially devastating tissue infection, and all such cases must be discussed with a specialised unit. Topical aloe vera is a commonly suggested therapy in minor frostbite cases due to its anti-prostaglandin actions, and whilst there is little evidence to recommend its use, it may be considered in minor cases [1, 2].

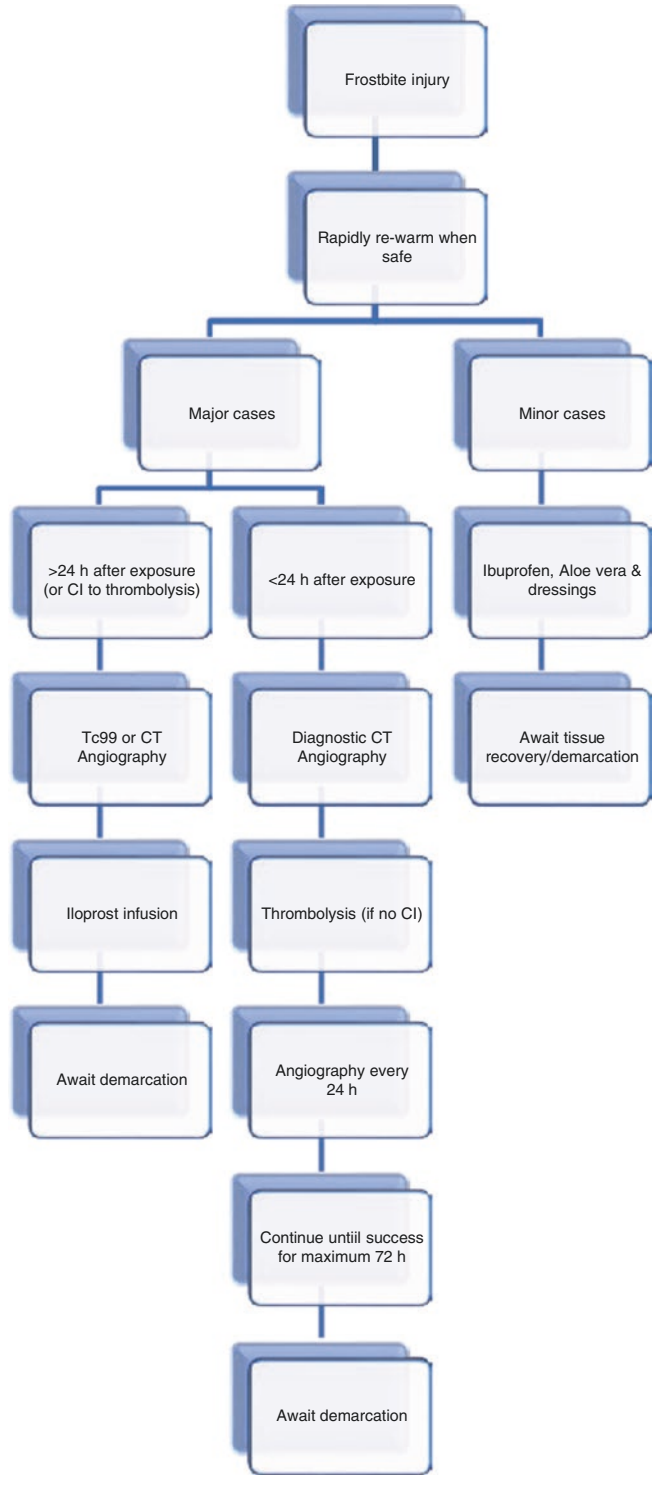
9.6.2 Physiotherapy Protocols

Regardless of the clinical appearance, the affected area needs to be elevated in order to reduce venous stasis and tissue oedema. Similarly, all affected tissues will be fragile and easily disrupted through even gentle mechanical stresses; thus, all lower limb injuries must be placed on a strictly non-weight-bearing status to protect against ischaemia. These measures are designed to prevent extension of injury through progressive tissue oedema, thrombosis and ischaemia, and frequently areas that initially appeared non-salvageable will recover.

9.6.3 Surgery

Early surgical debridement of frostbite injuries is nearly always contraindicated, as the reversibility and progression of the frostbite injury cannot be quantified in the early stages. Debridement is best delayed until definitive demarcation of devitalised tissues at approximately 6–8 weeks post-injury. With appropriate management surgery is frequently not required, despite the initial appearance of the injury. Similarly it may be appropriate to leave demarked areas to autoamputate if expert surgical input is not available or if the patient has substantial co-morbidities making anaesthesia unsafe. Exceptions to this conservative approach to surgery include injuries with uncontrolled severe infection, concurrent severe limb trauma and compartment syndrome, all of which may require urgent limb surgery. Fortunately, these are infrequent and are more commonly seen in freeze-thaw-refreeze injuries (Table 9.4).

Table 9.4 Treatment algorithm for frostbite injuries



Adapted from Hallam et al. [1]

9.7 Summary Points

- Prevention is paramount.
- Treat any serious or life-threatening conditions as a priority.
- Do not rewarm frozen tissues until there is no risk of refreezing occurring.
- Rewarm nonfreezing cold injuries slowly in air.
- Rewarm freezing cold injuries at 37–39 °C or 40–41 °C in a whirlpool device or foot spa for minimum 30 min with a mild antiseptic, and continue treatment twice daily until improvement is seen.
- Any patient with actual tissue loss should be given empirical broad-spectrum antibiotics.
- Discuss all significant cases with a specialised unit.
- Consider treatment adjuncts such as thrombolysis following discussion with a specialised unit.
- Avoid early surgical debridement.

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How to Manage Radiation Injuries

10

Chikako Murakami-Senju, Masaki Fujioka, and Sadanori Akita

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10.1 Introduction

Complex chronic ulcers due to irradiation are sometimes seen in patients who have undergone radiation therapy for malignancies or X-ray fluoroscopic procedures for ischemic heart disease. These undesirable complications bring continuous distress for the patients and decrease their quality of life.

Radiation-induced ulcers are difficult to treat because of the poor state of the wound bed. Radiated tissues result in insufficient vascularity and tissue damage, leading to erythema and dermal atrophy, which leads to tissue necrosis, infection, and later fibrosis, characteristics of chronic radiation injury syndrome [1].

Radiated wounds are treated with adequate debridement both in depth and in width and by resurfacing with well-vascularized tissues or by stem and regenerative cells [2].

10.2 Ionizing Radiation

Ionizing radiation causes damage to tissue by means of energy transference. The primary targets of damage are cellular and nuclear membranes and deoxyribonucleic acid (DNA). The most sensitive cells are those that divide rapidly, such as cells of the skin, bone marrow, and gastrointestinal tract. The morbidity from radiation depends on the dose received, time over which the dose is received, volume of tissue irradiated, and quality or type of radiation [3].

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Stage/symptoms	Dose range (Gy)	Time of onset (d)
Erythema	3~10	14~21
Epilation	>3	14~18
Dry desquamation	8~12	25~30
Moist desquamation	15~20	20~28
Blister formation	15~25	15~25
Ulceration (within skin)	>20	14~21

Table. 10.1 Diagnosis and treatment of radiation injuries (IAEA [4])

Table 10.1 shows the dose range and time of onset of clinical signs when the skin has been exposed to γ radiation or high-energy X-rays.

Time of onset of clinical signs of skin injury depends on the dose received.

10.3 Radiation Ulcers

Radiation treatment causes endothelial damage and fibrosis, leading to impairment of vascular and lymphatic flow. This impairment produces hypoxic, hypocellular, and hypovascular tissue, which is unable to maintain normal tissue turnover, resulting in tissue necrosis, infection, and ulceration [5].

Dry and moist desquamations are skin clinical manifestations of the keratinocyte mitotic death, and necrosis is the consequence of manifestations of tissue subcutaneous structures such as the muscles, vessels, and sometimes even bone [6].

10.4 Management of Radiation Ulcers

10.4.1 Debridement

Local wound care with standard wet or wet-to-dry dressings is rarely successful in promoting satisfactory debridement, cleansing of the wound, and subsequent growth of supported granulation tissue.

Radiation ulcers frequently progress and become much worse over time. The underlying ischemia sets in motion a cycle of infection and necrosis, leading to the development of additional ulcers in the surrounding tissue and finally to frank gangrene. Debridement of all nonvital tissue is required at the first stage of treatment. When the damage extends deep into the muscles or bones, extensive debridement should be done [7].

10.4.2 Methods of Wound Closure

10.4.2.1 Surgical Treatment

Radiation ulcers will not heal by aggressive medical wound management. Skin grafts and local cutaneous flaps located within the radiation field are unreliable and rarely provide adequate stable coverage because of the poor state of the wound bed. Salvage surgery with musculocutaneous flap is the recommended method to heal these complex wounds.

Case 1

A 77-year-old female underwent an unknown quantity of radiation treatment due to breast cancer after ablation of the tumor. Chronic chest ulcers, which formed fistulae penetrating to the rib, were observed. Intraoperative examination of surgery showed necrotic ribs, which were ablated with the parietal pleura. The pleura was restored using artificial substances. The radiation ulcer was reconstructed without disturbance of shoulder movement.

Necrotizing rib was exposed (Fig. 10.2a). After debridement, the pleura was restored using artificial substances (Fig. 10.2b). Latissimus dorsi musclo-cutaneous flap transfer from the back (Fig. 10.2c). Six months after the surgery, the wound was resurfaced (Fig. 10.2d)

10.4.2.2 Stem Cell Therapy

Autologous adipose-derived regenerative cells (ADRCs) are high yielding and contain several types of stem and regenerative cells, including adipose-derived stem (or stromal) cells (ADSCs) and endothelial and smooth muscle cells and their progenitors and preadipocytes [8]. The ADRCs have the capacity to differentiate into multiple lineages and cell types, including mesodermal tissues such as fat, bone, cartilage, endothelial cells of endodermal origin, and neurons and epidermal cells of ectodermal origin, as seen in the mesenchymal stem cells [9, 10].

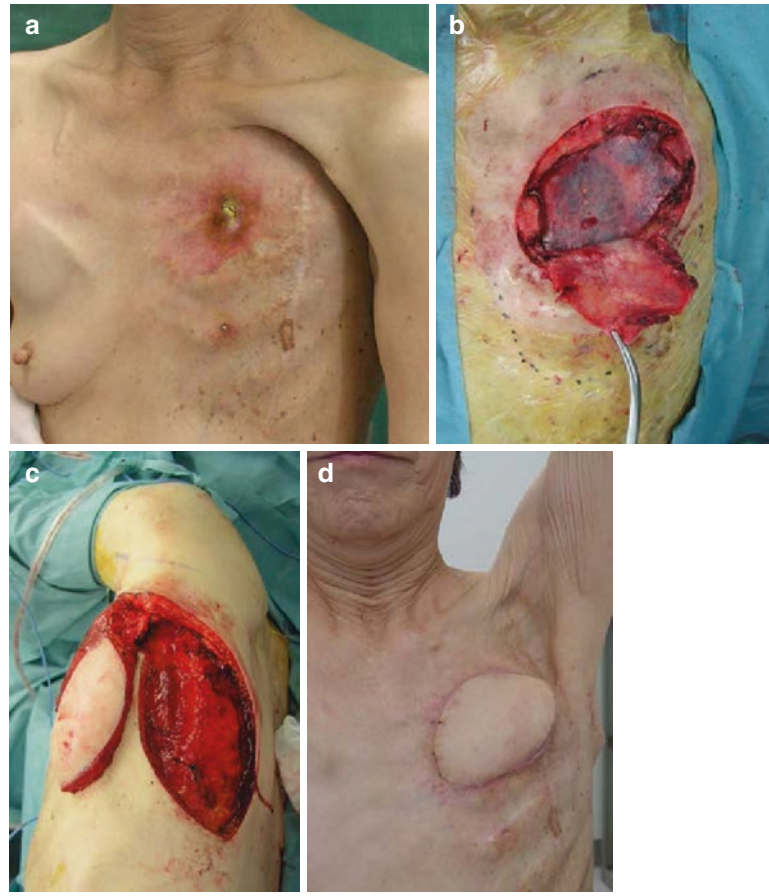

Fig. 10.2 A 77-year-old female underwent an unknown quantity of radiation treatment due to breast cancer after ablation of the tumor. Necrotizing rib was exposed (Fig. 10.2a). After debridement, the pleura was restored using artificial substances (Fig. 10.2b). Latissimus dorsi musclo-cutaneous flap transfer from the back (Fig. 10.2c). Six months after the surgery, the wound was resurfaced (Fig. 10.2d)

Case 2

A 52-year-old female was suffering from intractable chronic radiation wounds. The thyroid cartilage was exposed, and the carotid artery was adjacent to the exposed cartilage. After surgical debridement, the size of the defect was 25×17 mm and reached partially to the left thyroid cartilage. ADRCs were injected into the debrided wound margin and in the wound base. At 75 days after surgery, the wound had healed completely. Six months later, the injected subcutaneous lesion maintained its soft texture and demonstrated thick and vascularized soft tissue (Fig. 10.3).

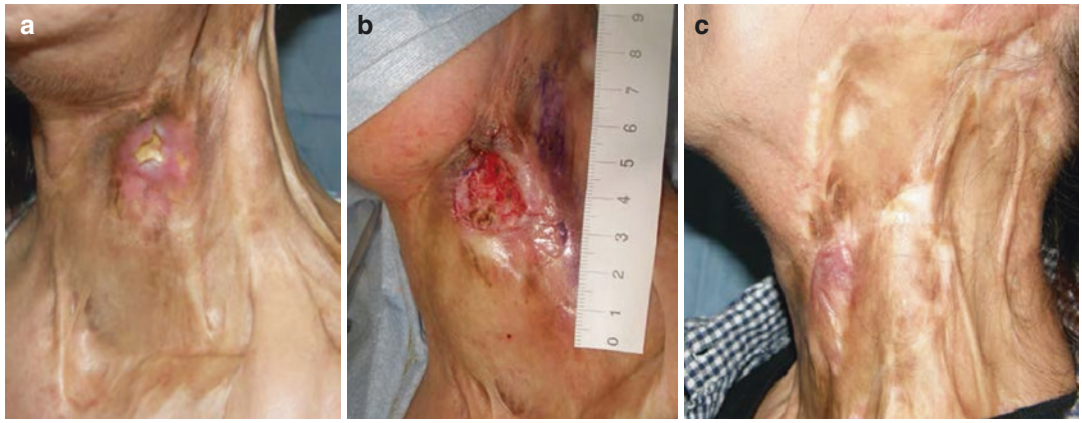

Fig. 10.3 (**a**) The thyroid cartilage was exposed during neck radiation injury. (**b**) After debridement, the wound defect was 25 × 17 mm. (**c**) Two months after the surgery, the wound was resurfaced

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Pressure Necrosis in Geriatric Patients

11

Joyce Black

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11.1 Background

The elderly remain one of the highest at-risk populations for pressure ulcers, with about 70 % occurring in individuals over the age of 70 [1, 2]. The incidence of pressure ulcers in the elderly population varies by care setting, but evidence on risk factors indicates that age will increase the probability of pressure ulcers, particularly in patients with limited mobility [3–5].

11.2 Etiology/Pathophysiology

Pressure ulcers are aptly named because they develop due to pressure. Pressure is a static, direct compressive force on tissue leading to hypoxia of the skin and soft tissue by restricting blood flow. When pressure reaches magnitudes that deform cells, the resulting injury is classified today as deep tissue injury, in that the pressure was applied to the deep tissues (muscle, fascia) and deformed the cells leading to their death [6, 7]. Pressure of less magnitude and of long duration creates tissue ischemia. Ischemia of tissue also leads to necrosis, but the mechanism is due to depletion of oxygen and glucose and accumulation of lactic acid [8].

The time needed to create ischemia in soft tissue and skin which leads to necrosis is elusive. In an ischemic animal models, 70 % of cell viability remained for over 22 h. In contrast, cell deformation which would lead to deep tissue injury was

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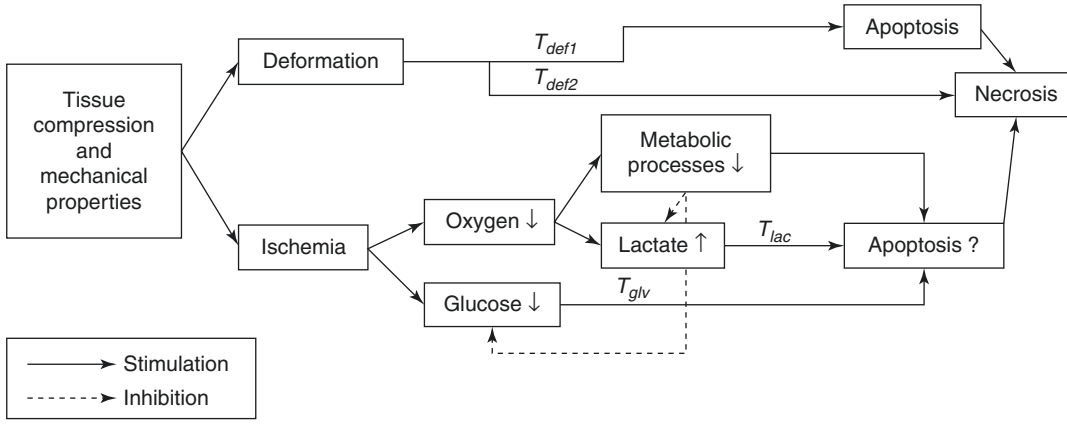


Fig. 11.1 Model of proposed sequence of events leading to necrosis of tissue. Deformation of tissue leads to damage when the threshold is met (T def 1) and cells will start a programmed cell death leading to necrosis. If the deformation of the cell exceeds its tolerance, the cells will die immediately from necrosis. Cells can also be injured from ischemia, reducing the metabolic substrates needed and leading to anaerobic metabolism and accumulation of lactic acid. Both cellular starvation and acidification lead to apoptosis and cellular necrosis (From Stekelenburg [16])

evident within the hour [9] (see Fig. 11.1). Of the various tissues that are at risk of death due to pressure, muscle tissue is damaged first, likely because of its increased need for oxygen and higher metabolic requirements. By the time ulceration is visible in the skin, significant damage of underlying muscle may already have occurred. The tissue fed by the vertical perforators through the muscle remains viable for a while; a series of cases showed the first sign of skin injury from intense pressure was apparent 48 h after the pressure was applied (Black J, The natural history of deep tissue injury pressure ulcers, 2002). An additional finding from this case series is that patients who sustained deep tissue injury were not aware of the ischemia; they were unconscious.

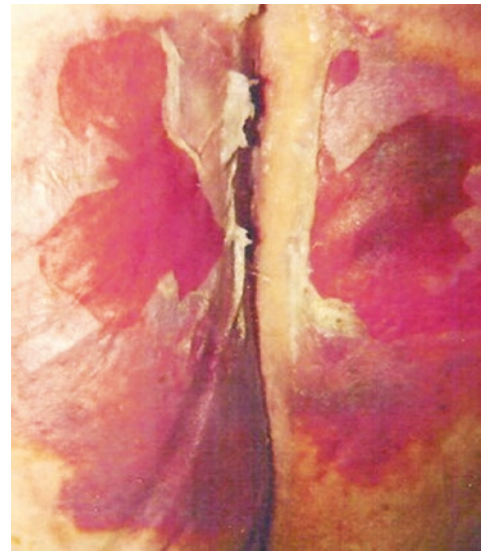
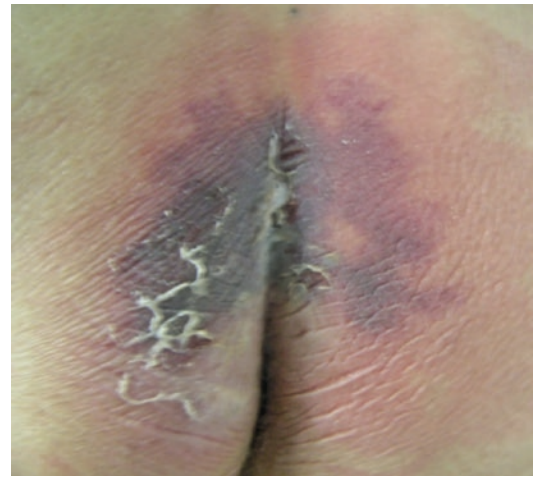
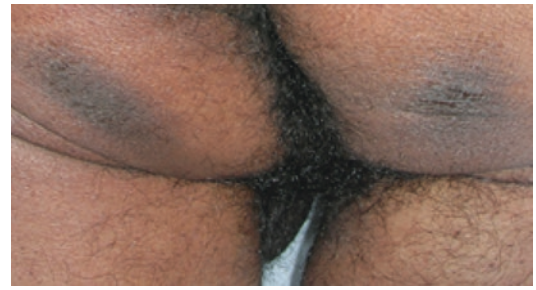
Restoration of blood flow to an ischemic area of tissue, or reperfusion, has recently been suggested as a cause of more damage to the injured area, causing a pressure ulcer to enlarge or fail to heal. One mechanism of harm to tissue may be from reduction in capillary density from repeated loading and unloading along with ischemic insult [10]. The time to develop necrosis is reduced in patients with impaired circulation, such as those with peripheral vascular disease or hypotension.

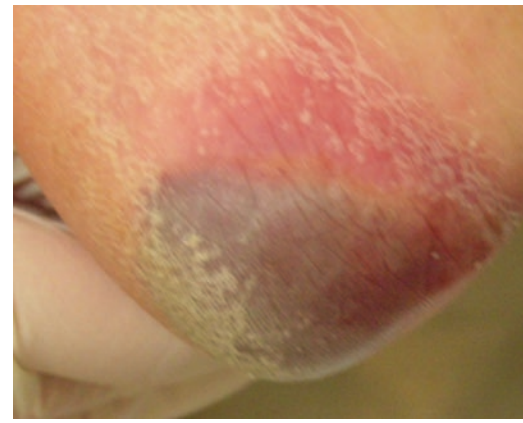
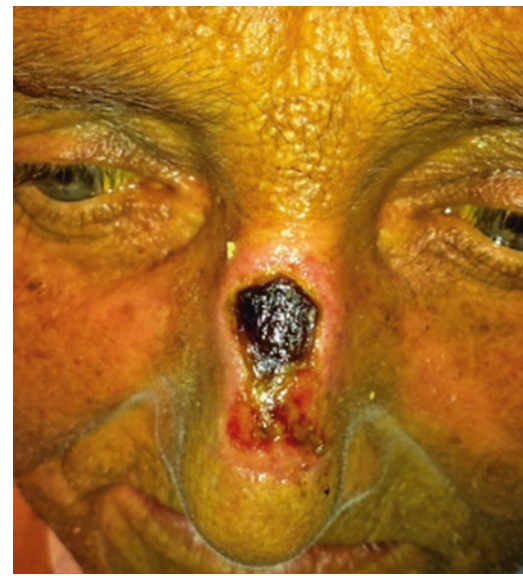
Shear is also a cause of pressure ulcers and undermining in existing ulcers. Shear is a tangential (angular) force associated with movement, for example, sliding down in bed or being pulled over to the side of the bed. Shear forces distort blood vessels in the skin, making the effect of pressure more deleterious because the tissue is already hypoxic. Research has shown that positioning a patient at 45° head of bed elevation leads to the most detrimental combination of pressure and shear on the sacrum, because the shear stresses combined with pressure cause greater obstruction and distortion of capillaries in skeletal muscle around bony prominences than does pressure alone [11].

Microclimate, the moisture and heat of the skin, increases the risk for pressure ulcers because the moisture macerates the skin. The boggy skin does not glide against bed sheets and leads to superficial tissue injury. Skin exposure to urine or stool also injures the skin and increases risk of tissue damage from pressure and shear. Gefen [12] has provided a recent theoretical explanation of the ways in which a changing microclimate may influence the development of superficial pressure ulcers. From a mathematical model, Gefen postulated that four microclimate changes may influence pressure ulcer development – increases in skin temperature, increasing ambient temperature, increasing relative humidity, and decreasing the permeability of sheets or clothing.

11.3 Differential Diagnosis

Pressure necrosis appears on tissue that has been subjected to intense pressure in patients who cannot feel the pressure or respond to it and change positions. High-risk patients and the common locations for pressure necrosis are as follows:

Position	Common location of pressure necrosis	Example pressure necrosis leading to deep tissue injury
Flat in supine position (e.g., during surgery, hypotensive)	Buttocks tissue, unless patient is quite thin, with no buttocks tissue Necrosis appears bilaterally	
Supine with head of bed elevated 30–45° or slouching in a chair	Sacrum and adjacent buttocks tissue	
Sitting erect in chair	Ischial tuberosities	

Position	Common location of pressure necrosis	Example pressure necrosis leading to deep tissue injury
Supine with heels on the bed	Posterior heel in patients with immobile legs, neuropathic legs, or peripheral vascular disease	
Wearing medical devices that are tight	Bridge of the nose from noninvasive positive pressure masks, behind the ears from oxygen tubing, shin, top of foot, and along Achilles tendon from stockings	

Differential Diagnosis

Abscess
Bruising
Cellulitis
Critical limb ischemia
Fournier's gangrene
Hematoma/Morel–Lavellée lesions
Incontinence-associated dermatitis
Ischemia of the skin beneath tightly wrapped dressings
Necrotizing fasciitis
Terminal ulcer
Skin failure

11.4 Prevention

Reducing the duration and magnitude of pressure is paramount. The duration of pressure is reduced by turning the patient off of high-risk areas. Most pressure necrosis develops on the sacrum and therefore immobile patients should be turned to

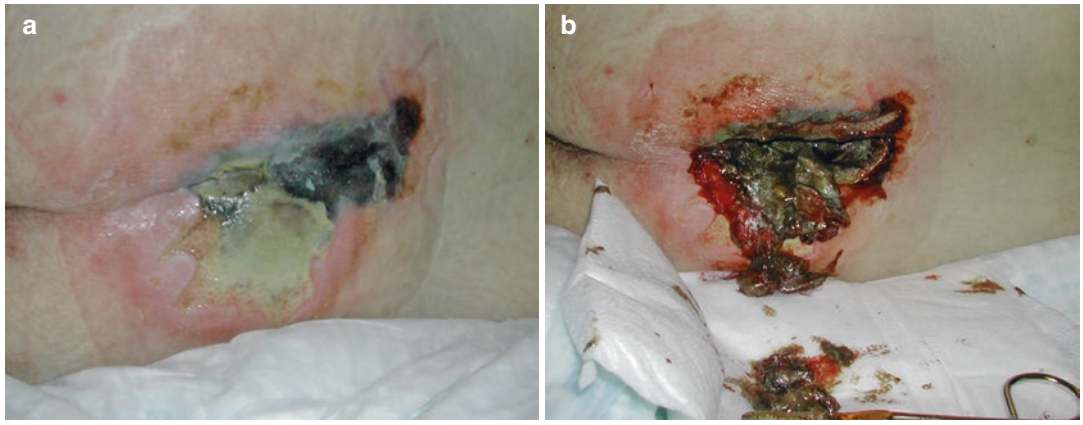


Fig. 11.2 (**a**) This patient is a 65-year-old male who refused to move from his bed at home for several days. When admitted to the hospital, he was septic. Cellulitis and frank necrosis are visible on the sacrum and buttocks. (**b**) His wound was debrided at bedside in the ICU due to the wound being the cause of the sepsis

the side to relieve pressure. The magnitude of pressure can also be reduced by placing the patient on a support surface with adequate envelopment and immersion. High-density foam mattresses have been shown to be effective in reducing pressure injury as long as the patient is moved about in bed. For very-high-risk patients, alternating pressure mattress helps prevent tissue damage; however, the patient still must be moved on these support surfaces. No support surface replaces turning the patient to reduce duration of pressure [13]. Use mattress of 4 in. of viscoelastic foam during times when patients cannot be moved, such as surgical cases over 3 h, cardiopulmonary bypass cases, and in the emergency department.

Heels should be elevated from the bed in high-risk patients. Heel elevation can be done with a pillow placed under the calf of the leg in order to "float" the heel from the bed. Pressure-relieving boots can be used when patients do not stay in place on pillows; however, boots themselves can create pressure points. Therefore, boots need to be removed 2–3 times daily to assess for early signs of pressure injury.

Medical devices should be removed 2–3 times a day, if only long enough to inspect for signs of pressure on the skin [14]. High-risk areas, such as the bridge of the nose and face, should be padded with thin dressings prior to the use of noninvasive positive pressure masks [15]. Oxygen tubing should be padded to reduce the intensity of pressure behind the ear.

11.5 Treatment

Pressure necrosis of the sacrum, buttocks, and ischia will need debridement to viable tissue if healing is the goal for the patient (Fig. 11.2a, b). During the healing process, pressure on the wound must be limited to 1 h 3 times a day (for meals). Nutrition must also be adequate to promote healing and reduce the risk of infection. Biofilm quickly develops in these wounds, so biofilm-resistant antiseptics should be used (silver, cadexomer iodine, honey) [13].

Pressure necrosis of the heel should not be debrided in patients with ischemic limbs. As long as the eschar remains stable, local wound care with topical iodine is recommended. The eschar will lift from the edges and should be trimmed to prevent it from snagging on clothing. If the eschar cap is removed from the wound, or the eschar cap is softened, infection rapidly develops. The poor inherent blood flow in the limb reduces the likelihood of healing and often leads to amputation due to critical limb ischemia [13].

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Part III

Toxic Origin

Infection Context: Necrotizing Fasciitis

12

Sadanori Akita

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12.1 Introduction

The deep skin and soft tissue infections (SSTIs) mainly caused by group A streptococcus are composed of necrotizing fasciitis and muscle necrosis. Necrotizing fasciitis is a deep-tissue infection of the subcutaneous tissue that results in the rapidly progressive destruction of fat and fascia. Necrotizing fasciitis (NF) may be monomicrobial (type II), where group A streptococcus (GAS) alone or accompanied with *Staphylococcus aureus* is the most common cause, or polymicrobial (type I), in which a mixture of Gram-positive and Gram-negative aerobes and anaerobes is identified. In monomicrobial, NF is more frequently seen in "community-acquired" or "idiopathic" cases, while after head and neck or Fournier's gangrene (genitourinary tract) surgeries, more polymicrobial causes are typical. Risk factors for invasive group A streptococcus SSTIs are multiple including minor traumas, most recent initial varicella zoster virus infection (with this, the lesion becomes superinfected), diabetes, and use of nonsteroidal anti-inflammatory agents, even though this can be happening to healthy individuals [1]. Group A streptococcus necrotizing fasciitis was once considered very uncommon, but population-based studies estimate as many as 1,500–3,000 cases per annum of necrotizing fasciitis [2]. In addition to increasing incidence, very rapid and dramatic clinical manifestations and high morbidity and mortality rate of the NF have been paid attention to in the study of

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pathogenesis. Despite vigorous studies, essential questions to group A streptococcus pathogenesis in NF remain unanswered [3].

12.2 Epidemiology

The US Centers for Disease Control and Prevention (CDC) reported that more than 500–1,000 cases of NF are diagnosed each year in the USA. However, the accurate estimation is difficult to confirm due to various synonyms of these entities. The annual rate of NF has been accounted for 0.4 cases per 100,000 populations and increasing in an exponential rate [4]. The cause of NF is infection with predisposing factor of drugs, hypersensitivity, cardiovascular diseases, burn, insect bites, or trauma. NF may bring about severe sepsis, especially among immune-suppressed, diabetic, cancer, drug abuse, and chronic kidney disease patients. NF is observed more frequently in winter, with exception of necrotizing fasciitis by *Vibrio vulnificus*, which is seen more in summer and more in males [4] and occurs at any age group. About 50 % of patients have a history of skin injury, 25 % experienced blunt trauma, and 70 % have at least one chronic disease. Half of necrotizing fasciitis occurs in a unilateral lower limb and 30 % in a unilateral upper limb.

12.3 Symptom

NF is at first difficult to diagnose in the early stage of nonspecific signs such as swelling, erythema, and pain in the affected site which resemble non-severe soft tissue infections such as cellulitis and erysipelas [5], even though magnetic resonance (MR) imaging may help differentiate necrotizing infectious fasciitis from nonnecrotizing infectious fasciitis by measuring the thickness and detecting the presence of low signal intensity in the deep fascia on fat-suppressed T2-weighed images, the presence of nonenhancing areas in the deep fascia, or involvement of three or more compartments in one extremity [6].

NF often accompanies with severe pain at onset proportional to physical findings [4].

12.4 Clinical Course and Features of Necrotizing Fasciitis

NF is a rapidly progressive, destructive bacterial infection to superficial and deep soft tissues including the skin, subcutaneous tissue, fascia, and muscle. In hours to days, the infection can progress from visibly benign skin lesion to a highly mortal condition (Fig. 12.1). Many clinical studies reported that the rapid both deep-enough and wide-enough surgical debridement of infected tissue within 12–24 h from the original clinical manifestation is pivotal to lifesaving [4]. The bacterial infection spreads along the fascial planes and should separate adjacent muscles. In the fascia, loose fibrous connective tissue and neurovascular structures within contain little anatomic barrier against pathogens' dissemination. The GAS proliferates in the sterile sites and rapidly attacks with acute inflammatory cells. Then, severe tissue damage combined with many potent protease and degenerative virulent factors expressed by invading GAS and host-releasing polymorphonuclear (PMN) leukocytes result in severe tissue damages (Fig. 12.2).

12.5 Diagnosis and Tests

12.5.1 Physical Diagnosis

The odds ratios (OR) of fever, tachycardia, and hypotension between necrotizing fasciitis and non-severe soft tissue infection are 3.4 (1.6–7.4),

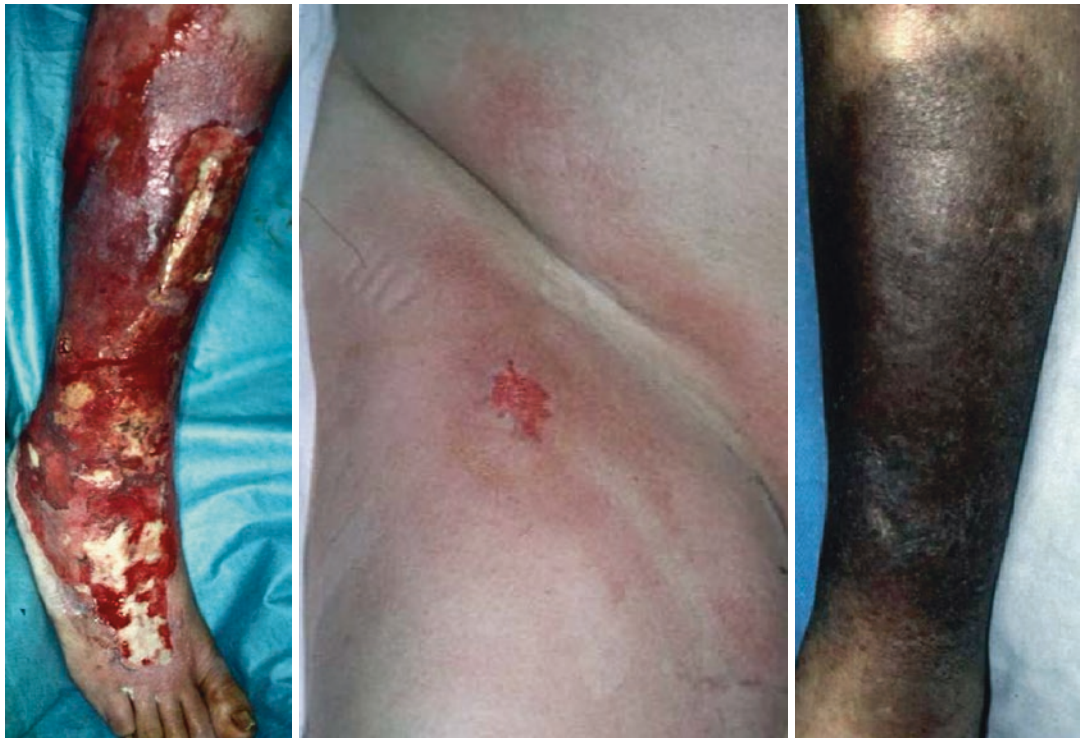

Fig. 12.1 A 66-year-old female, over years of medication of oral steroid (15 mg prednisolone) due to idiopathic thrombocytopenic purpura (ITP). Sudden onset of group A streptococcal necrotizing fasciitis in her right calf (*right*), ipsilateral thigh and inguinal lymph node inflammation (*middle*), and contralateral calf pigmentation largely due to ITP and continued hemorrhage (*right*)

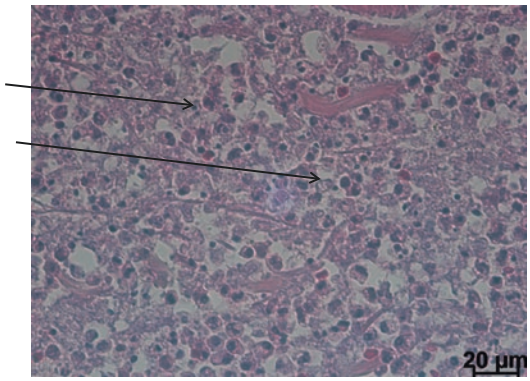

Fig. 12.2 Severe tissue damage deep to the fascia by invading group A streptococci and host-releasing polymorphonuclear (PMN) leukocytes (*arrows*)

4.5 (1.7–11.8), and 2.6 (1.1–6.0), respectively [7]. The likelihood of the presence of bullae in NF in comparison to non-severe soft tissue infection is 3.5 (1.0–11.9). Skin necrosis is present in 6 % of NF and in 2 % of non-severe soft tissue infections. At first, physical findings of NF include erythematous and ecchymotic skin lesions, and these rapidly evolve into bleeding bullae, indicating occlusion of deep blood vessels in the fascia or muscle compartments; thus, the presence of the bullae is crucial for clinical diagnosis. Ludwig's angina (submandibular space) and Fournier's gangrene (scrotum and penis or vulva) are variant forms of NF

and often demonstrate explosive and aggressive clinical courses.

12.5.2 Laboratory Tests

The Laboratory Risk Indicator for Necrotizing Fasciitis (LRINEC) score is developed expecting diagnostic clues for NF. Among the total 13 scores, retrospective study suggests that a score of 6 and more is highly indicative of NF with 92 % positive predictive value and 96 % negative predictive value [8]. LRINEC score is helpful in categorizing patients into risk factors of NF.

12.6 Treatment

12.6.1 Medical Therapy

Suspected NF patients should be empirically and immediately administered with broad-spectrum antibiotics, which may cover the common suspected pathogens. The first-line antimicrobial agents to necrotizing fasciitis are depicted in Table 12.1. In type I (polymicrobial) infection, the selection of an antimicrobial should be based on medical history and Gram staining and culture. The coverage against anaerobes is important in type I. Metronidazole, clindamycin, or beta-lactams with beta-lactamase inhibitor or carbapenems are of choice against anaerobes. In patients already exposed to antibiotics in advance, broader Gram-negative coverage should be taken into account for an initial empirical therapy. Ampicillin-sulbactam, piperacillin-tazobactam, ticarcillin-clavulanate, newly generated cephalosporins, or carbapenems are the candidates for this purpose. In type II (monomicrobial), the most causative pathogen is group A streptococcus, but sometimes Methicillin-Susceptible Staphylococcus Aureus (MSSA)/ Methicillin-resistant Staphylococcus Aureus (MRSA) The use of tetracyclines and third-generation cephalosporins is crucial to managing *Vibrio* infection. The systemic antibiotic therapy for NF may continue 4–6 weeks as the deep-seeded infection is established. Intravenous immunoglobulin (IVIG) is a desirable option to neutralize streptococcal toxins.

Table 12.1 Treatment of necrotizing fasciitis, first-line antimicrobial agent

Mixed infection	*Streptococcus* infection
Ampicillin-subactam	Penicillin
or	*plus*
Pipellacillin-tazobactam	Clindamycin
plus	*S. aureus* infection
Clindamycin	Cefazolin
plus	Vancomycin (for resistant strains)
Ciprofloxacin	Clindamycin
Imipenem/cilastatin	*Clostridium* infection
Meropenem	Clindamycin
Cefotaxime	Penicillin
plus	
Metronidazole	
or	
Clindamycin	

12.6.2 Surgical Therapy

Early wide-enough and deep-enough surgical debridement is the core treatment of NF and results in significantly better mortality compared to those who underwent surgery with a few hours of delay [9]. When NF is considered and the patient is brought to the operating room, aggressive and extensive surgical debridement is explored. The tissue involved should be completely removed until no further evidence of infection. When further debridement is required, the patient must be returned immediately. In this context, the temporal coverage using the artificial dermis after debridement is useful because of no loss of the patient's own tissue yet easier for "second-look" surgery or secondary reconstruction [10] (Fig. 12.3).

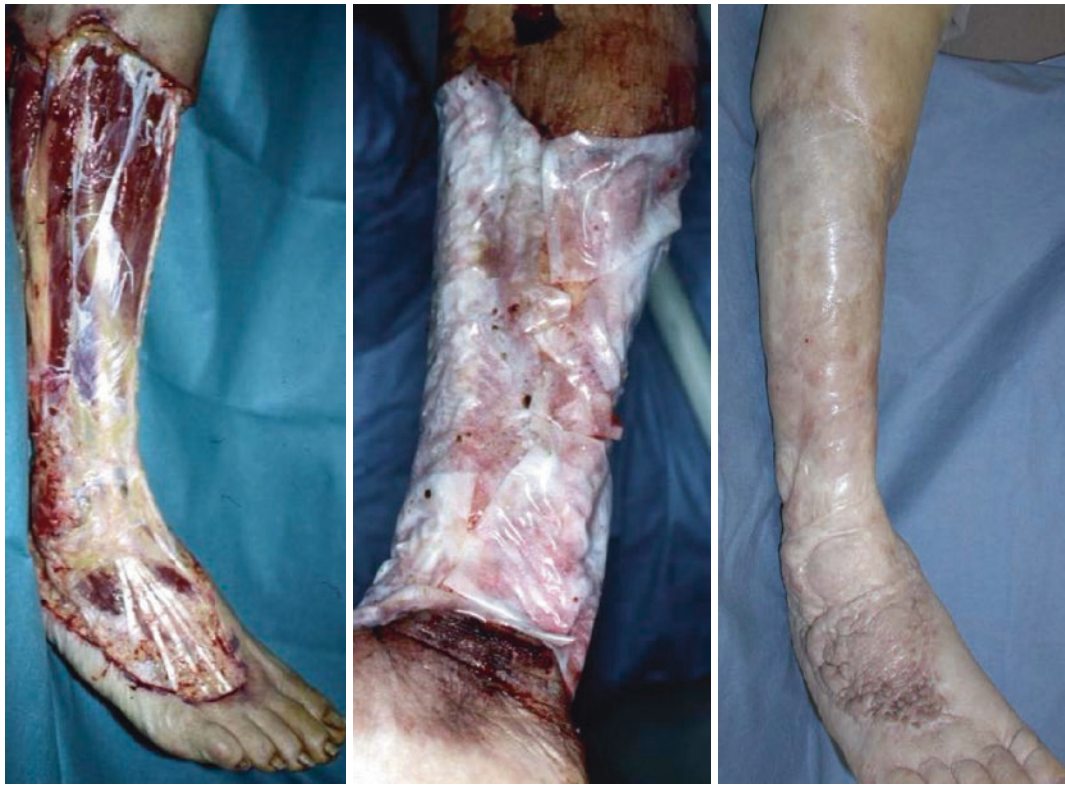

Fig. 12.3 Immediate (within 2 h from the onset) thorough debridement up to the fascia (*left*), temporal coverage with artificial dermis (*middle*), and 6 years after secondary split-thickness skin grafting (*right*)

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Resuscitation Foot Necrosis: A New Entity for a Complex Management?

13

Franck Duteille and Pierre Perrot

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13.1 Introduction

As in every medical discipline, resuscitation techniques are regularly progressing, allowing more and more patients to survive. In these departments, acute skin problems are observed, particularly those linked to the use of vasopressive drugs prescribed to maintain a stable patient haemodynamics. Once the acute phase is solved and the patients are stabilised, the consequence of the use of these vasopressive drugs may appear and become the main difficult problem. The context is variable, but most of these patients have presented or still present with prolonged haemodynamic shocks (septic shock, purpura fulminans, etc.) [1].

Since the last decade, we have been confronted with a series of patients presenting with skin and tissular distal extremities necrosis following intensive care. Problems were essentially involving the hands and feet. This new capacity of resuscitating desperate life-threatening situations in patients who already died creates a series of new challenging tissular reconstruction. The management of these patients is delicate in terms of the therapeutic decisions (amputation or limb salvage) but also of the OR planning and modalities. We hereby propose action to be taken and the elements of management which have shown to be important in view of our clinical experience.

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13.2 Clinical Presentation

This dry necrosis has probably evolved from the superficial to the deep structures. The whole skin and subcutaneous tissues may be affected (skin, subcutaneous cellular tissue, muscles). The damage is essentially located at the level of the toes but also involves the plantar vault leaving intact the calcaneal area, a sign of pejorative evolution.

Lesions appearing on the dorsal aspect of the foot are usually less extended than on the plantar aspect and appear secondarily. The pathophysiology is linked to vasoconstriction (linked to amines) potentialised by the existence of a haemodynamic failure already present in these patients. This drop in blood flow linked to vasoconstriction may lead to small-diameter vessel thrombosis explaining the clinical situation: necrosis from superficial to deep toe necrosis with thrombosis of the collateral arteries.

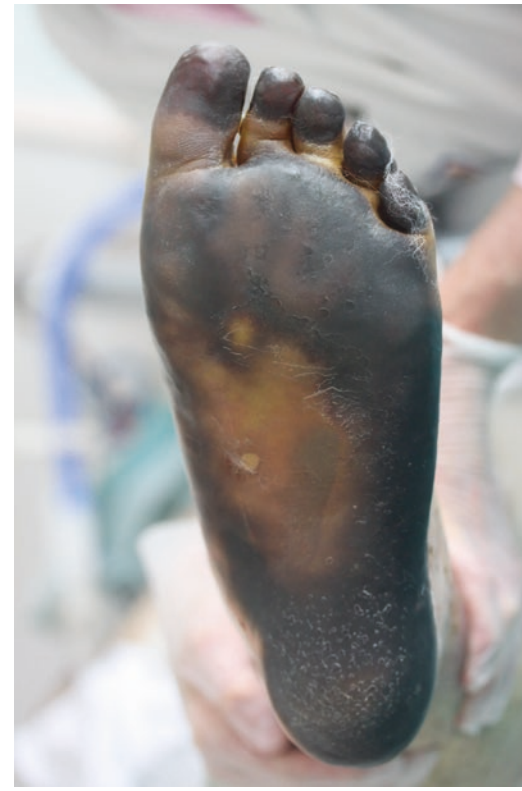

Fig. 13.1 Initial state of a patient still taking vasopressive drugs

13.3 The Therapeutic Decision

13.3.1 Evolution

The choices made during the surgical debridement procedure should be carefully balanced because of their impact on the whole success. This decision must be made in careful consultation with the critical care team. The evolution of this necrosis is different to those found in arterial patients. In fact, intensive care patients are often young and do not present with preliminary vascular lesions or permanent heart failure. The vascular injury observed in resuscitation is therefore an epiphenomenon, and the improvement of the haemodynamic status associated with the limitation of vasopressive drug administration will sometimes allow the partial recovery of tissue which initially appeared as destroyed. Also in Fig. 13.1, this patient presents with an extremely disturbing situation of the foot arch and for which we observed a complete or partial tissue recovery (with the disappearance of the shock associated with the suppression of amines). The necrosis was limited to the superficial part of the cutaneous tissue; the toes could not be saved. There is therefore a real danger in planning a surgical procedure before the patient is in a completely stable status. In our experience, the surgical procedure started 15 days at the earliest after the stabilisation of the clinical status and the suppression of amines. An earlier debridement can conduce to excise tissue with uncertain evolution. This is equally true of a certain number of intensive care specialists who ‘push’ to debridement partly because the fever presented by the patients may be linked to necrotic tissue (Fig. 13.2).

13.3.2 The Strategy Concerning the Therapeutic Attitude

The therapeutic decision is complex and does not comply with the established decision tree. It mainly depends on the experience of the

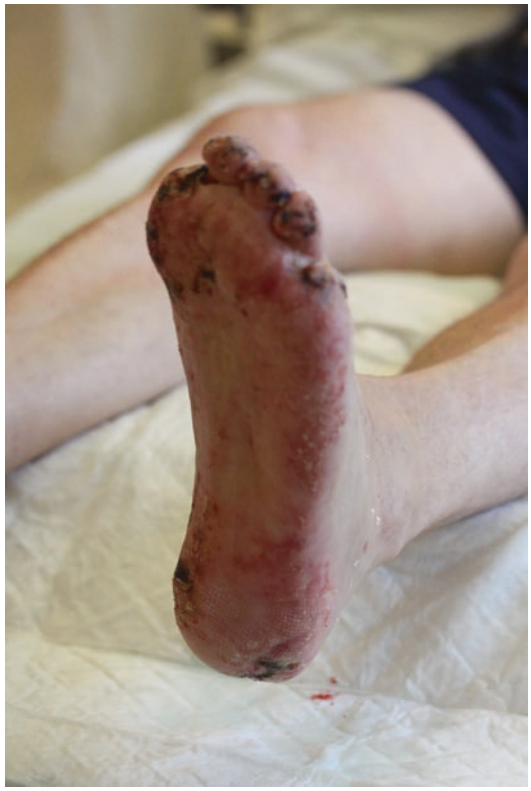

Fig. 13.2 Evolution 3 weeks after and the stopping of vasoactive drugs and amputation of the toes

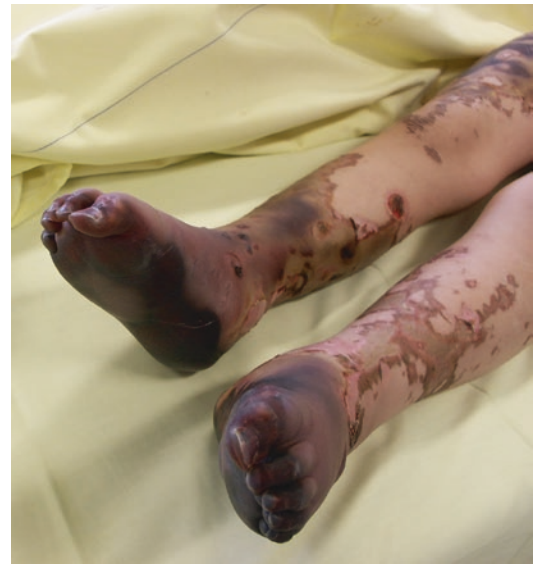

Fig. 13.3 A young boy 6 years of age presenting with necrosis of 2 ft going up to the ankle. Surgical exploration having confirmed this extensive necrosis with notable necrosis in the two ankle bones, no solution has unfortunately been envisioned

practitioner, but the final decision often comes from the patient himself.

We exclude the situations relying on classical techniques of healing (skin graft, treatment by negative pressure, etc.). We have limited ourselves to the most serious situations where the only solution is to perform a free flap to avoid the amputation of the leg [2]. Situations exist where all attempts at salvage are excluded due to the clinical situation: necrosis affecting the entire foot (plantar side, dorsal side, and heel cup) and especially when the necrosis reaches the proximal aspect of the ankle (Fig. 13.3), the contraindications to microsurgery (arterial patient, heart failure, renal failure…) and a patient who has no donor site (latissimus dorsi muscle). When a solution seems conceivable, the patient must be seen awake and the therapeutic stake must be clearly explained, as well as the risks of amputation, in case of failure. These patients should be in complete physiological and mental recovery, and this decision does not need to be taken urgently. It is also necessary to see the patient several times to be sure that the situation and the potential complications are completely understood. Of course, all the elements will be taken into account in the therapeutic option (age, professional activity, uni- or bilateral injury…). As in many of these difficult decision-making moments, care must be taken to avoid increasing the number of people involved as this makes the decision process more complicated for the patient. Nevertheless, we ask a rehabilitation doctor specialised in limb prostheses to visit the patient, so that the patient has a complete picture of the problems. The options can be simplified to salvage or amputation of one or more limbs or parts of the limbs. The objective is saving the foot but toes were usually not be saved. The aim is therefore to anticipate a back to normal walking. However, running will definitively be compromised.

The salvage require a microsurgical muscle transfer. Usually the latissimus dorsi muscle is used (isolated or associated with the dental mus-

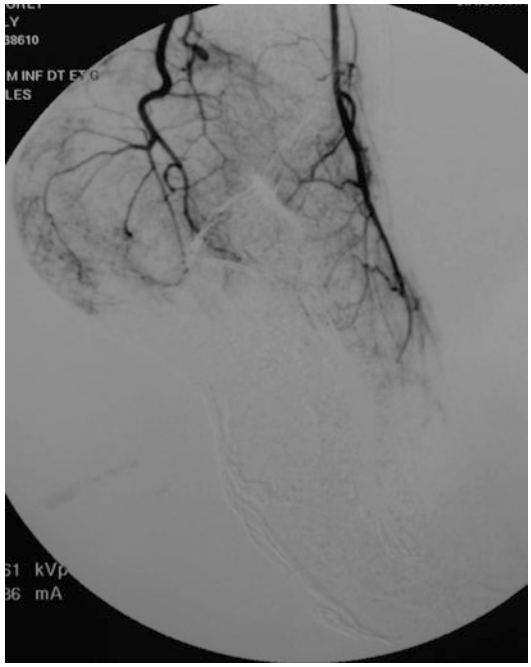

Fig. 13.4 Arteriogram of a 42-year-old patient presenting with a 'resuscitation foot' with a clear interruption of the flow and a desert afterwards

cle) to cover this large loss of substance. The choice of muscle (versus cutaneous flap) is fundamental. This choice remains controversial [3], but for us, it will be the only way to fill the dead space volume after debridement, the only way to be sufficiently thick to ensure a secondary support and avoid the soaping phenomenon, and it is the best way to reduce the risk of infection. In addition, we think that the blood reserve that represents the muscle allows debridement to be limited because certain undefined tissue limits may benefit the vascular supply brought locally by the revascularised muscle. The only negative in this strategy is the sacrifice of the latissimus dorsi muscle which may be detrimental if the intervention fails, and the use of crutches proves to be necessary.

If the decision is taken, a vascular assessment is performed in order to explore the arteries of the lower limbs. The choice of an arteriogram or an echo/Doppler with a flux calculation may be performed. The arteriogram usually shows a clear interruption of the arteries with a healthy network before and a vascular desert after (Fig. 13.4).

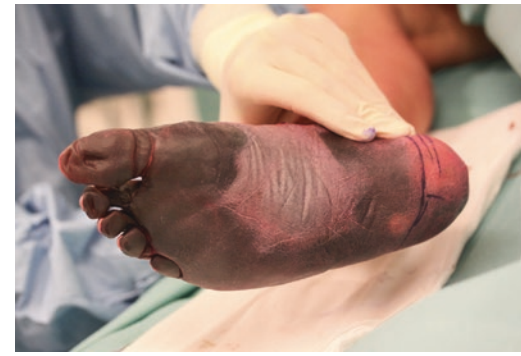

Fig. 13.5 A 42-year-old patient presenting with necrosis of almost all of the instep following a visit in rehabilitation for septic shock and the use of vasoconstrictive drugs

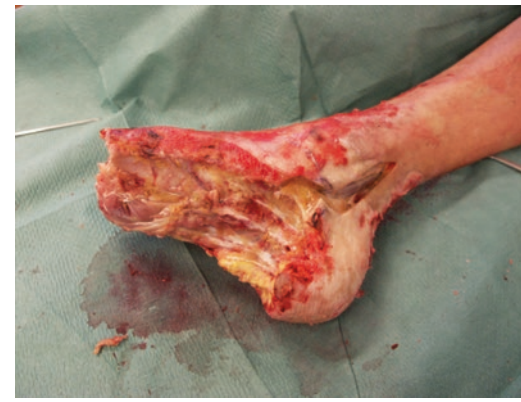

Fig. 13.6 The foot of the same patient after the surgical debridement (we may note that the heel cup is partially preserved, which is often the case), the debridement is not exhaustive, and certain tissues have uncertain vitality but are left in place because we hope for a certain part of 'revascularisation' contributed from the free flap

13.3.3 Surgical Intervention

Debridement and free flap will be performed during the same operation. Debridement must remove all the necrotic tissue but must try to leave in place the tissue which is in doubt or especially limit the bone structures for the reasons explained earlier. The flap specimen will only be started (by a second team if possible) once the debridement has been performed and the salvage indication has been confirmed (Figs. 13.5 and 13.6). The vessels must be addressed in a healthy zone. On the strategic plan, it is necessary to expect an option for covering pedicle anastomoses of the free flap because

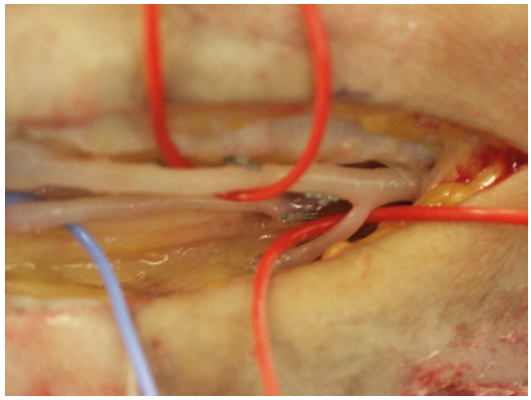

Fig. 13.7 Expose the vessels of the patient; these appear healthy during the surgical exploration

complete debridement does not offer any option of covering the remaining tissue on the foot. For these, the Z incisions (allowing a V/Y closure) are made opposite to the recipient vessels. In addition, the entire latissimus dorsi is removed (level with the tendinous insertion). The high part of the muscle may also be redriven over the vessels after anastomosis completion in order to cover them.

The recipient vessels have always been of good quality, in our experience (Fig. 13.7), because it concerns a young patient with no mechanical avulsion and trauma. The limit between the healthy and pathological zone is actually extremely clean. Technically, this microsurgical act does not at all differ from the standard free flap. During the follow-up period, we apply the normal protocols: fasting during 12 h in case it is necessary to perform further surgery, bed rest for 5 days, and regular monitoring of the flap. The dermo-epidermal skin graft on the muscle is performed between the 5th and 8th day associated with the restructuring of the flap.

13.3.4 Follow-Up

When complete healing of the flap has been achieved, it is necessary to be sure of its very bulky aspect and especially its temporary characteristics (Fig. 13.8). Volume reduction will take place progressively and may require between 2 and 6 months (Fig. 13.9).

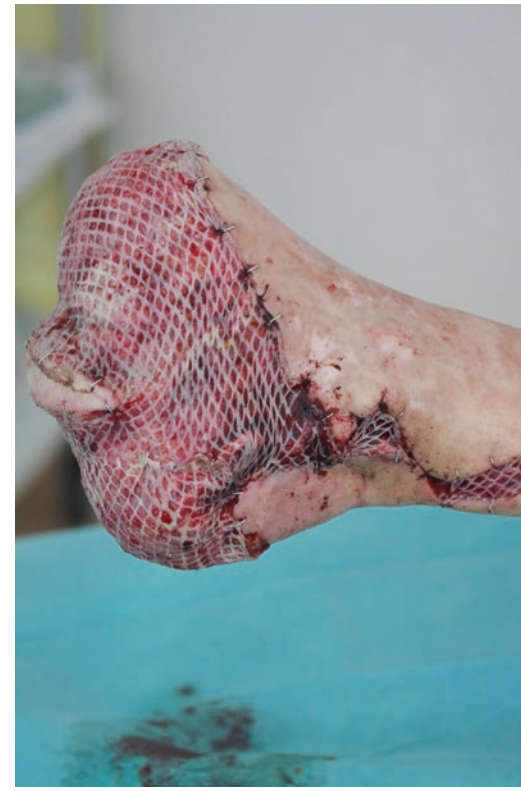

Fig. 13.8 The flap is put in place and grafted 15 days after the intervention. Its bulky appearance is only temporary

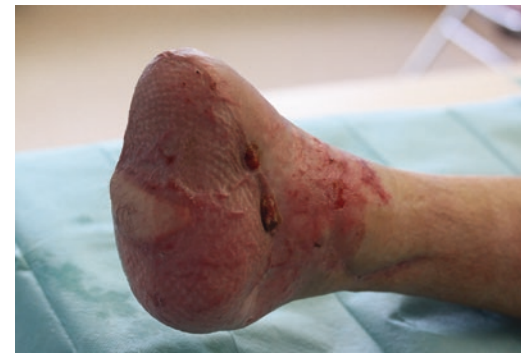

Fig. 13.9 The result at 4 months with slight decrease in the size of the flap allowing a normal walking for the foot supported by adapted shoe inserts

Compression stockings are applied 21 days after the surgical intervention as well as when leaving the rehabilitation centre where walking will be gradually recommenced.

Patients are seen every 3 months then every 6 months; often there are inflammation episodes which translate into an inflamed pressure, most often on a fragment of necrotic bone. Surgical action must be done sparingly. Usually walking limitation by a 10-day course of antibiotics allows the problem to be resolved. Sometimes the radiographic assessment highlights a bony fragment potentially in relation with the clinical signs. A surgical excision may then be suggested, preferably conducted by the same physician who performed the free flap. We would not cover all aspects of rehabilitation here (learning to walk again, shoes and adapted shoe inserts, etc.) which remain a fundamental part of the patient learning to walk normally again.

Conclusion

The advancement in resuscitation has led to the appearance of a new type of pathology that we commonly call 'pied de réanimation'. It refers to a necrosis of all or part of the foot (and sometimes other extremities) by a phenomenon resulting from a combination of haemodynamic shock and the use of vasopressive drugs in high doses.

These necroses are often major and the challenge for the plastic surgeon to envisage the possibilities of 'limb salvage'. This is done via the execution of a large-sized muscular free flap (still the latissimus dorsi) in our experience. This surgery presents an increased failure rate than the usual rate of failure but a 77 % success rate is still acceptable.

The follow-up of patients nevertheless shows a large majority who are able to walk, enjoy leisure activities, and live a normal life, and this pushes us to continue this method of treatment (Figs. 13.7 and 13.8).

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Skin Necrosis and Ulcers Induced by Medications

14

Joachim Dissemond

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14.1 Introduction

In recent decades, it has been reported for numerous medications that their systemic administration can lead to the development of skin necrosis and subsequently to ulcerations. Allergic as well as nonallergic etiologic mechanisms have been discussed. Most of the relevant pathological reactions induced by these medications should be a type of vasculitis or vasculopathy. Although these reactions often manifest as a rash or other skin diseases, some medications lead to the formation of skin necrosis and ulcers [9]. Therefore, in this chapter, an exemplary number of widely used drugs which had been discussed to be responsible for the development of skin or mucosal necrosis and ulcers should be presented (Table 14.1).

14.2 Medications

14.2.1 Hydroxyurea

Hydroxyurea, synonym referred as hydroxycarbamide, is a hydroxylated urea derivative which inhibits as an S-phase-specific inhibitor of ribonucleotide reductase the DNA synthesis. It is clinically used for the treatment of patients with chronic myelogenous leukemia, essential thrombocythemia, and polycythemia vera.

In a retrospective study, 41 patients were presented in which a leg ulcer was caused by

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Table 14.1 Overview of the systemic given medications that may be associated with the development of skin necroses and ulcerations

Amezinium methylsulfate [25]
Anagrelide [36]
Barbituric acid [32]
Coumarin [13, 31]
Diltiazem [4]
Erythropoietin [16]
Estrogen combinations [40]
Furosemide [39]
Heparin [18, 27]
Hydralazine [24]
Hydroxyurea [2, 14, 41]
Leflunomide [19, 22, 26]
Levamisole [12, 34]
Methotrexate [1, 8]
Nicorandil [3, 30, 45]
Nifedipine [28]
Pentamidine [17]
Pentazocine [7, 35]
Propylthiouracil [20, 21]
Warfarin [5, 15]

hydroxyurea. In these patients with a mean age of 67 years, it came after an average treatment period of 5 years with hydroxyurea to the onset of ulceration. In total, 80 % of patients with ulcers healed after discontinuation of the medication. Clinically, in most patients, multiple ulcerations in the area of the malleoli could be found [41]. Comparable data have been presented by Best et al. in a study of 14 patients [2].

Hydroxyurea is the most widely publicized medication that is associated with the development of leg ulcers. It has been described that the first appearance of this extremely painful ulcerations is usually 1–10 years after starting treatment with hydroxyurea [10, 11, 14]. Hydroxyurea-induced ulcers are manifested in particular symmetrically in the area of the malleoli, dorsum of the foot, or heel (Figs. 14.1, 14.2, 14.3, and 14.4). The underlying pathogenesis is so far not fully understood. It was discussed that a graft-versus-host-like reaction with degeneration of the basal keratinocytes and an epidermodermal gap formation could be directly related to cytostatic effects of hydroxyurea on the basal keratinocytes. In addition, a disturbance of microcirculation by effects on erythrocytes with decrease in their number, increase of their mean volume, and thus reduced deformability has been described [41, 44]. The atrophie blanche was discussed to be a clinical indicator for an underlying disturbed microcirculation (Fig. 14.5). Several of these lesions are not reversible, so that despite discontinuation of therapy in some patients, recurrence of ulcerations can be found [23].

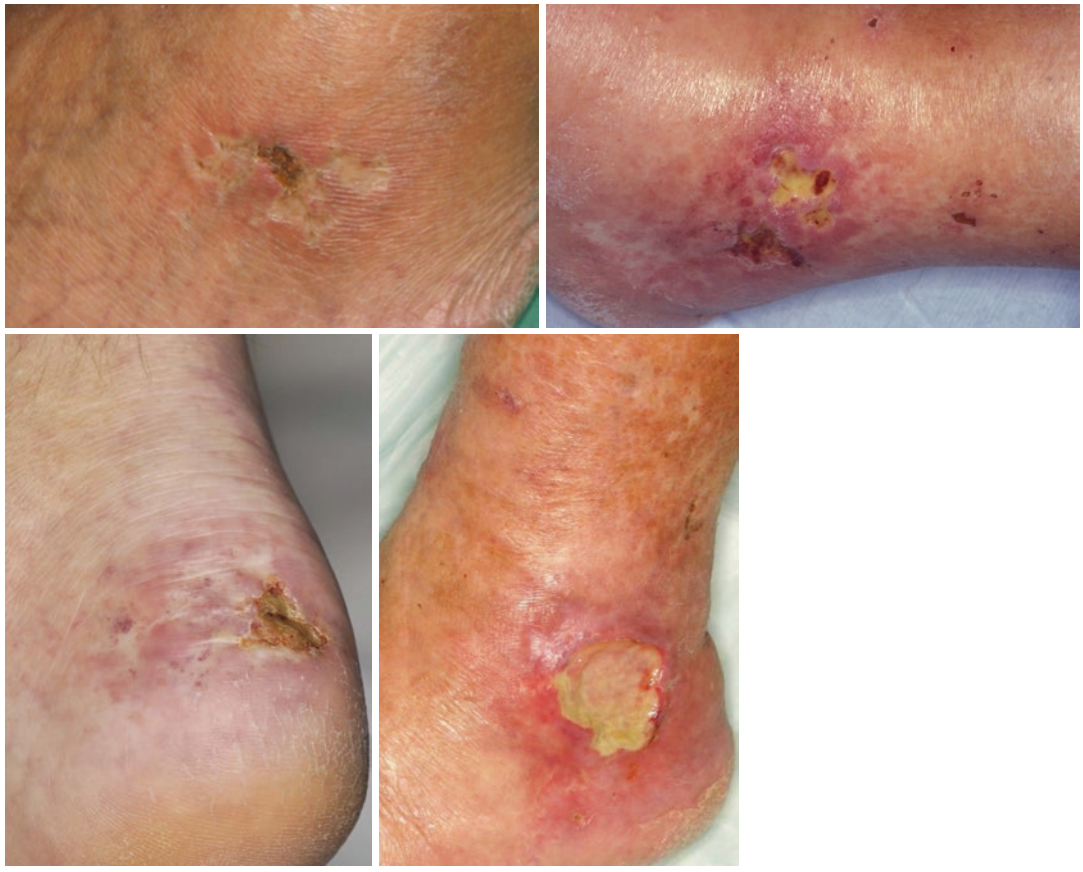
14.2.2 Anagrelide

Anagrelide is an imidazoquinazoline derivate, which is used for the treatment of patients with myeloproliferative diseases such as essential thrombocythemia. The inhibitory effect of anagrelide on human platelets is mediated by formation of a delay of maturation of megakaryocytes by inhibiting cyclic AMP phosphodiesterase III.

In a case report, our group reported a 38-year-old patient with extremely painful ulcers with atrophie blanche on both outer ankles, which occurred 6 weeks after starting treatment with anagrelide (Figs. 14.6 and 14.7). Despite an intensified advanced wound therapy, the wounds were refractory. A complete healing of the ulcer was achieved after stopping of the medication. An underlying disturbed microcirculation comparable to hydroxyurea effects was discussed [36].

14.2.3 Coumarins

Coumarins derived from 4-hydroxycoumarin compounds are well known as drugs with an inhibitory effect on coagulation. Coumarins have a structure similar to vitamin K. They are used clinically as for the treatment and prophylaxis of thrombosis and embolism. The effect as anticoagulants is based on the inhibition of plasmatic coagulation. Coumarins bind instead of vitamin K to the enzyme vitamin K epoxide reductase, block it, and thus inhibit competitively the formation of active clotting factors. The two most commonly used in medicine are phenprocoumon coumarins and warfarin.



Figs. 14.1, 14.2, 14.3, and 14.4 Extremely painful ulcerations of the lower legs in different patients after long-term intake of hydroxyurea

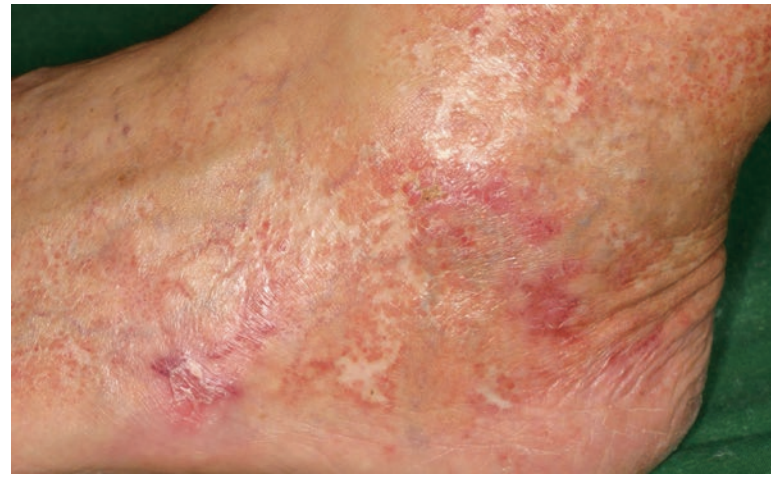
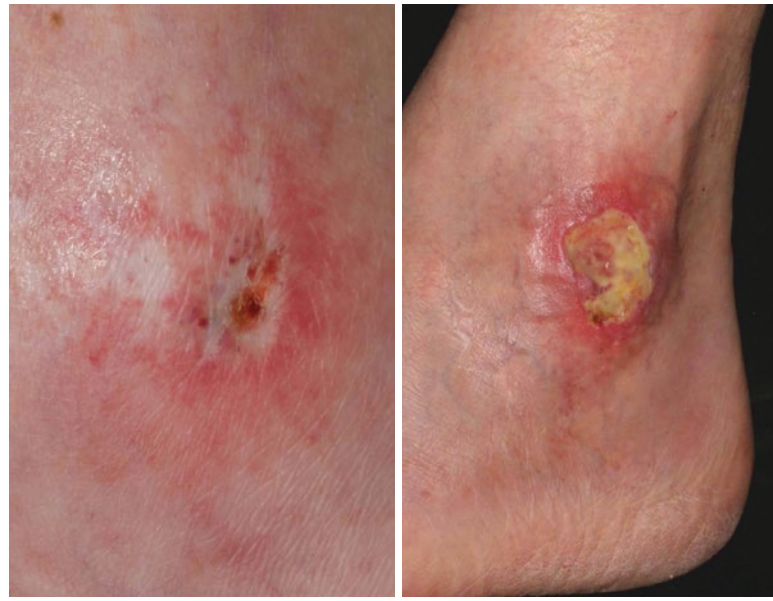


Fig. 14.5 Livid erythema with clinically typical atrophie blanche in a patient after many years of taking hydroxyurea



Figs. 14.6 and 14.7 Patient who developed 6 weeks after he starts taking anagrelide an atrophie blanche (Fig. 14.6) and shortly later very painful ulcerations in the area of both lateral ankles (Fig. 14.7)

In a case series report, three patients were described in which it came within 5 days after initiation of therapy with warfarin to painful, sharply defined erythema, which ulcerated secondary. All patients were obese. The authors discussed the fact that the coexistence and may be other individual factors are important for the development of coumarin necrosis [13]. Another case report described a 67-year-old patient with the occurrence of leukocytoclastic vasculitis of the lower limb 4 weeks after he starts coumarin therapy [42]. Skin necrosis occurred at 0.01–0.1 % of all patients after taking coumarins. This necrosis can be observed more frequently in patients with congenital protein C deficiency or rarely described association with a deficiency of protein S [31]. In addition, the affected patients may be more common in obese women. Skin necroses usually appear symmetrically on the chest, abdomen, or buttocks. Besides severe pain, often petechiae, erythema, and ecchymoses are the first clinical signs. As the condition progresses, crusts, hemorrhagic bullae, necrosis, or ulcer can be observed. As the underlying pathophysiology at the beginning of therapy with coumarins, hypercoagulative statuses by the imbalance of the various anticoagulant mechanisms have been discussed. The resulting microvascular thrombotic occlusions typically cause necroses. The first clinical symptoms start within 1–10 days, usually on day 3–6 [5]. Only in rare cases, it can also occur even after several years of the onset of necrosis [15]. The median age of onset is 54 years; about 75 % are women, and about 60 % of the necroses are localized at the legs, breasts, or buttocks [5].

14.2.4 Heparin

Heparin is a mucopolysaccharide polysulfate, which binds to among others antithrombin III, causing the inactivation of many coagulation factors. Thereby, its anticoagulant effects are enhanced. Heparin preparations are used for the prophylaxis and treatment of thromboembolic disorders. The occurrence of purpura with necrosis in the injection areas and in other parts of the body has been reported. As a potential pathogenic mechanism, a leucocytoclastic vasculitis is described.

Another pathological reaction is the heparin-induced thrombocytopenia type II (HIT II), which may lead to arterial and venous thrombosis with necrosis. HIT is caused by the formation of autoantibodies against the heparin platelet factor

4 (PF4) complexes and occurs in 0.1–2 % of all patients treated with heparin. After the beginning of heparin treatment, HIT II usually occurs within 10–14 days. If a heparin treatment has been done in the previous 100 days, the disease can manifest itself much more rapidly [18].

In a 66-year-old woman with diabetes and hemodialysis who received intravenous heparin during hemodialysis, the occurrences of ulcers of the lower legs were described [27]. Our group already described a 38-year-old patient in whom HIT II led to multiple necroses and ulcers on the mucous membrane and integument. The painful, sharply defined necroses with inflammatory surroundings were not localized at the injection sites [18].

14.2.5 Methotrexate

Methotrexate (MTX) is an analog of folic acid and competitively inhibits dihydrofolate reductase. As an antimetabolite, it inhibits DNA and RNA synthesis. The drug is dosed higher in oncologic patients as part of chemotherapy. Lower doses are widely used in the treatment of patients with rheumatoid arthritis or psoriasis vulgaris.

In the literature, a 39-year-old woman with non-Hodgkin's lymphoma was described. Two months after starting a therapy with 15 mg MTX once weekly, painless ulcerations on the malleoli appeared. One year ago, similar ulcerations occur after a combination therapy with 7.5 mg MTX and indomethacin was initiated. After discontinuation of the therapy within 2 months, the ulcers healed completely [8]. The occurrence of generalized erosions and ulcerations of psoriatic plaques was described in a case series report in 47 patients. As a risk factor, the co-medication with NSAIDs has been described [33].

14.2.6 Leflunomide

Leflunomide is a drug from the group of immunosuppressants, which is used as a therapy for patients with rheumatoid arthritis and psoriasis. The active metabolite of leflunomide, A771726, inhibits the enzyme dihydroorotate dehydrogenase, a key enzyme for de novo biosynthesis of pyromidine [38].

Our group described a 68-year-old woman with rheumatoid arthritis who developed ulcers during treatment with leflunomide. The patient described 3 months after starting treatment with leflunomide the appearance of a purpura which ulcerated in the following days. As the result of a vasculitis, an extremely painful, sharply demarcated ulceration with livid edges above the right malleolus occurs [19, 26]. Another case report described a 78-year-old woman with rheumatoid arthritis and ulcers, which appear 6 months after starting treatment with leflunomide. It was discussed that a direct toxic effect of leflunomide on epidermal cells could be relevant, since leflunomide blocked in vitro, for example, epidermal growth factors [29]. In another case report, a 63-year-old patient who had suffered for 14 years from rheumatoid arthritis developed 10 months after initiation of leflunomide treatment on both lower legs spontaneously ulcerations. Neither serological nor histological signs for an underlying vasculitis could be found. After discontinuation of leflunomide therapy, the ulcers healed after 8 months [22].

14.2.7 Hydralazine

Hydralazine is a derivative of phthalazine. In some countries, it is used therapeutically as hydralazine hydrochloride in combination, for example, with atenolol or metoprolol and hydrochlorothiazide or for the treatment of essential hypertension.

In a 50-year-old man, very painful ulcers on the Achilles tendon were described after the intake of hydralazine for 3 years. The histology showed newly occurred autoantibodies comparable to the first manifestation of systemic lupus erythematosus. The authors discussed the occurrence of the ulcer as a manifestation of a drug-induced lupus erythematosus. After discontinuation of hydralazine, the ulcer healed ulcers quickly and completely [24].

14.2.8 Amezinium Methylsulfate

Amezinium methylsulfate is an indirect α-sympathomimetic which is used therapeutically in patients with essential and symptomatic hypotension. Amezinium methylsulfate inhibits the intra-dimensional monoamine oxidase, thus causing decreased norepinephrine degradation. Furthermore, it inhibits norepinephrine reuptake in the sympathetic neuron. Through these mechanisms, the noradrenalin amount increases in the peripheral receptors. This leads to vasoconstriction and the blood pressure rises.

A case report described a 52-year-old patient, who suffered for 22 years from a chronic glomerulonephritis, had hemodialysis, and had already developed a generalized vascular calcification. One year after starting treatment with amezinium methylsulfate, he developed painful leg ulcers which were refractory to different treatments for over 7 months. After discontinuation of the drug, the ulcers healed within a few weeks. The authors discussed that the vasoconstrictive effects of the drug can be an important cause for the ulceration [25].

14.2.9 Diltiazem

Diltiazem belongs to the group of calcium antagonists. The drug is used as diltiazem hydrochloride in patients with coronary heart disease or angina pectoris. As an antiarrhythmic drug for the treatment of cardiac arrhythmias, diltiazem can be used preventively against paroxysmal supraventricular tachycardia and in patients without Wolff-Parkinson-White (WPW) syndrome in slowing the heart rate in atrial fibrillation and atrial flutter. Another application of diltiazem is the treatment of arterial hypertension.

In a 59-year-old man with leg edema, livid erythema and ulceration of both lower legs as a result of a cutaneous vasculitis arise 2 months after starting a therapy with diltiazem. After discontinuation of the drug, the ulcerations healed completely after 3 months of therapy [4].

14.2.10 Propylthiouracil

The thiouracils are thioureylene that belong to the family of thioamides. Propylthiouracil inhibits the intrathyroidal peroxidase system. Therefore, it is used as a thyroid drug in patients with hyperthyroidism.

The intake of propylthiouracil over a period of 13 years for the treatment of Graves' disease was described in a 26-year-old woman. After increasing the dose to 50 mg/day, she developed 2 months later livid erythema and painful ulcers of both lower legs. Five months after discontinuation of propylthiouracil, the wounds healed. After retaking the medication, it came after a period of only 5 days to a relapse [21]. In another case report, a 27-year-old man with Graves' disease was described. Two years after beginning a therapy with propylthiouracil, it came to the occurrence of very painful ulcers on both lower legs. These ulcers developed from erythematous plaques with pustules, were sharply demarcated, and showed bizarre configured wound edges. A pyoderma gangrenosum was diagnosed, and a causal relationship with the medication was discussed. After discontinuation of propylthiouracil therapy and initiation of treatment with prednisolone and cyclosporin A, the ulcerations healed after 1 month [20]. Moreover, there are several case reports on the occurrence of intraoral ulceration after administration of propylthiouracil [43].

14.2.11 Nicorandil

Nicorandil is a nicotinamide nitrate ester, which is used for the treatment of patients with angina pectoris. The substance has the characteristics of nitrates but acts in addition as an activator of ATP-dependent potassium channels. The opening of potassium channels leads to hyperpolarization of the cell membrane and to a decrease in intracellular calcium. This causes relaxation of smooth muscle cells and vasodilation. Nicorandil is a peripheral and coronary vasodilator, lowers systolic blood pressure, and increases heart rate reflex.

A 73-year-old woman took nicorandil twice daily for 2 years, until for the first time leg ulcers over her Achilles tendon occurred. At the same time, there was also an onset of perianal ulcerations. After discontinuation of nicorandil, all ulcers healed after 5 months [30]. The occurrence of ulcers located intraorally or on the penis and perianal region is a well-documented side effect when taking nicorandil [3, 45]. For example, in a case series of 10 patients in an average of 26.6 months after starting a therapy with nicorandil, it came to the occurrence of ulcers. After discontinuation of the drug, the ulceration healed after 12 weeks (median) [6].

14.2.12 Levamisole

Levamisole is the levo-isomer of tetramisole and belongs to the group of imidazothiazole. It is an antihelmintic agent which is clinically employed as an immunomodulating drug in particular in the treatment of children with nephrotic syndrome. In addition, levamisole is also used for the adjuvant treatment of patients with colon carcinoma.

In a 67-year-old woman with rheumatoid arthritis, already healed venous leg ulcers were described. After she starts taking levamisole, the leg ulcer recurred. At the same time, livid erythema on the arms and intraoral ulcerations occurred. After discontinuation of the drug, all ulcers healed within 1 month completely [12]. In another case report, an 11-year-old boy with heterozygous factor V Leiden mutation and nephrotic syndrome developed leg ulcers after he had already taken for the last 3 years levamisole. Furthermore, at the same time, livid erythema and ulcers on the forearms, hands, and ears could be observed. After discontinuation of levamisole and initiation of therapy with cyclophosphamide, the ulcerations healed after about 4 weeks [34]. The occurrence of lesions in the form of purpura and/or lichenoid papules 12–44 months after initiation of systemic therapy with levamisole has been repeatedly described in particular on the ears. Although the underlying pathogenic mechanism is unclear, a potential connection between the levamisole intake and an infection was discussed. In some patients, the formation of autoantibodies such as Antineutrophil cytoplasmic antibodies (ANCA) and lupus anticoagulant with an immune complex vasculitis or an occlusive vasculopathy could be shown [37].

14.2.13 Pentazocine

Pentazocine is a benzomorphan derivative from the group of opioids which are used as highly potent analgesic drugs. It is not only a strong analgesic but also a sedative and respiratory depressant.

In an article, a total of 10 patients with ulcers were described after taking pentazocine. There were 4 men and 6 women aged between 20 and 43 years. Prior to the first occurrence of the ulcers, the patient had been taking pentazocine 10 days to 7 years. Most of the patients had multiple ulcerations on the extremities [35]. In a 55-year-old man, chronic ulcers over both shins were described after taking pentazocine [7].

Conclusion

The pathophysiological relevance of the systemic intake of medication on the onset of necrosis or ulcers of the skin is not always clear. For most of the medications, there exist only a few case reports which describe an association with skin necrosis or ulcerations. Several of these patients took multiple medications and suffered from various underlying diseases that could potentially also cause ulcers. Necrosis and ulcers from the intake of medications are therefore usually a diagnosis of exclusion that can be discussed because of a temporal relationship. An exception with greater case report series is medications that contain the drug hydroxyurea or coumarins.

In summary, it is important that all therapists recognize medications as a rare but potentially relevant factor for skin necrosis or ulcers. If this correlation is not recognized early, this can lead to severe and prolonged problems for the patients.

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Toxic Syndromes

15

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15.1 Introduction

Toxic shock syndrome (TSS) is an acute, multisystem, toxin-mediated illness, often resulting in multiorgan failure. It represents the most fulminant expression of a spectrum of disease caused by toxin-producing strains of *Staphylococcus aureus* and *Streptococcus pyogenes* (group A streptococcus). TSS results from the ability of bacterial toxins to act as superantigens. Most *S. aureus* and *S. pyogenes* infections begin on the skin or mucosal surfaces from direct inflammatory or cytotoxic effects of exotoxins. Despite a mortality rate higher than that of meningococcal septicemia, TSS has not achieved the same level of awareness among health-care professionals, who will generally encounter very few recognized cases during their careers. TSS may present anywhere within the health-care system, from occupational health departments to specialist hospital units, and may progress with a rapidity that, once seen, is never forgotten. It is therefore essential that all health-care practitioners have a sound appreciation of the clinical features, diagnosis, pathophysiology, and treatment of TSS.

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15.2 Epidemiology and Clinical Features

15.2.1 Staphylococcal Toxic Shock Syndrome

S. aureus is a ubiquitous and virulent pathogen. It colonizes the skin and mucous membranes of 30–50 % of healthy adults and children, most commonly in the anterior nares, skin, vagina, and rectum [1]. The organism causes a wide range of infections from folliculitis and skin abscesses to bacteremia and endocarditis. The Centers for Disease Control and Prevention (CDC) proposed a revised clinical case definition of TSS in 1981, which remains in use (Panel 15.1).

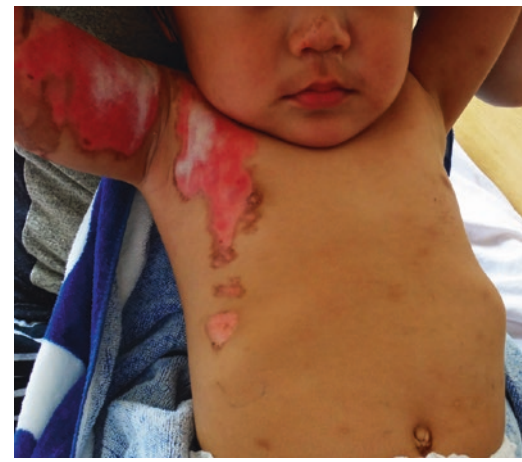
Panel 15.1 Staphylococcal Toxic Shock Syndrome Clinical Case Definition

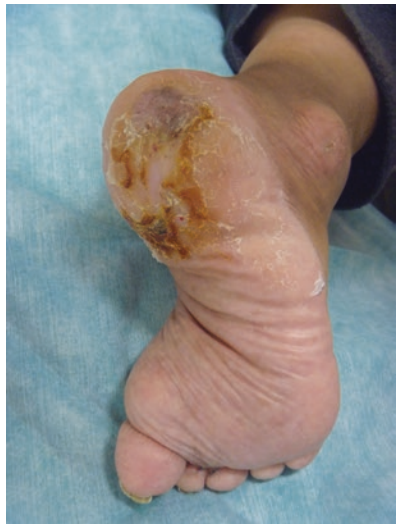
1. Fever ≥38.9 °C
2. Rash-diffuse macular erythroderma
3. Desquamation–1–2 weeks after onset of illness, especially of palms and soles
4. Hypotension–systolic blood pressure ≤90 mmHg for adults
5. Multi-system involvement–3 or more of the following:
A. Gastrointestinalvomiting or diarrhea at the onset of illness
B. Muscular–severe myalgia or elevated creatine phosphokinase
C. Mucous members–vaginal, oropharyngeal, conjunctival hyperaemia
D. Renal–blood urea nitrogen or creatinine twice-upper limit of normal
E. Hepatic–total bilirubin twice-upper limit of normal
F. Haematological–platelets $\leq 100 \times 10^9$/L
G. CNS–disorientation or alterations in consciousness without focal neurological signs
6. Negative results on the following tests:
A. Blood, throat, or cerebrospinal fluid culture (blood culture may be positive for *S aureus*)
B. Rise in title to Rocky Mountain spotted fever, leptospirosis, or measles
Case classification
Probable: case with five of the six clinical findings described
Confirmed: case with all six of the clinical findings described

Non-menstrual TSS may result from any primary staphylococcal infection, or indeed from colonization with a toxin-producing strain of *S. aureus* (including methicillin-resistant *S. aureus* [MRSA]). In light of this, TSS should be considered in patients with shock and infection with *S. aureus*. If present, a focus of infection is more likely to be superficial, may complicate burns or a surgical wound, or may result from a foreign body. Postoperative TSS usually occurs within 48 h of surgery, and in many cases, evidence of clinically significant surgical site infection is lacking at the time of presentation.

15.2.1.1 Skin Manifestation

A variety of skin manifestations are seen in TSS. The initial erythroderma involves both the skin and the mucous membranes and is characterized by a diffuse, red, macular rash resembling sunburn that also involves the palms and soles. In postoperative TSS, the erythema may be more intense around the involved surgical wound site. Late-onset skin manifestations include a pruritic maculopapular rash that may occur 1–2 weeks after the disease onset and desquamation of the palms and soles that characteristically begins 1–3 weeks after illness develops. Since desquamation occurs late, the acute diagnosis of TSS cannot take advantage of this clinical feature.





15.2.2 Streptococcal Toxic Shock Syndrome

Severe invasive group A streptococcus (GAS, e.g., *Streptococcus pyogenes*) infections are defined as bacteremia, pneumonia, or any other infection associated with the isolation of GAS from a normally sterile body site [2]. Invasive infections also include necrotizing fasciitis and spontaneous gangrenous myositis. GAS TSS is defined as any GAS infection associated with the acute onset of shock and organ failure (Panel 15.2).

Panel 15.2 Streptococcal Toxic Shock Syndrome Clinical Case Definition

1. Isolation of group A β-haemolytic streptococci:
   - A. From a normally sterile site–blood, CSF, peritoneal fluid, tissue biopsy
   - B. From a non-sterile site–throat, vagina, sputum
2. Clinical signs of severity:
   - A. Hypotension–systolic blood pressure ≤90 mmHg for adults
   - B. Two or more of the following signs:
     - (a) Renal impairment–creatinine >2 mg/dL (177 μmol/L)
     - (b) Coagulopathy–platelets $\leq 100 \times 10^9$/L or disseminated intravascular coagulation
     - (c) Hepatic involvement–alanine aminotransferase, aspartate aminotransferase, or total bilirubin twice the upper limit of normal
     - (d) Adult respiratory distress syndrome
     - (e) Generalised, erythematous, macular rash that may desquamate
     - (f) Soft-tissue necrosis, including necrotizing fascitis, myositis, or gangrene

Case classification

Probable: case fulfills 1B and 2 (A and B) if no other cause for the illness is found

Definite: case fulfills 1A and 2 (A and B)

The most common portals of entry for streptococcal infections are the skin, vagina, or pharynx. However, among patients who develop GAS TSS, a portal of entry cannot be identified in 45 % of cases. These patients frequently develop deep-seated infections such as necrotizing fasciitis or myositis within 24–72 h at the exact site of minor trauma such as a bruise, strained muscle, or sprained ankle, frequently without a visible break in the skin. Pain may be more severe and relentless than that of staphylococcal TSS and is a common reason for seeking medical attention. Hypotension and organ dysfunction are rapidly progressive.

15.2.2.1 Skin Manifestation

Clinical signs of soft tissue infection typically consist of localized swelling and erythema followed by ecchymoses and sloughing of skin which progresses to necrotizing fasciitis or myositis. A variety of clinical presentations may be observed in patients without soft tissue findings. The most common initial symptom of GAS TSS is diffuse or localized pain, which is abrupt in onset, severe, and usually precedes tenderness or physical findings.

15.3 Pathophysiology

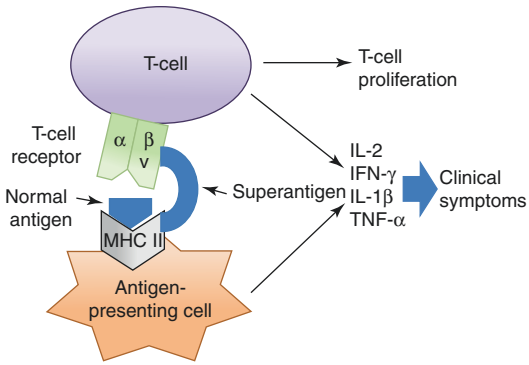
Superantigens are a group of staphylococcal and streptococcal exotoxins capable of including a variety of human diseases, including TSS. More than 20 different superantigens have been identified from *S. aureus* isolates, including staphylococcal enterotoxins, enterotoxin-like proteins, and TSS toxin-1 (TSST-1) [3–5]. More than 60 % of clinical *S. aureus* isolates carry at least one superantigen. These superantigens are able to activate T lymphocytes and antigen-presenting cells (APCs). As a result, activated T cells and APCs induce a massive release of cytokines and chemokines and cause the symptoms observed in TSS.

Superantigen mechanism of action: Superantigens bind to Major Histocompatibility Complex (MHC) class II molecules of APCs (i.e., macrophages) and Vβ region of T-cell receptor in a non-antigen-specific manner, which leads to massive release of cytokines and chemokines, as well as the clonal expansion of certain clonal types of T cells.

15.4 Treatment

15.4.1 Antibiotic Therapy

In patients with TSS due to MSSA or MRSA, we use clindamycin plus vancomycin. Once the diagnosis of GAS TSS is established, we recommend therapy with clindamycin in addition to penicillin G.



15.4.2 Surgical Therapy

An examination for the presence of foreign material should be undertaken, and this material should be removed. Drainage and debridement of any identified infectious focus is essential. In postsurgical patients, surgical wounds may not appear to be infected because of the decreased inflammatory response but should nevertheless be explored and debrided if the patient fulfills the clinical criteria for TSS. In GAS TSS, more prompt and aggressive exploration and surgical debridement of suspected deep-seated *S. pyogenes* infection is mandatory. It is critically important that surgeons be involved early in GAS TSS, since surgical intervention may be impossible later in the course due to toxicity or because infection has extended to vital areas that are difficult to debride (e.g., head and neck, thorax, or abdomen).

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Skin Necrosis due to Snakebites

16

Masaki Fujioka

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16.1 Introduction

More than five million people are bitten by venomous snakes, resulting in 125,000 deaths, mostly in Asia and Africa, every year. Many patients survive, but most victims suffer from local complications. A snakebite often results in skin necrosis if blisters are present [9].

This article presents a review of published reports on the incidence, pathology, and treatment of snakebites; focuses on the prevalence of necrotic wounds; and discusses surgical treatment.

16.2 Systemic and Local Complications After Envenomation

Snake venom contains more than ten enzymes, several nonenzymatic proteins, and peptides, which can be a combination of many toxins, including cytotoxins, hemotoxins, neurotoxins, and myotoxins. Systemic clinical manifestations encompass a wide variety of problems including pain, weakness, dizziness, nausea, vomiting, hypotension, thrombocytopenia, tachycardia, and anuria. On envenomation, the enzyme hyaluronidase catalyzes the hydrolysis of the main interstitial constituents, increasing tissue permeability. Proteolytic enzymes destroy the endothelium and basal membrane of capillaries. Phospholipase A acts directly on erythrocyte membranes, which leads to intravascular

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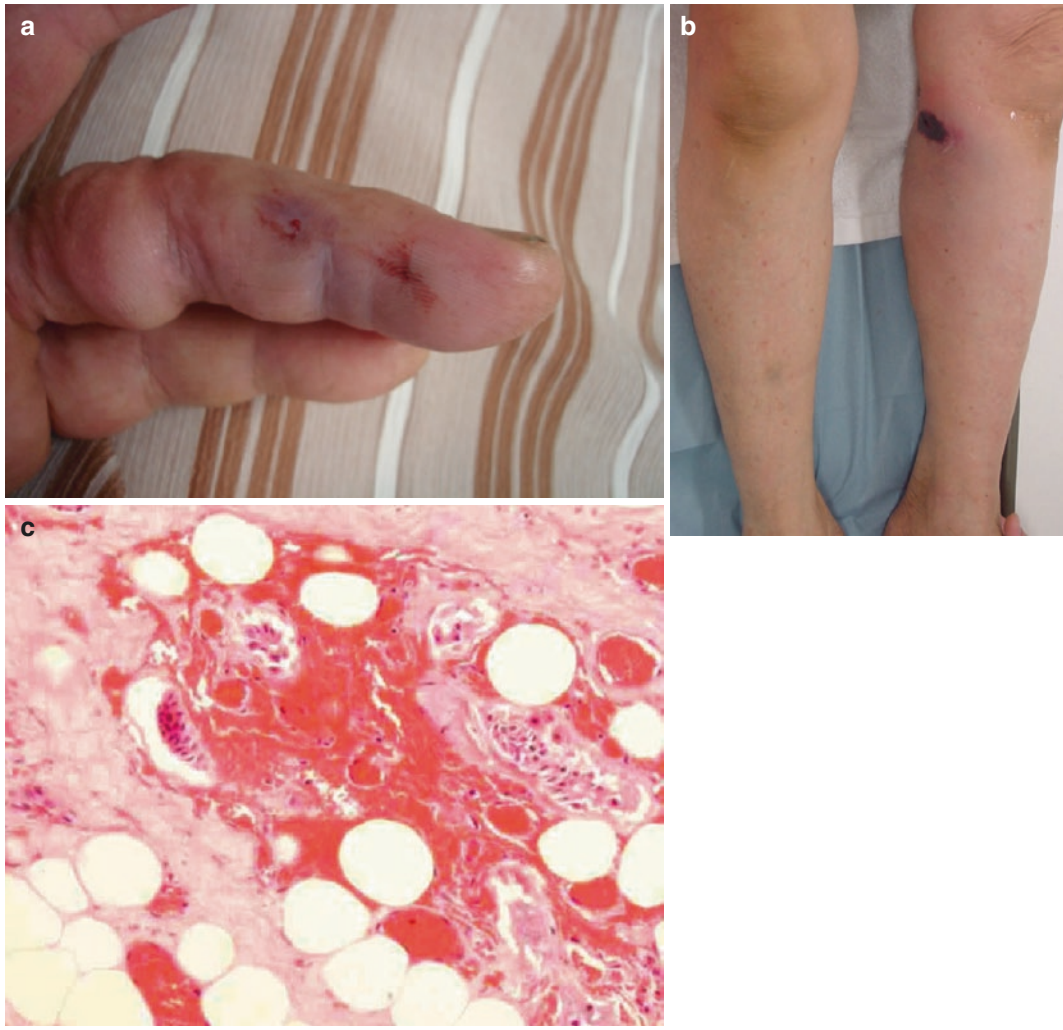

Fig. 16.1 (a) The picture shows two fang marks on the left ring finger. Swelling and tissue necrosis are visible around the fang marks. (b) The picture shows that the left knee was swollen with an area of soft tissue necrosis measuring 3.5 × 2.0 cm around the fang marks. (c) Histopathological findings of the fang mark site immediately after injury. The image shows red cell extravasation, vessel fibrinoid necrosis, and subcutaneous hemorrhagic necrosis with neutrophil infiltration

hemolysis. Local edema with pain and swelling, which can progress rapidly and may involve the entire extremity, can be attributed to the phospholipase A2 and metalloproteinases. Serous or hemorrhagic blisters appear around the fang marks (Fig. 16.1a). Some enzymes destroy tissue, resulting in necrosis (Fig. 16.1b, c) [3].

16.3 Dry Bite

The severity of a snakebite depends on the size of the snake and severity of envenomation. Venomous snakes sometimes bite without injecting venom. Such "dry bites" are known to occur in a number of venomous snake species

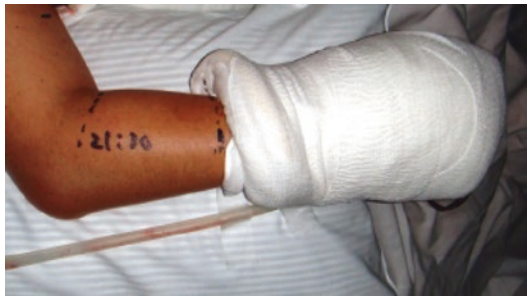

Fig. 16.2 Pressure immobilization using a compression bandage

and may account for in excess of 50 % of "accidental" bites in some species. The quantity of venom can vary depending on the size of the snake, and the venom contents also vary at the time of the bite [8].

16.4 First Aid

"Guidelines for the Management of Snake-Bites" by the World Health Organization (2010) [10] recommends the following: the victim must avoid physical activity, and the bite site should be immobilized and kept below heart level to prevent venom absorption and systemic spread. Tourniquet application, incision, excision, or mouth suction should not be performed. Many organizations, including the American Medical Association and American Red Cross, recommend washing the bite with soap and water. The use of a compression bandage is generally as effective; however, some guideline states that nonprofessionals should not apply a pressure bandage (Fig. 16.2) [1].

16.5 Antivenom Treatment

Antivenom is still the only effective treatment for envenomation. It is indicated to reduce convalescence time in moderate to severe cases and prevent death in severe cases. The British National Formulary suggested that antivenom should be given whenever there is any evidence of systemic envenoming or when local symptoms of envenoming are severe if, within 4 h of a bite on the hand or foot, swelling extends beyond the wrist or ankle [8]. There is evidence that antivenoms limit the spread of necrosis by inhibiting protease activity and reducing edema, leading to decreased risk of compartment syndrome.

16.6 Allergic Reactions to Antivenom

Allergic reactions to antivenom are possible. The most common reaction to antivenom is an anaphylactoid reaction, in 3–54 % of patients. Ismail et al. reported that 40 % of patients showing early reactions develop systemic anaphylaxis.

Serum sickness-type reactions have been reported to occur in 10–75 % of patients receiving equine antivenin. The onset of delayed serum sickness usually occurs within 3 weeks after antivenin treatment and consists of fatigue, itching, urticaria, arthralgia, lymphadenopathy, periarticular swelling, albuminuria, and, rarely, encephalopathy [6].

Patients who have had prior reactions to horse serum and those who have had previous antivenin treatments can develop severe, delayed hypersensitivity reactions.

16.7 Surgical Treatment

Most of the literature is focused on snakebite mortality. However, many patients survive and suffer from local complications. Although snakebites are most commonly treated with specific antivenoms, surgical management has also been practiced. A meta-analysis reported an incidence of 5.5 % sequelae and 3 % amputations. Snakebite patients with skin necrosis require serial wound debridement, followed by reconstructive surgery using skin grafting and/or a flap. Chattopadhyay et al. reported that 28 % of 58 patients required debridement to treat local necrosis. Maintenance of necrotic tissue in the

wounds will certainly aggravate the local and general conditions of patients [2]. Surgery plays an important role in the management of snakebite patients with tissue necrosis. However, this involves late debridement, performed after skin necrosis has occurred.

16.8 Immediate Debridement of Fang Marks

If a snakebite is intracutaneous, the venom slowly spreads through lymphatic and superficial venous vessels, but there has to be a sufficient venom concentration to reach the systemic circulation in a few hours.

Recent guidelines for first aid against viper envenomation call for avoiding incision and recommend the administration of antivenom. However, antivenom carries the risk of an anaphylactic reaction, so its usage should be approached with extreme caution.

Since the snakebite severity depends on the amount of venom injected into the victim, if even a small part of it can be removed, patients should present milder symptoms.

Even in the case of perfectly performed incision and suction, only 20 % of venom can be removed. Also, since snake fangs are curved, the venom is not directly under the bite marks; therefore, only a very deep incision can reach it [1]. To prevent later sequela, snakebites are best treated acutely by surgical debridement to remove as much venom as possible, which consequently decreases inflammatory responses and the necessity of antivenom [7].

In dry bite cases, radical ablation of fang marks should not be performed until local signs of envenomation appear. Since the aim of this procedure is the removal of injected venom, all necrotic soft tissue and inflamed skin must be debrided.

The standard method of wound management was presented in 2003 as a guideline for wound-bed preparation, stating that "efficient debridement is an essential step in acute and chronic wound management. Regular debridement is necessary to reduce the necrotic burden and achieve healthy granulation tissue. Debridement also reduces wound contamination." Furthermore, it is well known that all animal bites present a high risk of infection. Once tissue undergoes necrotic changes, it cannot survive. Thus, the removal of necrotic tissue as soon as possible is a reasonable option from the viewpoint of wound management and infection control. Moreover, this procedure ensures the removal of the remaining venom in necrotic tissue [5].

Although immediate radical ablation can reduce the volume of injected venom, total removal is impossible. Continuous observation is indispensable after ablation, and if severe systemic symptoms of envenomation occur, antivenom treatment should be indicated with no hesitation [4].

16.9 Case Reports

The Japanese viper (*Gloydius b. blomhoffii, Japanese mamushi*) is responsible for the majority of venomous snakebites in Japan, and more than 1,000 cases of Japanese viper bites are believed to occur annually. I present successful cases of immediate radical ablation of fang marks due to Japanese viper bites.

Case 1

The left index finger of a 74-year-old man was bitten by a Japanese viper. About 30 min after the injury, the victim arrived at our emergency unit, where the initial examination revealed that the finger was swollen with an area of soft tissue necrosis measuring 1.5 × 0.6 cm around the

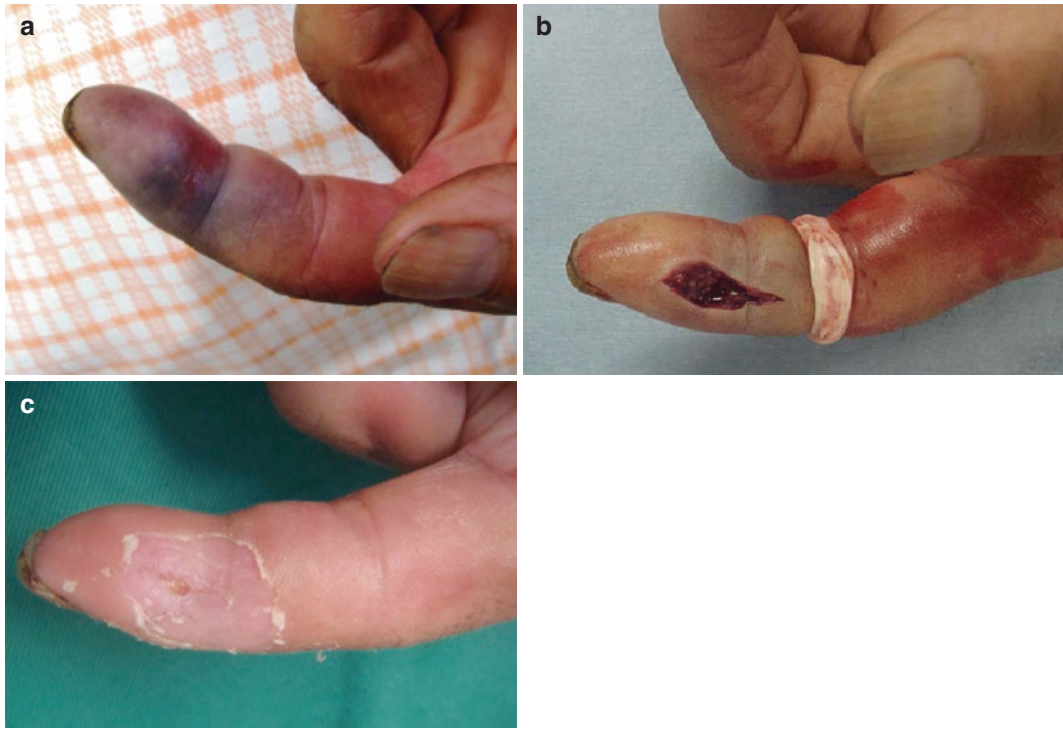

Fig. 16.3 (**a**) Case 1. At 30 minutes after being bitten, the finger was swollen with tissue necrosis. (**b**) The picture shows the wound after the removal of a 2.0 x 1.0-cm area of soft tissue. (**c**) Two months after injury, the picture shows that the wound has completely healed

fang marks (Fig. 16.3a). Immediate ablation was performed of the damaged skin, including the surrounding inflamed surface, covering a total area of 2.0×1.0 cm (Fig. 16.3b). Antivenom was not administered, since the general condition and laboratory data of the patient indicated stability. Treatment with ointment was performed, and the wound healed within 2 months with no sensory or functional impairment (Fig. 16.3c).

Case 2

A 72-year-old woman was bitten on her left leg by a Japanese viper and arrived at our unit 50 min after the injury. The left knee was swollen, with an area of ecchymosis and necrotic soft tissue measuring 3.5×2.0 cm (Fig. 16.4a). Surgical debridement of the ecchymotic surface, as well as necrotic tissue, including the surrounding inflamed skin (total of 8.5×7.0 cm), was immediately performed (Fig. 16.4b). Antivenom was not administered as severe systemic symptoms were not observed. Two weeks later, the patient received a split-thickness skin graft. Six months after the injury, the patient could return to work without any complications (Fig. 16.4c).

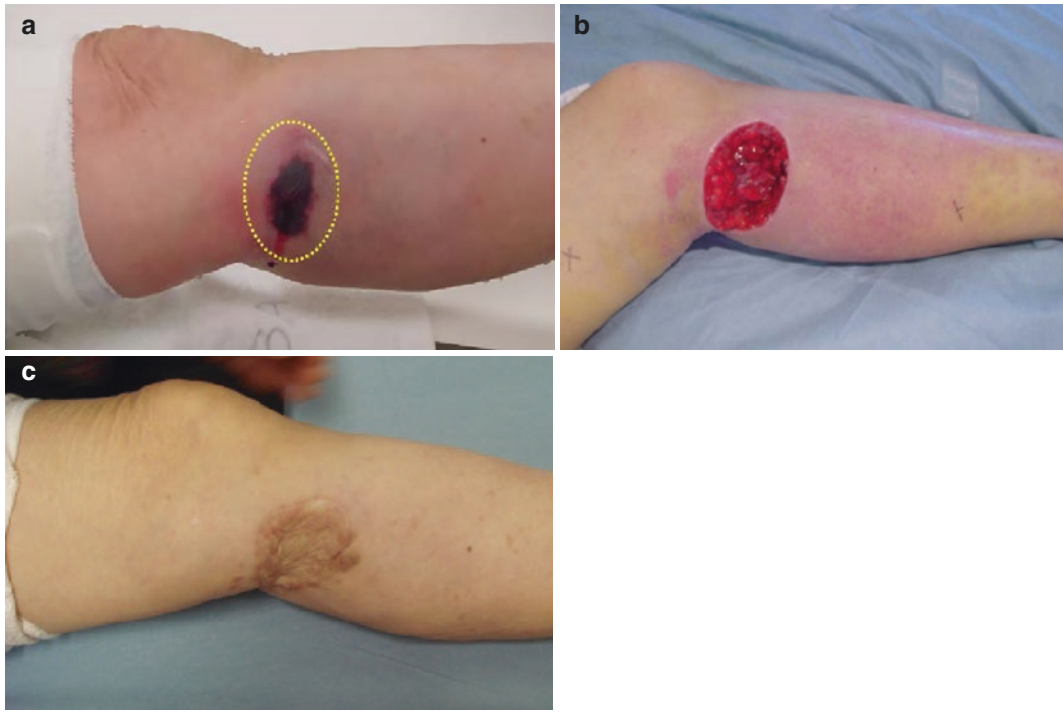

Fig. 16.4 (**a**) Case 2. At 30 minutes after being bitten, the left knee was swollen with an area of soft tissue necrosis measuring 3.5 × 2.0 cm around the fang marks. The dotted line indicates the debridement area. (**b**) The picture shows the wound immediately after surgical debridement of the ecchymotic surface, as well as ischemic and necrotic tissue, including the surrounding inflamed skin. (**c**) Six months after injury, the picture shows that the wound has completely healed

Case 3

A 78-year-old man was bitten on his left index finger by a Japanese viper and transferred to our emergency unit 1 h later. The finger was swollen with ecchymosis as well as ischemic soft tissue around the fang marks (Fig. 16.5a). The necrotic tissue and inflamed skin were ablated (Fig. 16.5b). The wound healed with no sensory or functional impairment within 2 months (Fig. 16.5c).

Conclusion

Although surgery is not as important as antivenom therapy for snakebites, surgical intervention will minimize functional loss [7]. Immediate radical ablation is a useful procedure that can reduce the amount of venom in tissue, which, consequently, decreases inflammatory reactions and reduces the necessity of antivenom usage.

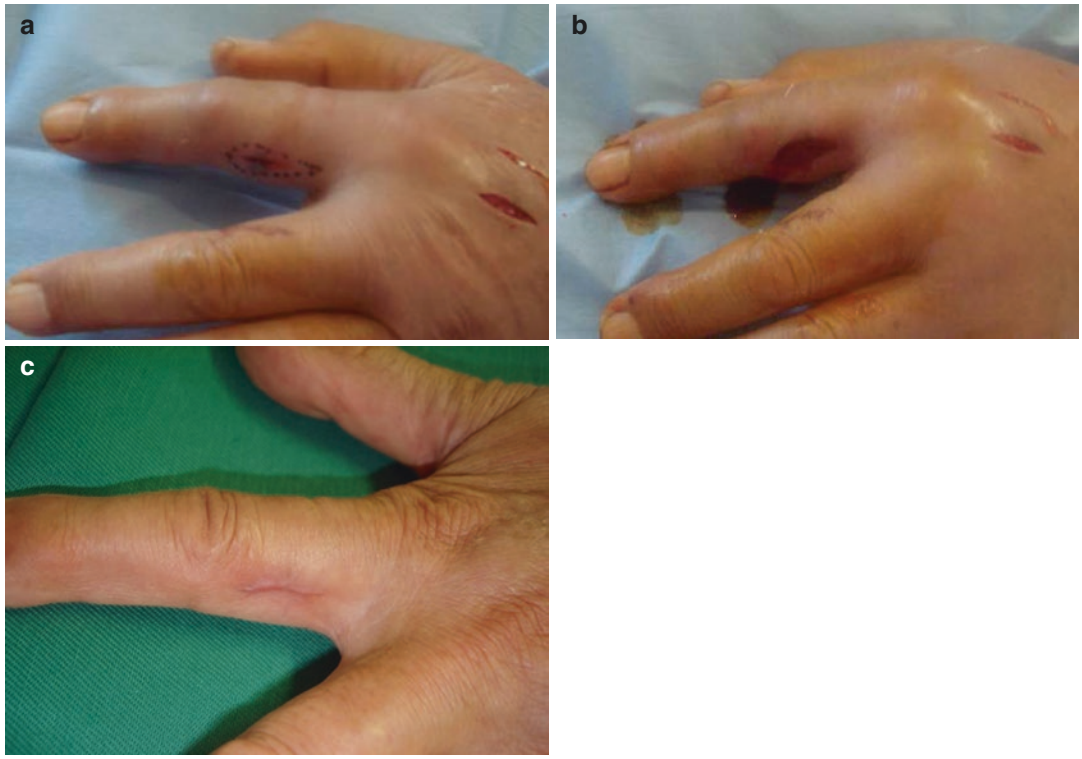

Fig. 16.5 (**a**) Case 3. At one hour after being bitten, the left index finger was swollen with tissue necrosis. (**b**) The picture shows the wound after the removal of a 2.5 × 0.6-cm area of soft tissue. (**c**) The photograph shows the wound 2 months after injury, with favorable resurfacing

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Part IV

Medical Origin

Rheumatoid and Systemic Collagenosis Vasculitis

17

Fujioka Masaki

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17.1 Introduction

Rheumatoid arthritis (RA) and systemic collagenosis vasculitis affect all the systems of the body, causing neurological, cardiovascular, pulmonary, hematological, endocrine-metabolic, and dermatological disorders [9]. Among them, ulceration in RA is a difficult clinical problem and a common cause of morbidity. Patients with RA and systemic collagenosis vasculitis appear to be at increased risk of developing chronic ulcers, and it was believed that 66 % of them had erosive skin disease [7].

Wound bed preparation has allowed uncomplicated wounds to heal quickly without surgery. However, the treatment of ulcers induced by RA and other inflammatory connective tissue disorders are hard to heal because of the combination of rheumatoid vasculitis (RV), venous stasis disease, and chronic glucocorticoid use.

This chapter focuses on the prevalence of complex wounds among patients with RA and

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systemic collagenosis vasculitis and shows effective and successive treatments of these wounds.

17.2 How Do Ulcers Develop in Patients with RA and Systemic Collagenosis Diseases?

Many inflammatory diseases affect the skin and joints. RA and several connective tissue diseases are considered to be rheumatic conditions with secondary skin involvement, which commonly result in ulcers or necrosis [7]. The frequency of leg ulcer in patients with RA may be up to 10 %. Ulcers in RA are usually multifactorial in etiology, including cutaneous vasculitis, peripheral arterial disease, venous insufficiency, skin fragility due to poor nutrition and corticosteroids, minor trauma, foot deformity, peripheral neuropathy, and peripheral edema [6].

17.2.1 Vasculitis

Ulcers are mainly attributed to vasculitis, which can be identified by histology and direct immunofluorescence [7]. Formerly, it was estimated that vasculitis had an ethological role in 18–37 % of leg ulcers in patients with RA; however, the prevalence of RV is now decreasing because of improved control of RA in the era of biologic therapy [8]. The ulcers secondary to vasculitis are painful and deep and showed well-demarcated or punched-out appearance (Fig. 17.1). The medium-vessel vasculitis can also lead to digital ischemia and necrosis (Fig. 17.2a, b).

Pathologic features of rheumatoid vasculitis include mononuclear cells or neutrophilic infiltration of the vessel wall of small and medium vessels.

17.2.2 Neutrophilic Dermatoses

Neutrophilic dermatoses are the conditions that have an inflammatory infiltrate consisting of mature polymorphonuclear leukocytes with no evidence of infection; these include Sweet's syndrome and pyoderma gangrenosum. The pathogenesis of neutrophilic dermatoses is believed that these disorders represent a state of altered immunologic reactivity because they generally respond to systemic glucocorticoids and other immunomodulatory therapies [1].

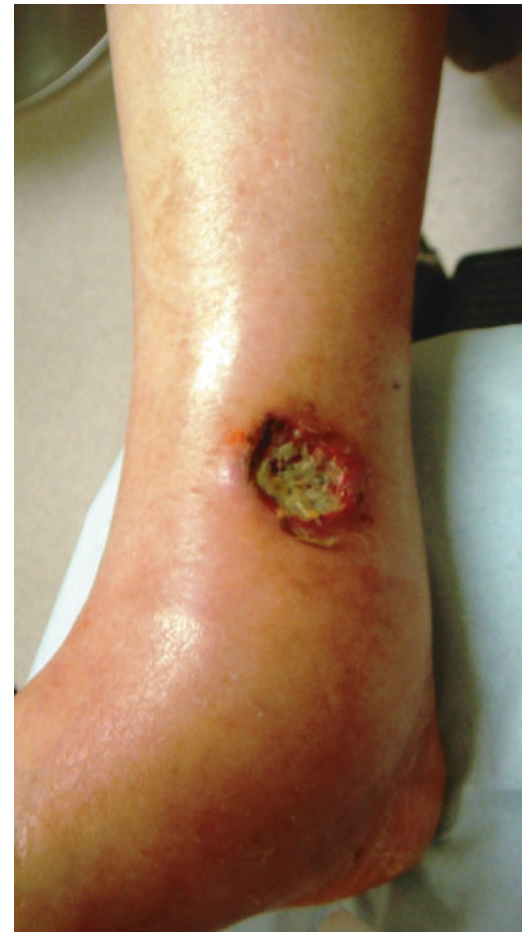

Fig. 17.1 Deep ulcer with necrotic eschar was found on the medial malleolus in patient with RA

17.2.3 Venous Stasis

Ulcerative lesions may also result from venous stasis. Ankle joint dysfunction caused by RA reduces ankle movement, which is responsible for impairment of the normal venous pump function and leads to venous hypertension [3].

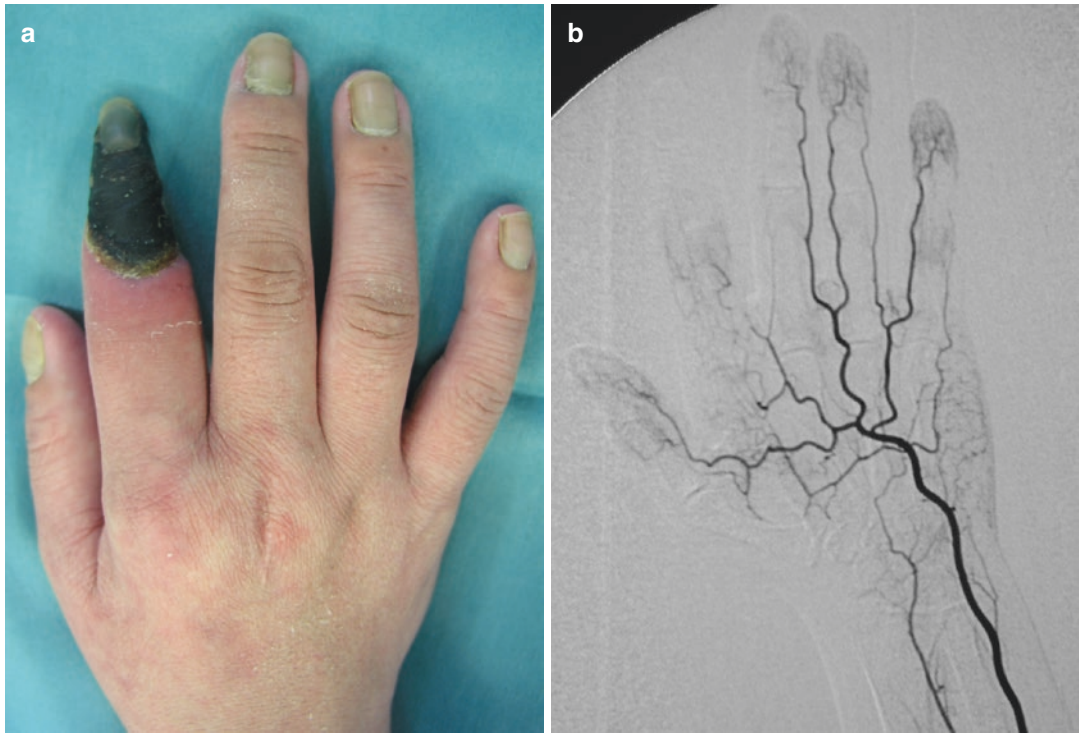

Fig. 17.2 (**a**) Right finger necrosis due to ischemia was found in patient with RA. (**b**) Angiography showed the obstruction of digital artery due to vasculitis of medium-peripheral vessel

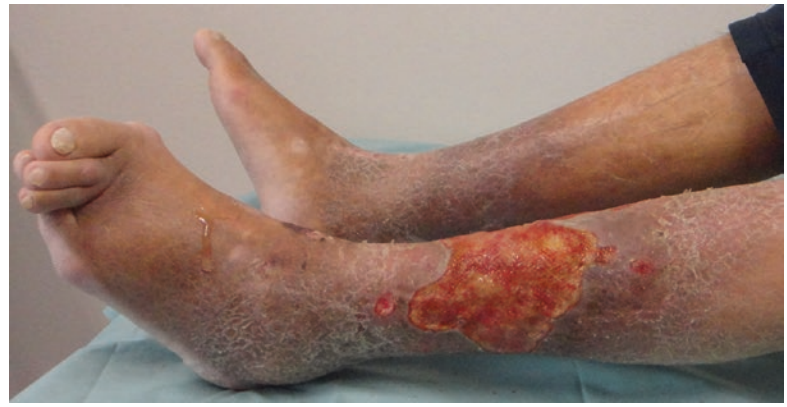

Fig. 17.3 Venous stasis ulcer located at the lower leg surrounded by varicosis. Toe and ankle deformities caused by RA were also found

This unfavorable state leads to increased tissue fibrosis and decreases the diffusion of oxygen to the skin, producing skin fragility and results in venous ulceration [1] (Fig. 17.3). Leg ulcers in RA are associated with venous disease in as many as 45 % [8].

17.2.4 Arterial Disease

Arterial insufficiency is one of the reasons to develop ulcer, especially, in the toes or feet of patients with RA and several connective tissue diseases, such as systemic sclerosis and

scleroderma. Pun et al. found arterial insufficiency in 36 % of ulcerated legs in 26 patients with RA, and Baker et al. did found ischemia in 41 % of those in 27 patients with RA [8].

17.2.5 Corticosteroid Therapy

Medications used to treat RA can cause skin changes [4]. It is a common clinical practice to use systemic glucocorticoids to suppress RV and other connective tissue diseases. Glucocorticoids are administrated to about half of patients with RA leg ulcers. Effects of glucocorticoids inhibiting wound healing include: stabilization of lysosomal membranes which inhibits the release of chemical mediators, suppression of fibroblasts and immunity, and inhibition of collagen fiber synthesis causing skin atrophy [5]. Atrophic skin of RA patients treated with continuous glucocorticoids can be easily torn and develop lacerations, which are likely to be more severe because infections are common (Fig. 17.4).

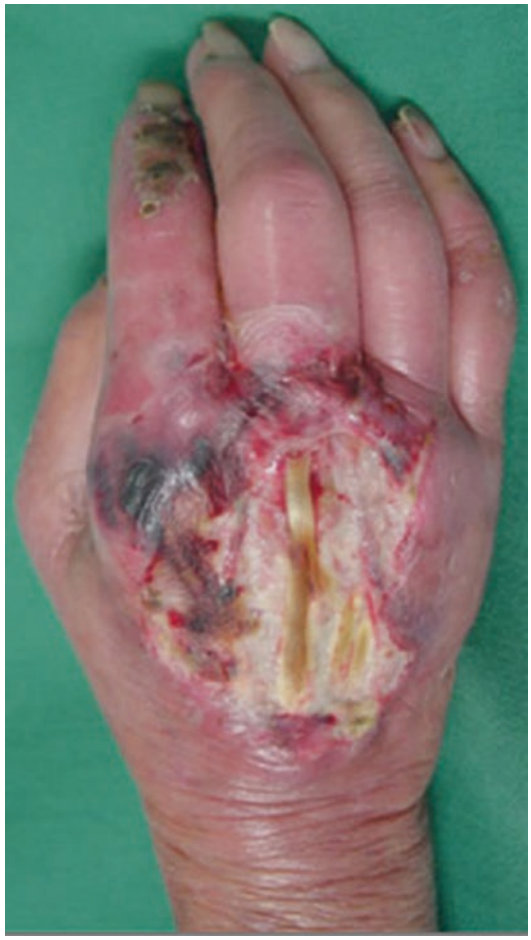

Fig. 17.4 Small wound of the hand of SLE patients has become more severe because infections occurred

17.3 Ulcers in Other Connective Tissue Diseases

17.3.1 Systemic Lupus Erythematosus (SLE)

Ten to twenty percent of patients with SLE develop cutaneous vasculitis and show purpuric papules, which sometimes cause ulceration [8]. The lower extremity is a common site and leg ulcer caused by leukocytoclastic vasculitis or necrotizing arteritis was found in 5–6 % of patients with SLE (Fig. 17.5).

17.3.2 Systemic Sclerosis

Sclerodermatous change develops usually in the feet and legs, which sometimes results in ischemic necrosis and ulceration of the toes. Early skin changes in systemic forms may include edematous change, which lasts or is replaced by thickening and tightening of the skin. Painful ulcerations appear, especially on the area of the skin overlying bony prominence. These lesions are hard to heal [4].

17.3.3 Dermatomyositis

A small-vessel vasculitis and calcinosis in the subcutaneous tissue cause ulceration usually on the feet. Healing is slow and ulcer often requires debridement of calcinotic material surgically [4].

17.3.4 Sjögren's Syndrome

Sjögren's syndrome is associated with RA, SLE, and some inflammatory connective tissue

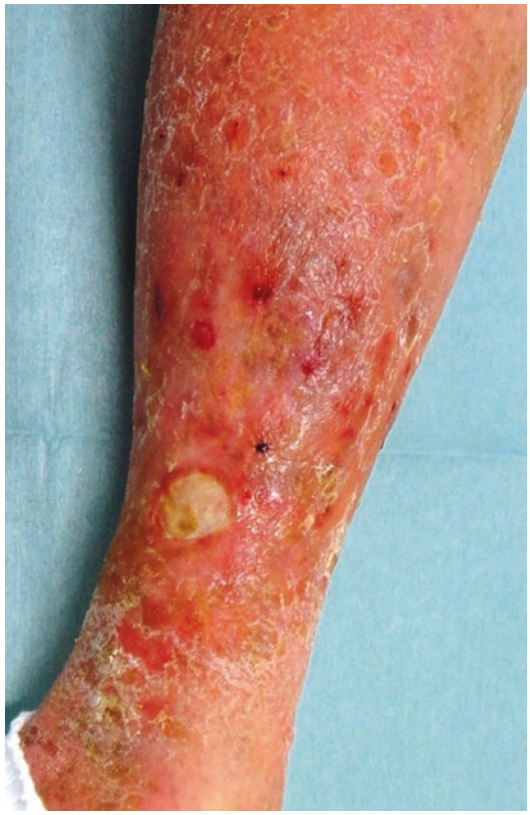

Fig. 17.5 A patient with SLE had a leg ulcer for 2 years

disease. Cutaneous magnifications include Raynaud's phenomenon (in 33 % of patients), dryness of skin, purpura, and vasculitic ulcers of the legs [4].

17.3.5 Scleroderma

Although scleroderma (SSc) is a clinically heterogeneous disorder, the loss of cutaneous elasticity and accompanying tightness followed by thickening and hardening of the skin is an almost universal manifestation. Painful digital ulcers that occur on the fingertips as a result of local ischaemia and vascular insufficiency are a frequent complication. While some SSc patients have skin lesions that remain largely confined to the extremities, others exhibit skin thickening that extends progressively from the extremities to the trunk [4].

17.3.6 Behcet's Syndrome

Behcet's syndrome develops arthritis, and pustule cutaneous ulcers are one of the classical triad of features. The small ulcers are due to vasculitis of small vessels and tend to relapse [4].

17.4 Treatments of Ulcers in Patients with RA and Other Connective Tissue Diseases

17.4.1 Systemic Approach

Treatment for rheumatoid vasculitis is determined by the degree of organ system involvement, and systemic vasculitis requires aggressive therapy. In general, this treatment regimen consists of the combination of high doses of glucocorticoids and a cytotoxic agent [3, 10]. Mild rheumatoid vasculitis involving the skin can be treated with prednisone (30–200 mg/day orally or IV) and methotrexate (10–25 mg/week orally or IM) or azathioprine (50–150 mg/day orally). More serious organ system involvement may require treatment with higher-dose steroids and cyclophosphamide or biologic agents [10]. Besides, tumor necrosis factor alpha antagonists are becoming the preferred choice when pyoderma gangrenosum is accompanied by rheumatoid arthritis, and rituximab treatment seemed to be effective in cases of vasculitis-associated cutaneous ulcers in RA patients.

17.4.2 Topical Wound Treatment

Chronic ulcers have a complex, inflammatory nature and produce exudates, which interfere with the healing process. Essentially, effective strategies to heal the chronic ulcers in association with RA can be developed by the principle of wound bed preparation [8].

17.4.2.1 Occlusive Dressings

Occlusive dressings may be beneficial in some respects, such as preventing crust formation,

encouraging migration of inflammatory cells into the wounds. An appropriate wound dressing changing can remove excess exudates while retaining a moist environment that can accelerate wound healing. Hydrogels, polyurethane foams, hydrocolloids, and hydrofibers are usually used to control the wound exudates.

17.4.2.2 Approach for the Wound Infection

Generally, open wounds have bacteria and many wounds involve colonization. The amount of bacteria can be minimized through adequate cleaning of the wound, absorption of drainage, and debridement if necessary [8]. When considering bacteriological findings, it is important to differentiate between colonization and infection. When infectious signs are noted, cleansing, wet-to-dry dressing or irrigation, and surgical debridement if necessary should be performed.

17.4.2.3 Several Adjuvant Devices in the Management of Hard-to-Heal Wounds

In this section, several adjuvant devices are presented, including growth factor, bioengineered tissues, and a negative pressure system, which are combined to improve the complex wounds. It was found that dermal wounds treated with collagen sponges seeded with fibroblasts or coated with bFGF show an increased degree of reepithelialization, indicating that this method facilitates early dermal and epidermal wound healing [2]. Combination treatment with bFGF and artificial dermis promotes proliferation and recruitment of fibroblasts, neovascularization, and synthesis of collagen fibers. Consequently, this method improves complex wounds and quickly prepares a favorable wound bed. We usually perform wound bed preparation with a combination of these therapies for the improvement of complex wounds (Fig. 17.6a–c).

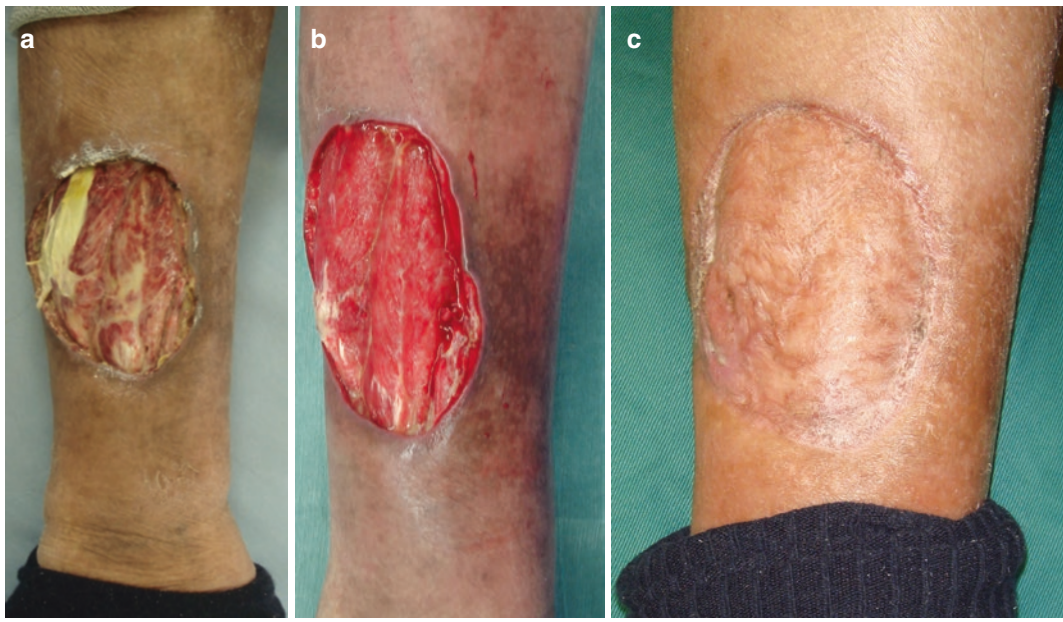

Fig. 17.6 (**a**) The photograph shows the unsatisfactory wound bed in patient with SLE at initial examination. The tendon was exposed, and infection had occurred. (**b**) The wound became clean, and a favorable wound bed had developed 2 weeks after the start of combination treatment with bFGF and artificial dermis. (**c**) The photograph shows the resurfaced wound 3 years after skin grafting, showing no relapse of ulcer

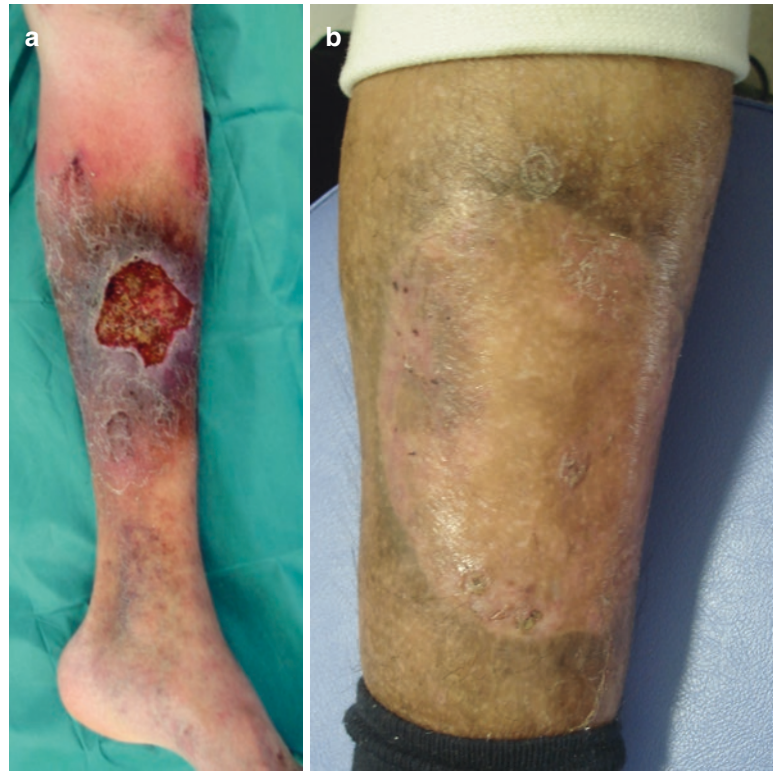

Fig. 17.7 (**a**) The photograph shows the unsatisfactory wound bed with infection in patient with pyoderma gangrenosum. (**b**) A photograph 6 months after skin grafting shows favorable wound resurfacing without relapse

17.5 Surgical Wound Closure for Patients with RA

The resurfacing of wounds is one of the most important procedures because such wounds will cause further infection, exudates, odors, and bleeding, which decrease the patient's quality of life. When a wound is covered with suitable granulation and no contamination is observed, split-thickness autologous skin grafts should be performed as soon as possible (Fig. 17.7a, b). In cases of bone- or tendon-exposed wounds, some vascularized flaps are required to resurface the wounds because grafted skin will not take directly on the tendon or bone (Fig. 17.8a–c).

17.6 Prevention of Recurrence

Once the ulcer has healed, the patients should be aware of the risk of recurrence. If venous insufficiency is present, compression bandaging should be considered. If there is peripheral arterial disease, cessation of smoking and lowering the serum cholesterol are important. Besides, adequate nutrition and appropriate footwear will reduce the risk of recurrence of leg ulcers [7].

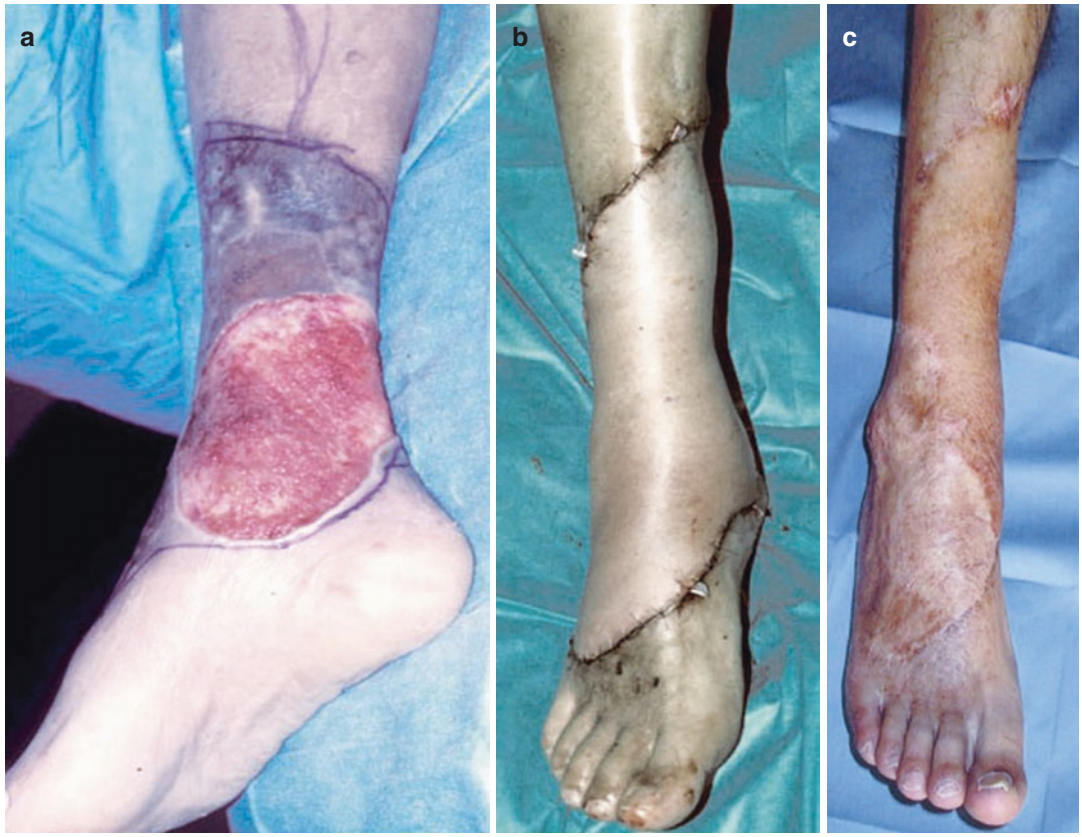

Fig. 17.8 (**a**) The photograph shows the venous stasis ulcer located at the lower leg in patient with RA. The patient underwent immediate debridement, consequently tendons were exposed. (**b**) The photograph shows immediate after the surgery. The wound was resurfaced with a free groin flap. (**c**) A photograph 6 months after the surgery shows favorable wound resurfacing without relapse

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Giant Cell Arteritis

18

Pauline Lecerf

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18.1 Introduction/ Physiopathology

Giant cell arteritis (GCA) or Horton's disease is a systemic granulomatous vasculitis of medium- and large-sized arteries. This is an antigen-driven disease with local T-cell and macrophage activation in the vessel wall and with an important role of proinflammatory cytokines. GCA is also called "temporal arteritis" because it involves often the superficial temporal arteries. The condition affects especially the extracranial branches of the carotid artery, but recently, GCA has been recognised to also affect limb arteries and the aorta with high prevalence [1, 2].

18.2 Diagnosis

(a) *Medical context*

- GCA is the most common vasculitis in the elderly.
- Incidence increases with ageing of the population.
- GCA affects mainly white individuals over 50 years of age, with a peak incidence in the 70–79-year-old age group.
- Women are mostly affected (sex ratio 3:1) [3, 4].

(b) *Semiology*

Symptoms are correlated with the localisation of the vasculitic involvement of the arteries.

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Classical form of GCA, with involvement of the extracranial branches of the carotid artery	
Early	Headache, jaw claudication, purpuric lesions and tender nodules in temporal region, temporal artery pain, temporal artery pulseless, weight loss, fever, visual manifestations, polymyalgia rheumatica (in 30–50 % of the cases) [5]
Late	Ulceration and/or gangrene of frontotemporal scalp or tongue
Involvement of limb arteries [6–8]	
Early	Swelling, pain, claudication
Late	Ulceration, necrosis (Fig. 18.1), gangrene of the distal parts of the limbs
Major complications	
Ischemic optic neuritis/blindness, stroke (mainly vertebrobasilar territory), aortic complications (aneurysms, dissection) [6]	

(c) *Criteria* (Table 18.1)

(d) *Routine evaluation*

- *Biology*
  - Elevated C-reactive protein (CRP), erythrocyte sedimentation rate (ESR)
  - Thrombocytosis
  - Anaemia

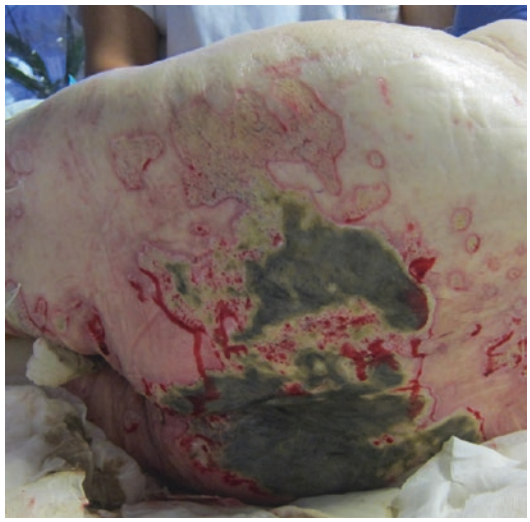

Fig. 18.1 Vast ulceration and necrosis of the buttock due to giant cell arteritis in a 76-year-old female, with associated signs: jaw claudication, temporal artery pulseless, weight loss, visual manifestations, and amputations of the left forefoot weeks before. Improvement of the ulcerations of the seat after initiation of glucocorticoid therapy

Table 18.1 ACR classification criteria for giant cell arteritis

Age ≥50 years at disease onset
New onset of localised headache
Temporal artery tenderness or decreased temporal artery pulse
ESR ≥50 mm/h
Biopsy: necrotising arteritis; mononuclear cell infiltrates or a granulomatous process with multinucleated giant cells
Presence of ≥3/5: sensitivity of 93 % and specificity of 91 % for distinguishing GCA from other primary vasculitis syndromes

American College of Rheumatology (ACR) – 1990

  - Abnormal liver function tests, particularly raised alkaline phosphatase
  - Raised α1 and α2 globulins on serum electrophoresis
  - No autoimmune disorders [2]
- *Histology*
  - *Temporal artery biopsy (TAB).*
    - Recommended in all suspected cases.
    - Should be performed soon after the onset of treatment.
    - The sensitivity and specificity of TAB has been reported to be around 75 and 90 %, respectively.
    - Histological features: inflammation of the vessel wall by infiltration of T cells and macrophages, presence of giant cells, granulomatous lesions, intimal hyperplasia and destruction of elastic fibres, and arterial lumen partially or completely occluded.
    - Histologic signs of inflammation may be missed in TABs performed in arteritis-free segments because GCA affects vessels focally and segmentally.
  - *Skin biopsies*
    - Histological features from limb ulcer edge, nodule, and purpuric patch show nonspecific ulceration if the biopsy is superficial and do not include deep medium or large vessels. The extracranial large vessel had similar histopathologic features to that seen in the temporal arteries

and showed a lymphocytic panarteritis with a variable number of giant cells. Direct immunofluorescence is negative [9].

- *Imaging*
  The prevalence of limb arteries involvement in GCA is clinically underestimated. Imaging studies are useful in identifying the involvement of the latter [2]:
  - Ultrasonography
  - Positron emission tomography (PET)
  - Computed tomography angiography (CTA)
  - Magnetic resonance angiography (MRA)

  It is also recommended to perform a screening for aortic aneurysms and for extra-aortic large-vessel involvement.

18.3 Treatment

High-dose glucocorticosteroid therapy is the first-line therapy as soon as the diagnosis has been established or if there is a strong clinical suspicion of GCA to prevent visual loss [10, 11].

1. Recommended starting dosages of glucocorticosteroids are:

Uncomplicated GCA (no jaw claudication or visual disturbance)	40–60 mg prednisolone daily
Evolving visual loss or amaurosis fugax (complicated GCA)	500 mg to 1 g of i.v. methylprednisolone for 3 days before oral glucocorticosteroids
Established visual loss	60 mg prednisolone daily to protect the contralateral eye

   Do not forget bone protection and proton-pump inhibitors for gastrointestinal protection.
2. Symptoms of GCA should respond rapidly to high-dose glucocorticosteroid treatment, followed by resolution of the inflammatory response. Failure to do so should raise the question of an alternative diagnosis.
3. Glucocorticosteroid reduction:
   - Should be considered only in the absence of clinical symptoms, signs, and laboratory abnormalities suggestive of active disease.
   - Introduction of MTX or alternative immunosuppressants should be considered as adjuvant therapy for recurrent relapse.

Fewer studies about tocilizumab (TCZ), an interleukin (IL)-6 receptor antagonist, to maintain disease remission in patients with giant cell arteritis have been conducted [12]. Biological therapies still require further study and are not yet recommended.

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Hidradenitis Suppurativa

19

Kian Zarchi and Gregor B.E. Jemec

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19.1 Introduction

Hidradenitis suppurativa is a chronic inflammatory skin disease affecting approximately 1% of the adult population [1–2]. It presents clinically as painful inflammatory nodules, draining sinuses, and abscesses, causing considerable pain, suppuration, and malodor. It has a substantial negative impact on quality of life, more so than many other skin diseases, such as eczema and psoriasis [3]. The disease is associated with physical and psychological morbidity, such as depression, metabolic syndrome, and an increased risk of cancer.

The typical age of onset is the early 20s; but the disease may present in younger ages, and occasionally affection of prepubertal children is seen. Symptoms persist for years to decades, characterized by periods of flares and remission. The disease activity often diminishes with age, as the prevalence decreases among adults aged 50 years and older. The sex ratio is 3:1, females to males. Family history is reported by 1 in 3 patients and an autosomal dominant pattern of inheritance has been described [1]. Other risk factors include obesity and smoking, both being associated with severe disease.

19.2 Diagnosis

Patients with hidradenitis suppurativa are usually diagnosed several years after onset of symptoms, mostly due to failure on the part of health-care

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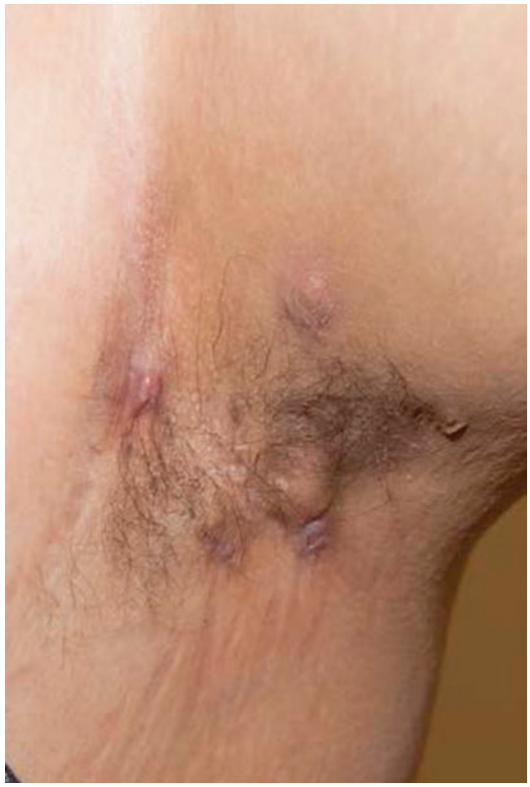

Fig. 19.1 Hurley stage II characterized by recurrent nodules and abscesses, formation of sinus tracts, and scarring

professionals to recognize the disease. The diagnosis is primarily clinical, based on the presence of recurring noninflammatory and inflammatory nodules, abscesses, and sinus tracts. The inflammatory nodules and abscesses are erythematous, tender, and not uncommonly painful. They may persist for weeks to months without any considerable change, or they may rupture, yielding purulent discharge. In moderate and severe disease, drainage also occurs through sinus tracts, causing malodorous suppuration. The lesions are distributed characteristically with predilection sites being the axillary, inguinofemoral, and anogenital regions. Extensions beyond these areas are occasionally seen.

The most commonly used classification system for hidradenitis suppurativa is that of Hurley (stages I–III), stage I representing solitary or multiple nodules and abscesses, stage II recurrent abscesses with sinus tract formation and scarring (Fig. 19.1), and stage III diffuse involvement of the area with

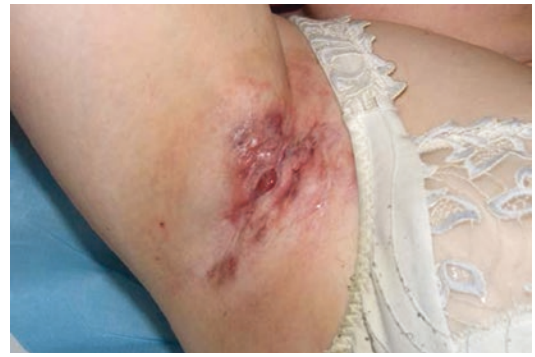

Fig. 19.2 Hurley stage III characterized by diffuse involvement of the area with multiple interconnected sinus tracts

multiple interconnected sinus tracts (Fig. 19.2) [4]. The majority of patients suffer from mild disease corresponding to stages I and II, while a smaller proportion progresses to severe disease which usually predominates in hospital populations.

Secondary lesions include cutaneous ulcerations, pyogenic granulomas, and hypertrophic scars, the latter appearing as indurated plaques or linearly ropelike scars. In contrast to closed comedones, which never occur in HS-affected areas, multiple, big, open comedones (the so-called tombstone comedones) may be seen in previously active areas.

Biopsies are rarely needed as the diagnosis is based on the clinical presentation; nonetheless, in some cases, differentiation from other skin diseases, such as pyoderma gangrenosum and cutaneous Crohn's disease, might be difficult and require histopathological investigations. The characteristic histological findings include follicular hyperplasia and hyperkeratosis, local infiltration of inflammatory cells, formation of sinus tracts, and presence of necrosis. Microbiological examinations most frequently fail to identify pathogens.

19.3 Pathophysiology

The folliculopilosebaceous unit is the primary focus of the pathologic processes involved in hidradenitis suppurativa; however, the etiology remains controversial. Different theories have

been proposed to explain the pathogenesis. These include the suggestion of an immune response dysfunction, as it has been proposed that the disease is a result of an inappropriate immunologic response to the normal skin flora, similar to the pathogenic processes involved in Crohn's disease. Indeed, elevated levels of proinflammatory cytokines, including tumor necrosis factor-α and interleukin-1β, and involvement of the interleukin-12–interleukin-23 pathway have been shown [5]. Further, the lack of expression of human beta-defensin-2, an important antimicrobial peptide of the innate immune system against Gram-negative bacteria, in HS lesions supports this theory. However, the histopathological findings in early disease and investigations of basal membrane zone in the folliculopilosebaceous unit point towards a structural defect in the sebofollicular junction as the possible main cause [6]. It is hypothesized that mechanical trauma makes the structurally defect folliculopilosebaceous unit release keratin and other mediators, thereby triggering inflammation and inducing tissue destruction and necrosis.

The possibility of HS being a defect in wound healing has also been discussed. It has been hypothesized that whereas breaches of the follicular epithelium are common following infections or physical trauma, the perpetuation of the subsequent inflammatory process which could lead to HS is not. It may, therefore, be speculated that a disturbed wound healing process following the inflammatory stage occurs as a major factor in HS. This theory is supported by the detection of highly elevated levels of matrix metalloproteinase-2 in keratinocytes, fibroblasts, sweat glands, and hair follicles in lesional HS skin, indicating dysregulated tissue repair and reconstruction following unspecific tissue damage [7].

19.4 Treatment

Treatment of hidradenitis suppurativa is often a challenge [8]. By the time the diagnosis is made, most patients have been treated with short-term antibiotic regimens for several years without experiencing any effect, as the lesions are commonly misinterpreted as furunculosis or common abscesses. Establishing a strong alliance with the patient, attempting to restore the patient's faith in the doctor-patient relationship and explaining the fluctuating nature of the disease are highly beneficial in minimizing the risk of low patient compliance. This is especially important in the case of resistant disease, where several therapeutic approaches might be carried out until the one or the combination inducing sufficient improvement is found.

Mild disease is often managed with topical therapy, such as topical clindamycin, or occasional intralesional glucocorticoid injections. However, in case of moderate to severe disease, topical agents are inadequate and systemic therapy usually indicated. Systemic treatment options include oral antibiotics with immunomodulatory properties such as tetracycline, doxycycline, clindamycin, and rifampicin; antiandrogenic therapies; and systemic immunosuppressive therapy, including tumor necrosis factor-α inhibitors [1].

In elements refractory to medical treatment and in the presence of scarred lesions, surgery, nonetheless, is a mainstay of therapy. Surgical approaches include exteriorization ("deroofing" of sinus tract, abscesses, and cysts [Fig. 19.3]) and surgical excision of lesional skin, with radical excisions being associated with lower recurrence rates. Alternatively, destruction of lesional hair-bearing skin is achieved using ablative CO_2 laser [9]. The surgical and ablative laser approaches are based on the removal/destruction of the cutaneous

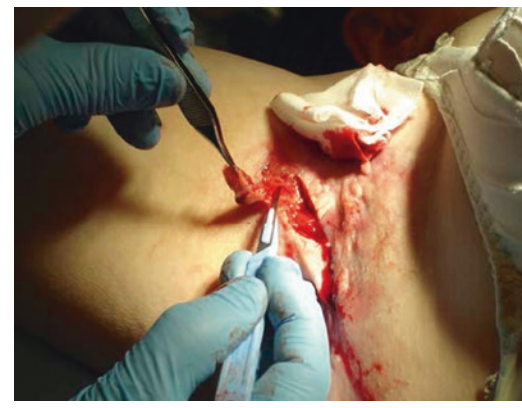

Fig. 19.3 "Deroofing" of a sinus tract

structures involved in the disease, thereby causing open wounds requiring closure or management.

Primary suture, skin graft, or flap reconstruction can be used to close the wounds depending on the extent of procedure, or closure may be achieved by secondary intention. Generally, secondary intention healing is recommended for all but the smallest excisions. A comparison of skin grafting versus closure by secondary intention using foam dressing in patients undergoing bilateral excision revealed that skin grafting led to more rapid healing; however, closure by secondary intention provided good cosmetic results and avoided the need for immobilization and a painful donor side and was preferred by the patients [10]. Long-term evaluation of healing by secondary intention suggests acceptable to excellent outcome qualities.

Secondary healing requires suitable bandaging for periods of up to 12 weeks. Since the disease affects concave surfaces of the body, it presents a practical challenge. Appropriate nonadherent dressings, such as foams, silicone-coated dressings, alginates, and hydrocolloids, are generally better suited to convex surfaces. Bandage type may be adjusted during the healing process as per normal, e.g., the initial combination of a saline gel and a silicone dressing may be gradually replaced by silicone dressing and ultimately a simple bandage to protect the final epithelialization of the wound. Individual adjustments may need to be performed, and once the wound is fully covered by granulation tissue, some patients prefer to avoid bandages all together. This non-recommended patient behavior most likely reflects the patients' experience with chronic suppurating preoperative lesions.

Vacuum-assisted therapy (VAC) may be used to promote angiogenesis of the underlying subcutaneous tissue, reduce bacterial counts, and stabilize skin grafts. VAC has been successfully used in treatment of large postoperative wounds.

19.5 Adjuvant Therapy

Although the primary aim of therapy remains the elimination or a substantial reduction in the inflammatory activities and the excision of severely involved lesional skin, providing adjuvant therapy throughout the disease course is necessary to improve the patients' quality of life. The disease presents many practical problems to the patients such as pain, tenderness, visible scars, suppuration, and malodor; hence, therapeutic decisions should address all those issues. Effective bandaging represents one of the challenges. Bandages should provide a secure and comfortable barrier against malodorous leakage and be absorbent to prevent maceration of the skin, easy to use and inexpensive. Currently no bandage meets all these requirements, and the available solutions are, therefore, combinations of products that are both expensive and difficult to apply to inverse area. As a consequence, the patients are often forced to turn towards alternative and inexpensive solutions such as sanitary pads, which are not designed for this purpose (Fig. 19.4). The morbidity due to HS is such that this issue of adjuvant therapy warrants more attention by health-care providers than it cur-

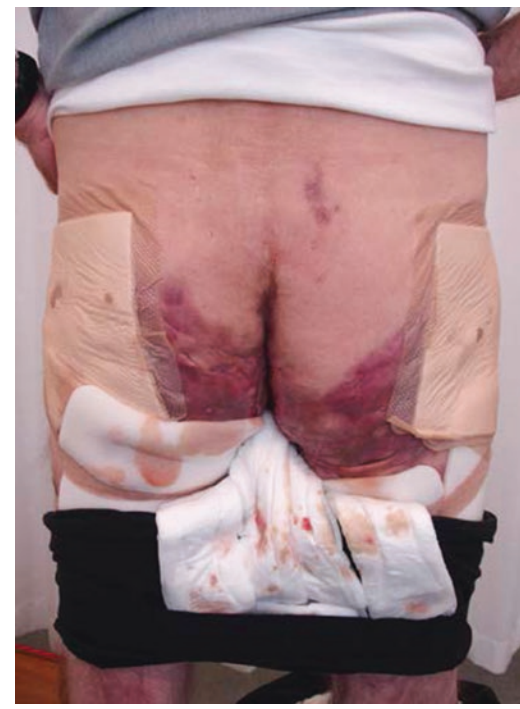

Fig. 19.4 Many HS patients are forced to use sanitary pads due to the lack of inexpensive appropriate dressings

rently receives. It is strongly recommended to address the practical problems of this hitherto neglected group of patients by providing appropriate attention to improved adjuvant therapy.

Conclusion

Although HS is an inflammatory skin disease, wound care is important in the treatment. Adjuvant therapy is an important aspect of this highly disturbing disease, because it provides both safe symptom management and patient empowerment. Most patients are left to their own initiatives due to lack of appropriate dressing materials, and when patients present in wound care clinics for treatment, they constitute a challenge for many.

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Vasculitis

20

Nicolas Kluger

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20.1 Diagnosis of Cutaneous Vasculitis Is Made on Histology

Physical cutaneous signs of vasculitis are wide and nonspecific. Cutaneous vasculitis (CV) affects the skin with varying intensity, depth, and distribution. Even though a certain number of syndromes have been described, a patient may present with symptoms that overlap with another clinical diagnosis making a diagnosis "at first sight" impossible. Most of all, vasculitis has a histopathologic definition; therefore, its confirmation comes only from the microscopic examination of the lesion [1–5].

The diagnosis of CV is made by microscopic examination of hematoxylin-eosin-stained biopsies. A list of criteria allows a trained pathologist to diagnose and distinguish an active vasculitis from chronic and healed lesions of vasculitis and changes that are adjacent to vasculitis and may help to define a subtype or the etiology of the CV. Inflammatory infiltrates within and around the vessel walls associated by intramural and/or intraluminal fibrin deposition (fibrinoid necrosis) confirm the diagnosis of vasculitis. Some changes are suggestive of active vasculitis such as red blood cell extravasation, perivascular nuclear dust (leukocytoclasia), eccrine gland necrosis, ulceration, and necrosis/infarction. In the absence of fibrinoid necrosis, the diagnosis of CV becomes more difficult. Lamination of the adventitia, media, and/or intima; perivascular nuclear dust

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(leukocytoclasia) without fibrinoid necrosis; loss of the elastic lamina with acellular scar tissue; or subendothelial intramuscular and/or adventitial inflammatory cells in large vessels are all other indications for vessel wall damages [1–5].

A direct immunofluorescence examination (DIF) is also mandatory in case of CV. It does not confirm the diagnosis of CV but allows to determine one or another diagnosis.

- The absence of immune complex is in favor for pauci-immune vasculitis: Wegener granulomatosis (WG), Churg-Strauss syndrome (CSS), and microscopic polyangiitis (MPA).
- Immunoglobulin (Ig) G, IgM, IgA, and/or C3 in or around the vessels may be found in immune-mediated vasculitis like cryoglobulinemia.
- In all cases of CV, immune depositions of Ig and complement may be found especially C3 and IgM.

However, the older the biopsied lesion is, the less immunoglobulin is found. After 72 h, only C3 is detected. Therefore, a negative DIF does not rule out the diagnosis of CV [1–5].

- The predominance of IgA is highly in favor for Henoch-Schönlein purpura (HSP) without being constant or specific.
- IgM depositions are observed, especially in case of circulating rheumatoid factor or cryoglobulinemia. IgA deposits are absent in case of cryoglobulinemia.

Of note, positive DIF without pathological assessment of CV is not relevant.

After confirmation of the diagnosis of CV itself, vasculitis may be defined more accurately by vessel size involvement (small, small to medium vessel, and medium to large vessel), the extent of the lesions (superficial perivascular to dermal and/or subcutaneous), and the predominant inflammatory cell infiltration. The finding of small-vessel vasculitis with predominance of neutrophilic infiltrate and positive DIF is indicative of cutaneous leukocytoclastic vasculitis, HSP, urticarial vasculitis, or erythema elevatum diutinum. More rarely, other cells may predominate such as eosinophils or lymphocytes. The presence of both small- and medium-sized vasculitides favors ANCA-associated/pauci-immune vasculitis (with negative DIF): CSS, MPA, WG or cryoglobulinemia, connective tissue disease (lupus, rheumatoid arthritis, etc.), or hypocomplemental vasculitis if DIF is positive. Polyarteritis nodosa is characterized by a neutrophilic infiltration associated with a medium-sized vessel vasculitis [1–5].

Some extravascular histologic pattern found in the surrounding tissue may be helpful to indicate a specific disease. Thus, palisading granulomatous dermatitis ("Winkelmann granuloma") is in favor for WG, CSS, rheumatoid arthritis, or systemic lupus erythematosus. The presence of eosinophils and flame figures associated with such granulomas is found in CSS, while neutrophils and basophilic debris in WG and rheumatoid vasculitis. Vacuolar interface dermatitis with sometimes dermal mucin deposition is associated with lupus erythematosus and dermatomyositis. Intraepidermal or dermal pustules with neutrophils small-vessel vasculitis is related to an infectious related vasculitis. Skin biopsy allows excluding pseudovasculitic disorders, a wide group of heterogenous diseases that may mimic cutaneous vasculitis [6] (Fig. 20.1).

20.2 Pitfalls

In order to enable the diagnosis of vasculitis, the choice of the "best" lesion is crucial [1–5]. A lesion of cutaneous vasculitis should be analyzed within the first 48 h after its appearance; otherwise, typical signs of vasculitis may be absent. A fresh purpuric lesion displays within the first 24 hours fibrin deposits in the vessel wall, neutrophilic infiltration, surrounding hemorrhage, and intranuclear debris.

After 24 h, lymphocytes and macrophages replace neutrophils.

After 48 h, lymphocytes predominate.

Moreover, skin biopsy of an infiltrated lesion must include the epidermis, dermis, and hypodermis to precisely determine the size of the affected vessels. Some CV affects typically the upper part of the dermis like HSP. Therefore, a punch skin biopsy will permit to show the lesions. In the case of polyarteritis nodosa (PAN), deep muscular vessels of the dermis-hypodermis and the hypodermis are affected which imply a deep incisional biopsy. Similarly, a livedo should be biopsied on

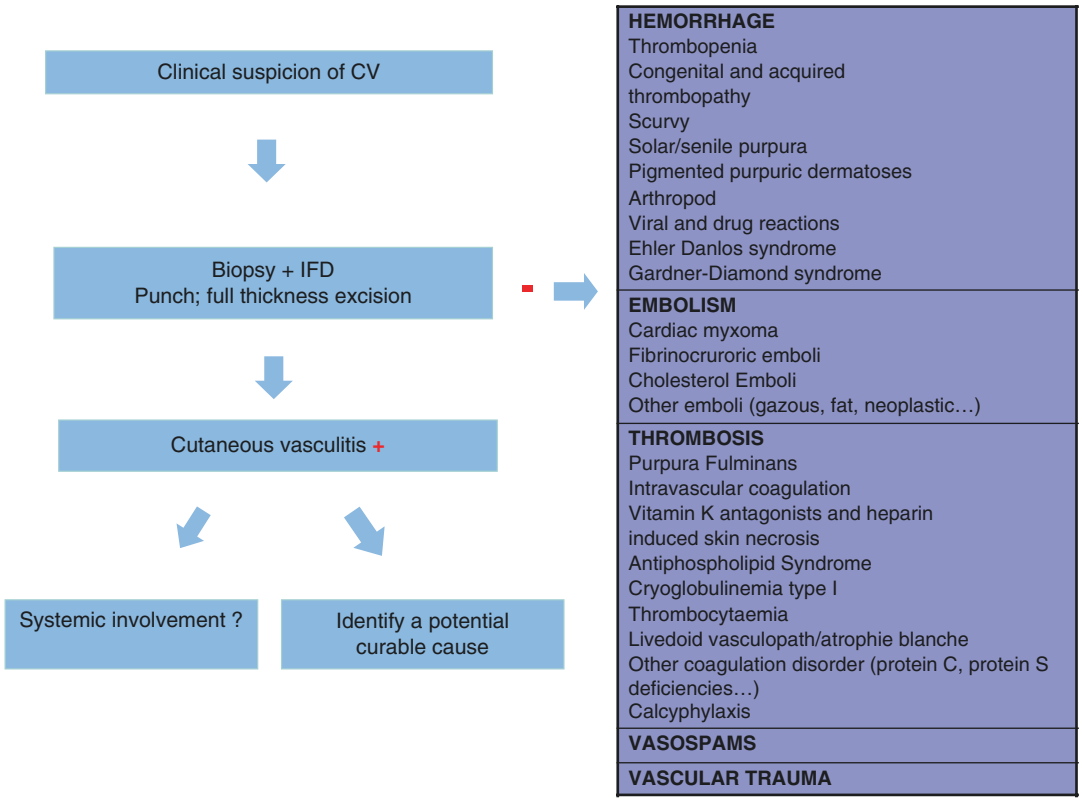

Fig. 20.1 Approach to the diagnosis of cutaneous vasculitis and its differential diagnosis [1, 6]

its most infiltrated or necrotic areas with similar deep incisional biopsy [7].

In some specific cases, an *incidental vasculitis* may be found on the skin biopsy. This pathologic statement should not mislead to diagnose a vasculitis:

- Biopsy performed on an ulcer
- Biopsy in lesions related to neutrophilic dermatoses (Sweet's syndrome)

20.3 Clinical Pathologic Correlation

The cutaneous lesions correlate sometimes with the size of the affected vessels [1–5]:

- Palpable purpura, infiltrated erythema, urticaria, vesicles, and blisters are mainly related to small-vessel vasculitis of the dermis.
- Subcutaneous nodules, ulceration, and gangrene are related frequently to medium-sized vessel vasculitis located at the dermo-hypodermal junction or in the subcutaneous fat.
- Necrosis and livedo occur when either small and/or larger vessels are involved.

20.4 Clinical Manifestations

Cutaneous vasculitis displays a wide range of elementary lesions that may be associated and lead to a pleomorphic appearance of the eruption [1–5]. CV may manifest variously as:

- Atypical *urticaria*, with distinctive feature from common urticaria (duration of the lesions longer than 24 h, presence of purpura, postinflammatory pigmentation or ecchymoses, and symptoms of burning rather than itching).
- *Palpable purpura*: the most frequent manifestation but nonspecific; asymptomatic or burning; localized on the lower limbs, ranging from tiny red macules and pinhead- to

coin-sized petechiae, but also sometimes to more extensive plaques and ecchymoses; may disclose a necrotic evolution leading to vesicles, blisters, erosions, ulcerations, and ulcer. It is often an association of different lesions simultaneously in the same patient: erythematous to purpuric macules, papules, and necrotic lesions.

- *Retiform purpura* is a peculiar clinical form of branching purpuric lesions in a fishnet pattern for which distinction from an infiltrated or necrotic livedo is difficult. Retiform purpura implies the performance of a skin biopsy like any infiltrated purpura or livedo.
- *Other manifestations*: infiltrated erythema; hemorrhagic vesicles; ulcers; inflammatory, tender, or painful dermal or hypodermal nodules; livedo racemosa; infarcts; and digital gangrene. Lesions affect primarily the lower limbs. Upper extremity, trunk, head, and neck involvement are not usual and may be considered as a sign of severity and/or of a systemic vasculitis (Figs. 20.2, 20.3, and 20.4).

Other skin manifestations associated with systemic vasculitis but do not display vasculitis upon histology [1]:

- *Extravascular necrotizing granuloma*: occurs during Churg-Strauss syndrome especially, red to purple papules or nodules involving symmetrically the extensor aspects of the elbows and the fingers, but other localizations have been reported.
- *Panniculitis:* recurrent crops of erythematous, edematous, and tender subcutaneous nodules; usually of symmetrical distribution on the thighs and the lower legs; spontaneous

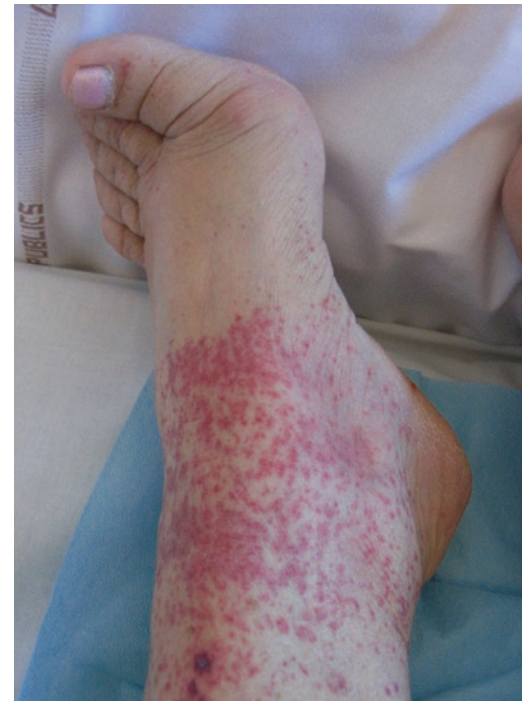

Fig. 20.3 Purpuric macules of the dorsum of the foot. Notice the absence of lesions due to the compression of the shoes

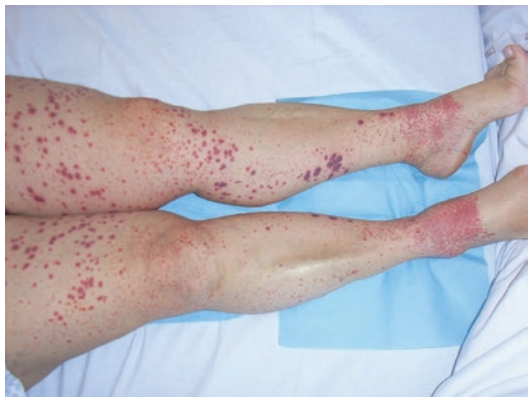

Fig. 20.2 Vasculitis of the lower limbs associating different clinical lesions of purpura: macules, papules, and vesicular lesions

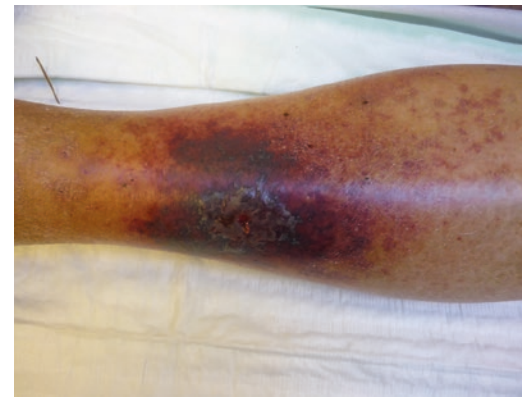

Fig. 20.4 Necrotic purpuric patch of the leg. Vasculitis was confirmed on the cutaneous biopsy

regression with hypopigmentation and atrophic scar due to fat necrosis (lobular panniculitis) or of the extensor aspects of the lower limbs with a spontaneous regression without atrophic scar (septal panniculitis).
- *Pyoderma gangrenosum.*
- *Granuloma*: granulomatous lesions with neither vasculitis nor central necrosis may be observed in systemic vasculitis, especially WG with a highly variable presentation ranging from papules, nodules, subcutaneous infiltration, and pseudotumor to chronic ulcers and affecting any site of the body.
- *Superficial thrombophlebitis.*
- *Gangrene* resulting from arterial occlusion may be observed in all vasculitis involving medium- or large-sized arteries.
- *Raynaud's phenomenon*: classically associated with all types of vasculitis. However, its prevalence is unknown in many vasculitis, and its diagnostic value is very low.

20.5 Classification

The classification of vasculitis is a real brainteaser [1]. The existence of overlapping clinical features, lack of knowledge regarding the precise etiopathogenic process of each vasculitis, and lack of "pathognomonic" clinical or laboratory or radiological findings make almost impossible to have a perfect classification. Several classifications have been proposed, each of them presenting advantages and weaknesses. The most commonly used criteria for classification of vasculitis are the American College of Rheumatology (ACR) criteria established in 1990 [8] and the Chapel Hill Consensus Conference (CHCC) in 1992 [9] and revised in 2012 [10]. Conversely, the CHCC definitions – based on pathological considerations – exclude small-vessel involvement in polyarteritis nodosa (PAN). However, classification criteria should be restricted to their primary use, i.e., stratify uniform populations who carry a diagnosis. In clinical practice, a final diagnosis should rely on the interpretation of clinical, laboratory, radiologic, and pathological findings.

20.6 Approach to the Diagnosis of Cutaneous Vasculitis

- With the first step being completed – having proved by a skin biopsy the presence of cutaneous vasculitis and analyzed this precise subtype (cell infiltration, size of the involved vessel, DIF) – the physician collects all the relevant data that will help him (1) to establish the severity of the CV by the absence or the presence of systemic involvement that will prompt to initiate immunosuppressive treatment and (2) to identify a potential curable cause [1] (Table 20.1 and Fig. 20.5).
- The precise diagnosis is made by the combination of clinical history and clinical, laboratory, and radiological findings. Therefore, patients' precise past medical data and history of the disease, including newly introduced drugs or episode evocative for acute infection, are mandatory. Indeed, any cutaneous vasculitis occurring in a patient with a known systemic vasculitis should prompt to look after intercurrent triggering factors like infection or a newly introduced drug before the diagnosis and flare-up of the disease. Physical examination must be complete and extensive. Of note, peculiar attention should be brought on relapsing retiform purpura in young adults as it can disclose the abuse of levamisole-adulterated cocaine. The patients do present a striking involvement of the ear that could be a clue to suspect such diagnosis [1].
- Physicians should not lose from sight and warn the patients that in 50 % of all cases of cutaneous vasculitis, no specific cause is found.

20.7 Management of Cutaneous Vasculitis

The management of biopsy-proven CV includes [1]:

(i) Looking for the presence of systemic involvement (heart, lung, kidney, etc.)
(ii) Identifying a potential curable cause

Table 20.1 Approach to the diagnosis of isolated, biopsy-proven, cutaneous vasculitis [1]

Establish the severity: systemic involvement
Complete physical examination
General manifestations: fever, night sweats, weight loss
Joints (arthralgias), muscles (myalgias), lung (hemoptysis, cough, shortness of breath, wheezing), heart (chest pain, murmur), gastrointestinal tract (abdominal pain, gastrointestinal bleeding), ear, nose, and throat (sinusitis, rhinitis) and ocular symptoms (scleritis, sicca syndrome), peripheral (paresthesia, numbness) and central (cephalgia, seizures) nervous system, urologic and genital symptoms (hematuria, testicular pain)
Laboratory studies
Kidney function every 3 months: urinalysis, proteinuria, blood urea/creatinine
Electrocardiography
Chest X-ray
Identify a potential cause
Recently introduced drug
Laboratory studies recommended in the absence of clinical relevant symptoms
Blood cell count, C-reactive protein, erythrocyte sedimentation rate
Serum electrophoresis
Liver tests: transaminases, hepatitis B and C virus serologies
Cryoglobulins
Antinuclear antibodies, anti-dsDNA, anti-extractable nuclear antigens (Ro/Ssa, La/SSb, RNP, Sm, etc.), rheumatoid factors
Antineutrophil cytoplasmic antibodies (ANCA)
Complement levels (CH50, C3, C4)
Antistreptolysin O titers
Complementary exams according to medical history and clinical findings
HIV test
Blood culture
Lumbar puncture
Echocardiography
Viral serologies (parvovirus B19, Epstein-Barr virus, CMV. etc.) proposed in case of pregnancy or in immunocompromised hosts
Sinus CT scan and teeth examination

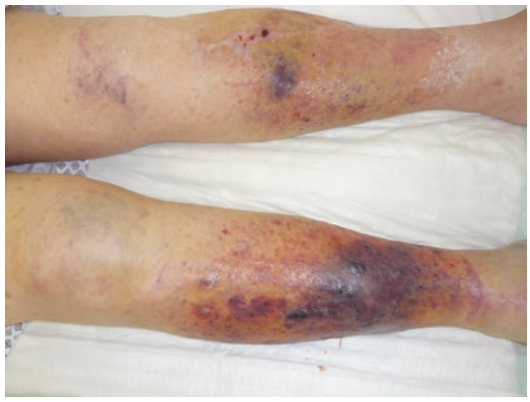

Fig. 20.5 Purpura of the lower limbs in an elderly disclosing a hematoma with no vasculitis on the biopsy and vitamin C deficiency on laboratory findings

(iii) Orienting complementary explorations by clinical context
(iv) Asking any patient with a known underlying disease that may be responsible for CV about any new drug intake and infectious-like episode and carefully examining to rule out another potential cause of vasculitis

In most of the cases, CV remains restricted to a single, self-limited, and short-lived episode of purpura of the lower limbs without any visceral involvement and any relapse (Table 20.2). In this frequent situation, treatment is not compulsory. However, support stockings or panty hose are recommended. Aspirin or anti-inflammatory agents can be given for symptomatic relief. Conversely, there is to date no indication for heparin therapy

Table 20.2 Treatment of cutaneous vasculitis according to severity

In single, self-limited, and short-lived episode of purpura of the lower limbs without any visceral involvement and any relapse
Treatment is not compulsory +/– support stockings or panty hose
Aspirin or anti-inflammatory agents for symptomatic relief
If the disease persists, worsens, or is symptomatic (burning sensation, pain) with a restriction to the skin
Colchicine (1–2 mg/day for 1 month); dapsone titrate (25–50 mg/day); pentoxifylline (400 mg, three times a day)
Extensive, recurrent skin disease with persistent lesions, vesicles, ulcers, nodules; intractable symptoms or systemic vasculitis with other organ involvement
Corticosteroids, methotrexate, azathioprine, cyclosporine, cyclophosphamide, or rituximab

or antivitamin K treatment for the management of vasculitis, except if additional thrombotic factors are found concomitantly (i.e., circulating antiphospholipids, Protein C deficiency, Protein S deficiency, etc.).

If the disease persists, worsens, or is symptomatic (burning sensation, pain) with a restriction to the skin, various drugs can be given, usually colchicine at the dose of 1–2 mg/day for 1 month. Alternatives include dapsone titrate (25–50 mg/day) or pentoxifylline (400 mg, three times a day) [1–5].

Extensive, recurrent skin disease with persistent lesions, vesicles, ulcers, and nodules; intractable symptoms; or systemic vasculitis with other organ involvement may prompt initiation of immunosuppressive therapies such as corticosteroids, methotrexate, azathioprine, cyclosporine, or cyclophosphamide. Rituximab may be of interest in case of severe vasculitis, especially in the ANCA-related group. The role of antitumor necrosis factor therapy such as infliximab remains to be established. Indeed, several cases of severe cutaneous vasculitis have been treated successfully with infliximab. Besides, infliximab does have a clear-cut indication for Behcet's disease. However, cases of vasculitis induced by infliximab, especially in patients with psoriasis, nuance its place.

Besides, management includes pain control and standardized care for necrotic and fibrous ulcers along with the control of the underlying process [1].

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Necrobiosis Lipoidica

21

Miruna Negulescu

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21.1 Introduction

Necrobiosis lipoidica (NL) is a rare chronic granulomatous skin disease usually associated with diabetes mellitus, especially type 1 [1].

In 1930, Oppenheim first described and called it dermatitis atrophicans lipoidica diabetica [2]. It was then named necrobiosis lipoidica diabeticorum (NLD) by Urbach in 1932 [3]. The several cases of NLD described in nondiabetic patients led to deletion of "diabetes" word from the denomination [2].

The relationship between NL and diabetes mellitus is still debated. First the link has been established by studies from the 1960s, which showed diabetes or abnormal glucose metabolism in over 60 % of patients with NL [4]. Since the sixties, no prevalence-based studies on NL have been conducted. Thereby, most studies are based on the 65 % incidence in their work [4].

Despite the increased prevalence of NL in diabetics, NL has also been met in patients with normal glycemia, autoimmune thyroiditis, rheumatoid arthritis, sarcoidosis, inflammatory bowel disease and monoclonal gammopathy [4].

21.2 Epidemiology

This pathology affects 0.3–1.2 % of the diabetic population with a female predominance (female-to-male ratio 3:1) [1, 4]. The early symptoms start typically in type 1 diabetic adults during

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the third decade of life and the fourth decade in type 2 or nondiabetic people [4]. In up to 14 % of cases, diagnosis of diabetes is realised after NL lesions, in up to 24 % is simultaneously made and in 62 % of cases occurs before LN lesions [4].

21.3 Pathogenesis and Histology

The pathogenesis of NL is still controversial. The diabetic microangiopathy has been involved [1, 4, 5]. An initial immune complex-mediated vasculitis is suggested by the presence of immunoglobulin M deposits, C3 and fibrin in the vessel walls in direct immunofluorescence [1, 2].

Histologically, a collagen degeneration, granulomatous formation, fat deposition and thickening of blood vessel walls are described [2, 4, 5].

21.4 Clinical Findings and Complications

Initial alterations present as papules and nodules matching to form yellow-brown, nonpainful patches, with active raised and erythematous borders (Figs. 21.1 and 21.2). The centre is atrophic, first appearing red brown and becoming yellow orange and smooth. Sometimes telangiectasia may occur [1, 4, 5].

As mentioned, the lesions are mostly painless due to nerve damage, but ulcerated lesions may cause pain. These ones may occur following minor trauma in up to 35 % of cases [4].

In 90 % of patients NL arises on legs, bilaterally and symmetrically [1]. Less frequently, lesions may appear on the scalp, face, trunk, forearms and penis, which are less considered associated with diabetes mellitus [1, 5].

The progression is slow, and sometimes regression of lesions may happen in 20 % of cases [1]. The main complication is ulceration [1, 4] with secondary infection [6]. Some exceptional cases of squamous cell carcinoma have been reported in long standing NL [1, 4]. The origin of malignant transformation is even unclear [4].

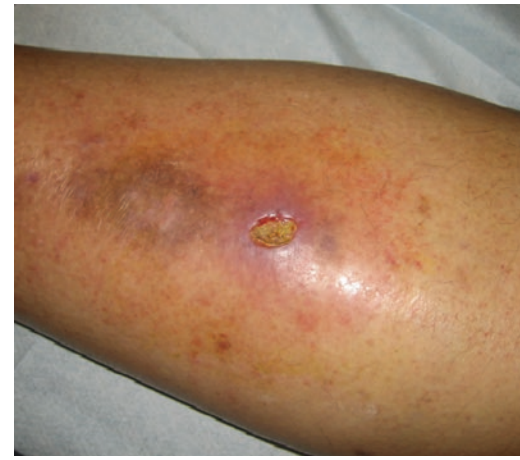

Fig. 21.1 Two lesions. The first one in the left side on the picture is atrophic, white centre surrounded by brown borders. The second one showed ulcerative centre containing fibrin, surrounded by erythematous, active borders

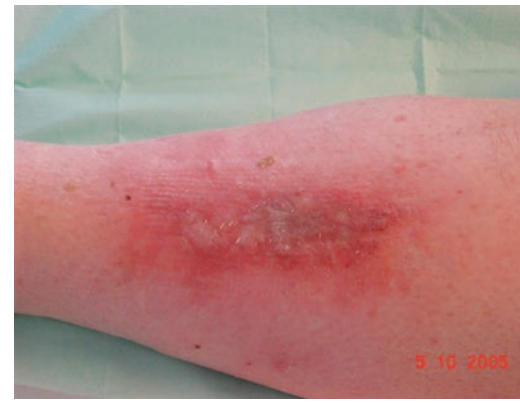

Fig. 21.2 Waxy, smooth, white plaque surrounded by erythematous borders

21.5 Treatment

The first step is to prevent lesions by avoidance of trauma [2]. Indeed, NL may also occur by Koebner effect, in addition to ulceration risk [2, 4]. Control of diabetes seems to be without any improvement [1, 4, 5].

Several treatments have been tested with random results. Most of them are based on case reports.

Treatment by topical corticosteroids is effective to prevent progression and reduce inflammatory process, especially on the active borders [1, 2, 4, 5].

Wound care is highly important in NL. Infected wounds must be treated by antiseptics and adapted dressings [2]. Sometimes systemic antibiotics are helpful [4].

Ulcerated NL are improved by granulocyte-macrophage colony-stimulating factor [4].

An association of aspirin and dipyridamole was suggested as NL treatment, but no trial has showed any improvement [2, 4]. The use of low-dose aspirin did not suggest any benefit in another trial [4].

The use of stanozolol, ticlopidine, inositol nicotinate, pentoxifylline and prostaglandin E1 seemed to have beneficial effects [2, 4].

Psoralen plus ultraviolet A (PUVA) therapy also seems to be successful. One study of 10 patients with NL showed 100 % healing rate after 47 sessions [4].

Tests with methyl aminolevulinate photodynamic therapy have been unsuccessful [4].

Some immunomodulatory drugs like oral cyclosporine and mycophenolate mofetil have been tested on ulcerating NL and showed improvement of lesions. In both cases, recurrence occurred after cessation of treatment [2, 4]. Infliximab, thalidomide and etanercept also have been tested, with beneficial results [2, 4].

Surgery is not recommended in the NL treatment because of Koebnerized lesions on surgical scars [2, 4]. Usually, lesions are excised down to deep fascia or periosteum to prevent recurrences [2, 4]. The defect is filled by skin graft. Cosmetic results after removal of lesions in these areas are substantial [2].

Occasionally, pulse dye lasers have been tested to treat telangiectasia, with mixed results [4].

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Purpura Fulminans

22

Céline Lecocq

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22.1 Introduction

Purpura fulminans (PF) is a rapidly progressing, potentially life-threatening disorder characterised by a diffuse purpura usually associated with sepsis. It is the cutaneous manifestation of disseminated intravascular coagulation.

The mortality is very high (25 % in extended forms) and long-term morbidity in survivors is about 30 %.

Common causes are severe infection (mostly due to meningococcus but also Haemophilus influenzae and pneumococcus) and blood deficiency of the natural anticoagulants protein C and protein S. In some cases, no cause is found [1, 2].

22.2 Diagnosis

(a) Epidemiology
PF occurs mainly in babies and children but there are also rare cases reported among adults. The incidence rate is highest before 1 year of age. In 2008, 689 cases are documented in France [3].

(b) Clinical presentation
Morbi-mortality of PF depends on the rapidity to recognise this affection. The diagnosis implies the recognition of skin lesions and signs of septic shock.

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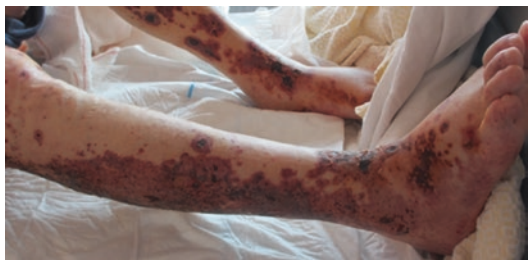
22.2.1 Skin Lesions

Initially, lesions appear as petechial rashes that become well-demarcated erythematous purpuric lesions. They usually occur on the thighs, buttocks, scrotum, and penis and are rare on the upper body and upper extremities.

Rapidly, an irregular bluish-black epidermal necrosis develops first in the lesions, and then, they usually progress to full skin necrosis.

When the dermis is necrotic, the lesions become painful and darker and frequently vesicles and haemorrhagic bulla form.

Finally, classical evolution of necrosis of bullous lesions is the formation of eschars [4].



22.2.2 Signs of Septic Shock

- High or very low body temperature
- Tachypnea (>20 breaths per minute)
- Heart rate (>20 beats per minute)
- Extreme weakness
- Cool, pale arms and legs
- Restlessness, agitation, lethargy, or confusion
- Late hypotension [5]

22.3 Supplementary Investigations

22.3.1 Haematological Investigations

- Complete blood count, hepatic and renal function, fibrinogen, prothrombin, thrombocytes, C-reactive protein
- Blood culture [6]

22.3.2 Skin Biopsy

The diagnosis is mainly clinical; therefore, the skin biopsy is rarely necessary. It demonstrates occlusive vasculopathy, nonspecific dermal inflammation, red cell extravasation, subepidermal cell-poor bulla, and purpura simplex [7].

22.4 Treatment

It implies the treatment of the underlying cause associated with intensive supportive care.

- Antibiotics: Third-generation cephalosporin (intravenous administration)
- Volume expansion
- Tissue oxygenation
- Aggressive and sequential debridement of necrotic tissue to decrease the risk of sepsis. Wounds are then covered with an antiseptic ointment (for e.g., silver sulphadiazine cream). Sometimes fasciotomia, skin grafts and even amputations are needed

Thus, treatment includes aggressive management of the septic state and management of skin lesions [8, 9, 10].

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Protein C and Protein S Deficiencies

23

Sébastien Humbert and Philippe Humbert

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23.1 Physiopathology

Protein C and protein S are vitamin K-dependent protein with natural anticoagulant properties that play a major role in the coagulation pathway. Protein C is activated by the thrombin/thrombomodulin complex. Activated protein C cleaves membrane-bound active factors V and VIII and inactivates them. Protein C inhibitor and α-1 antitrypsin are the main inhibitors of protein C. Protein S is a cofactor of activated protein C and can also directly bond to activated factors V and X.

Protein C and protein S deficiencies manifest usually as recurrent venous thromboembolism with an annual incidence of recurrent venous thromboembolism of 6.0 and 8.4 %, respectively. A severe deficiency can cause skin necrosis, especially in newborns as a purpura fulminans. The cause of protein C and protein S can be genetically determined or acquired (Table 23.1).

23.2 Diagnosis

- *Medical context:*
  - In newborn, homozygote protein C or protein S deficiency manifests in fatal purpura fulminans.
  - In adult with heterozygous protein C or protein S deficiency, introduction of vitamin K antagonist can induce skin necrosis within 3 to 5 days.

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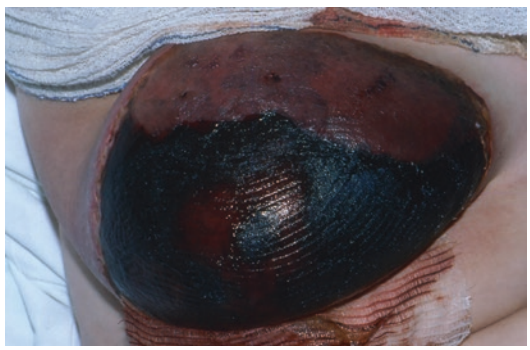
Table 23.1 Causes of protein C and protein S acquired deficiency

Acquired protein C deficiency	Acquired protein S deficiency
Vitamin K antagonist, vitamin K deficiency	Vitamin K antagonist, vitamin K deficiency
Hepatic insufficiency	Hepatic insufficiency
Disseminated intravascular coagulation	Disseminated intravascular coagulation
Autoimmune syndrome	Pregnancy
L-asparaginase therapy	Autoimmune syndrome
	AIDS, varicella-zoster virus
	Nephrotic syndrome

- *Semiology*
  - A massive thrombosis of the dermic vascular network can lead to large ecchymotic patches that can evolve to hemorrhagic bullae and then irreversible necrosis.
  - When vitamin K antagonists are involved, lesions are located in areas where the fat layer is the thickest: breast, thighs, abdomen, and buttocks. Genital involvement is also possible in men.

Picture 1: Skin necrosis of the breast after introduction of VKA



- *Biology*: increase in INR (international normalized ratio) and prothrombin time (if vitamin K antagonist), decrease or even collapse in protien C or protien S.
- *Histology*: we can observe obstructive thrombosis of capillaries and venules, vascular fibrin deposition, and dermal and fat tissue diffuse necrosis.

23.3 Treatment

- Prevent pain (morphinics)
- Prevent infection
- Stop vitamin K antagonist and vitamin K administration
- Heparin therapy
- Protein C concentrate
- Adapted local treatment: surgical excision of necrotic tissue and transplant

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Renal Insufficiency and Necrosis

24

Elia Ricci

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Renal insufficiency in itself is found to be correlated indirectly to cutaneous necroses. In fact, renal insufficiency may cause complications, which in turn lead to the formation of gangrenous cutaneous pathologies.

Renal insufficiency is classified into five progressive stages based on the values of glomerular filtration; Table 24.1 shows the KDOQI classification [1]. Alterations at the cutaneous level begin from stage III onward and become progressively more severe until they become evident in the so-called final stage. Renal disease itself leads to cutaneous alterations that may be summarised as follows:

- Xerosis: beginning with dehydration and reddening, prevalently in the areas of the extensor muscles of the limbs, progressively evolving into oedema and fissures. In the most advanced stages, there may be areas of lichenification and/or contact erythema. The fissured areas may allow bacteria to enter with consequent cutaneous infections. This form afflicts from 50 to 70 % of patients in dialysis.
- Pigmentary disorders: these are directly correlated to the duration of the renal insufficiency. They range from hyperpigmentation to a yellowish colouring, prevalently in the areas exposed to the sun. Pallor is associated with frequent anaemia in such patients. This form afflicts from 20 to 70 % of patients in dialytic treatment.
- Itching: frequent in such patients, it may be minimal but is found to be non-remittent and serious in 8 % of cases. It leads to a net deterioration in the quality of life.

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Table 24.1 KDOQI classification

Stage	GFR*	Description	Treatment stage
1	90+	Normal kidney function but urine findings or structural abnormalities or genetic trait point to kidney disease	Observation, control of blood pressure. More on management of stages 1 and 2 CKD
2	60–89	Mildly reduced kidney function and other findings (as for stage 1) point to kidney disease	Observation, control of blood pressure and risk factors. More on management of stages 1 and 2 CKD
3A 3B	45–59 30–44	Moderately reduced kidney function	Observation, control of blood pressure and risk factors. More on management of stage 3 CKD
4	15–29	Severely reduced kidney function	Planning for end-stage renal failure. More on management of stages 4 and 5 CKD
5	<15 or on dialysis	Very severe, or *end-stage* kidney failure (sometimes call *established renal failure*)	Treatment choices. More on management of stages 4 and 5 CKD

*All GFR values are normalized to an average surface area (size) of 1.73m^2

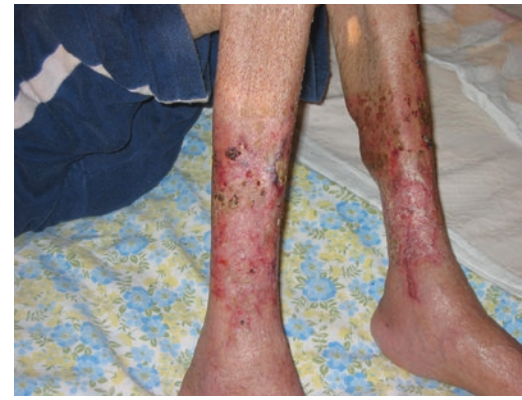

Fig. 24.1 NDF (nephrogenic dermal fibrosis)

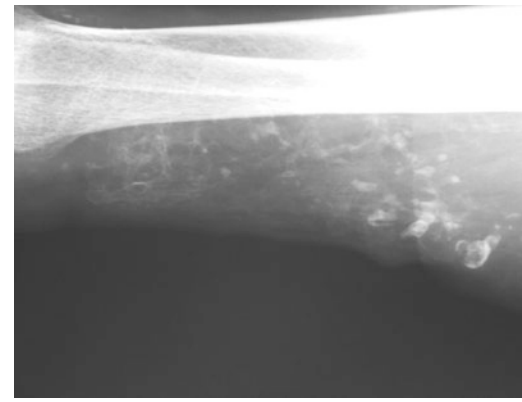

Fig. 24.2 Subcutaneous calcification in NDF

Another clinical situation of a dermatological type is NDF (nephrogenic dermal fibrosis). It was described in 2000 [2] and currently classified as systemic [3]. It is a pathology that is prevalently cutaneous and characterised by being associated with renal damage. Patients present oedemas and retractions prevalently in the lower limbs; the main symptoms are burning pain and itching. On a cutaneous level, there is the appearance of papules or plaques that are red or brown in colour and which, on rare occasions, may become ulcerous (Fig. 24.1). Around 5 % of these forms may exhibit aggressive and sudden worsening with the involvement of muscles, possibly leading to paralysis. As of now, the cause remains poorly defined: possible causes may include the use of gadolinium as a means of contrast [4], erythropoietin and the stages of hypercoagulability. Under X-ray inspection diffuse calcifications are noted on a subcutaneous level (Fig. 24.2).

End-stage renal disease (ESRD) in itself behaves as a form of comorbidity in pre-existing situations causing complications that lead to the formation of necrotic tissues, as well as exacerbation in the appearance of cutaneous ulcerous lesions. Lastly, as a direct cause, it leads to complications that progress to ulcers.

24.1 Comorbidity

ESRD in itself leads to a state of fragility in the patient, with reduction of the immune system defences and consequently a greater incidence of infective phenomena. The reduction in renal

clearing leads to an accumulation of catabolites that in themselves have an inflammatory action. A situation of increased phlogosis means healing times are lengthened, with a slowing down both of the retraction and the re-epithelialisation phenomena. Some examples: the frequent association with diabetes leads to a prognostic deterioration with an increase in the number of amputations and the evolution in a necrotic direction of the diabetic foot [5, 6]. Patients who have been in dialysis for long periods present a high rate of arterial disease which, with the phenomena of vascular calcinosis, may lead to the development of cutaneous necrotic ulcers of an arterial type [7]. Al Ghazal [8] also suggests a correlation with the development of forms such as pyoderma gangrenosum. Yates [9] has noted an increase in infections from MRSA in patients who have ulcers with ESRD.

24.2 Exacerbation

The forms in which we may define ESRD as exacerbation are forms in which there is a net increase in the incidence of cutaneous ulcerous disease in the presence of the combination. These are not actual syndromes, because there is no direct cause-effect relationship, but the frequent association, besides complicating the situation, leads to a therapeutic approach that must be combined.

The antiphospholipid antibody form, of itself, besides the cutaneous damage involved, may lead to renal damage. There is therefore an effect in negative synergical terms between the two forms [10], which on the one hand can lead to a worsening of the nephrological situation whilst on the other, in patients with ESRD and cutaneous damage, the form of hypercoagulability facilitates the development of ulcers [11] (Fig. 24.3) (see Chap. 18).

Ulcers from anticoagulants, or cutaneous necrosis from anticoagulants, are particularly frequent in patients with renal insufficiency. The increase in the coagulation time, combined with the reduced capacity for elimination of the medicine, facilitates the development of haematomas. The skin, modified in the presence of ESRD to become more rigid and fragile, tends to be damaged more easily in the case of even minor traumas. A haematoma, which itself tends to compress the skin, can easily lead to the onset of necrotic phenomena (see Chap. 13). The same mechanism is involved in the use of heparin, especially in patients subjected to dyalitic treatment.

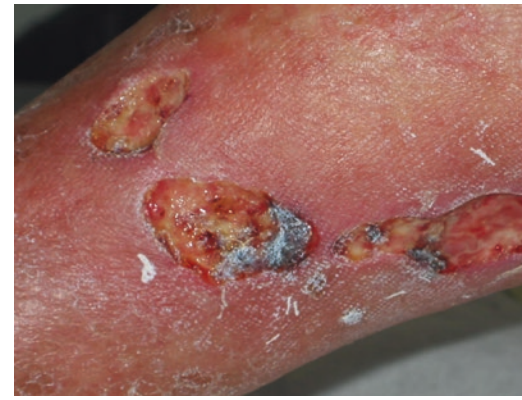

Fig. 24.3 Antiphospholipid antibody syndrome with ESRD V stage with skin ulcers

Some vasculitic forms are characterised by contemporaneous damage at the level of the renal glomerular, such as in the antiphospholipid antibody form, involving a synergical effect. The coagulative disorders, damage on a cutaneous level secondary to ESRD, lead to a vicious circle that moves beyond the simple situation of underlying comorbidity (see Chap. 22).

24.3 Direct Cause

The ulcerous form directly linked to ESRD is so-called calciphylaxis or calcified uraemic arteritis. This is a rare ulcerous form often with an inauspicious prognosis, which begins with necrotic cutaneous ulcerations with undefined edges (Fig. 24.4) and can spread extensively (see Chap. 14).

In a patient with ESRD, it is necessary to carry out a differential diagnosis, especially for the atypical forms that affect the lower limbs [12]. The differential diagnosis in terms of pathologies that must be considered is illustrated in Table 24.2.

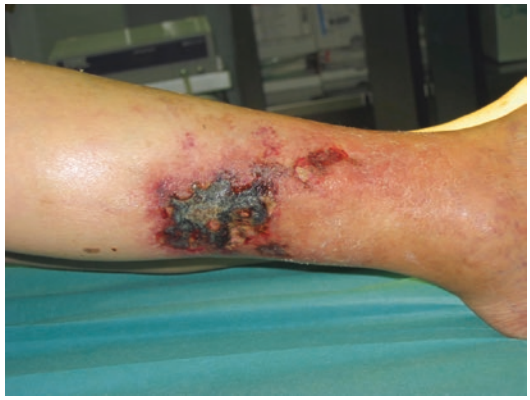

Fig. 24.4 Calciphylaxis, typical skin lesion

Table 24.2 Differential diagnosis in necrotic lesion on lower limb

Antiphospholipid antibody syndrome
Calciphylaxis
Vasculitis
Atheroembolic disease
Warfarin skin necrosis
Heparin skin necrosis
Spider bites

From Dean [12]

24.4 Treatment

Treatment is based on the re-equilibration of the renal situation through diet, diuretics, corticosteroids and/or immunosuppressants, dyalitic treatment or transplant if indicated.

The specific treatment of the various forms involves a correct diagnostic approach, with identification of the diverse pathological situation that has led to the cutaneous necrosis; for such treatments see the specific paragraphs.

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Calciphylaxis

25

Farida Benhadou and Véronique del Marmol

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25.1 Physiopathology

The complete physiopathology is still unclear: two separate process have been described: a progressive calcification of medium and small vessels of the subcutaneous and fat tissues related to an abnormal phosphate/calcium ratio occurring in the presence of predisposing factors (chronic vasculopathy, diabetes mellitus, obesity, renal insufficiency, etc.) and an acute phase caused by a decreased blood flow (hypotension, hemostatis perturbations and coagulopathy, infection, injury, etc.) causing the infarction of the tissues [4]. The main risk factor for calciphylaxis is the chronic renal insufficiency with or without a hyperparathyroidy [5]. It mostly occurs on a dialysed patient but may be also associated with other conditions (corticosteroids or antivitamin K therapy, neoplasia, chronic inflammation, etc.) [1].

25.2 Diagnosis

- *Medical context*: Mainly dialysis but may be associated with other underlying conditions (Table 25.1).

The cutaneous involvement may be associated with systemic necrosis (myocardium, bowel, nervous system, pulmonary system, etc.).

- *Semiology*: Painful and extensive skin necrosis, mainly associated with a livedoid aspect and often located in the abdomen and low extremities (Fig. 25.1a, b).

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Table 25.1 Risk factors and triggering factors involved in calcyphylaxis [7]

Risk factors	Activating factors
Impaired vascular status	Hypovolemic shock, hypotension, vasoconstriction
Obesity	Cardiac insufficiency, infection, hyperviscosity
Diabetes mellitus	Local injury, injection, local pressure
Female	Hemostasis perturbations
Antivitamin K therapy	Elevated blood level of calcium and phosphate
Impaired bone mineralization	
Hypercalcemia	
Hyperphosphatemia	
Hyperparathyroidy	
Dialysis	

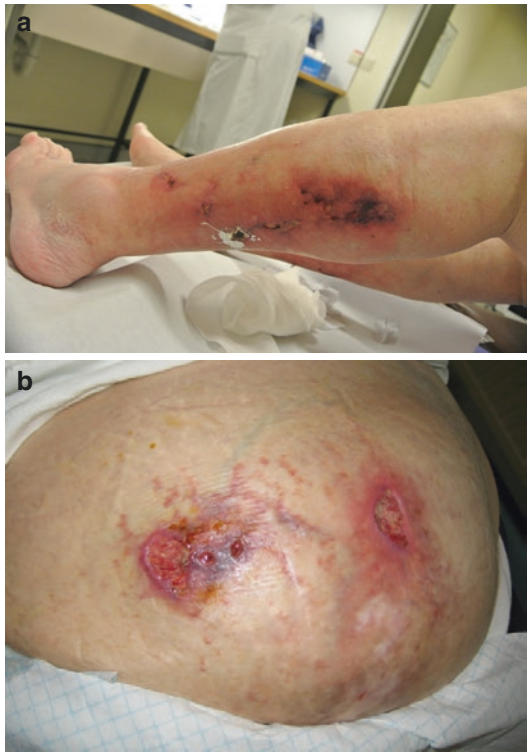

Fig. 25.1 Leg and abdominal involvement with ulceration and livedoid aspect

- *Biology*: Presence or absence of hyperparathyroidism, coagulopathy, and disorders related to underlying conditions [3, 4].
- *Histology*: One observe a transdifferentiation of the vascular muscle cells to osteoblastic-like cells causing extensive calcifications (vascular, muscular, and cutaneous involvements). Calcium deposition in the vascular walls and intraluminal thrombi can be found.

25.3 Treatment

- To improve the tissue oxygenation (hyperbaric oxygenation, increasing the dialysis frequency, revascularization if necessary, etc.)
- To avoid the pain (morphines, etc.)
- Parathyroidectomy (still in debate) [3, 4, 5]
- More recent publications refer to multi modal treatment of calciphylaxis with IV sodium thiosulfate [6]
- Adapted local treatment:
  - Debridement: Surgical debridement if possible that may improve the patient survival, otherwise other debridement methods to remove calcified tissues [2]
- To avoid infection
- To help skin healing
  - To correct nutritional status
  - To avoid wound pressure

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Livedo(id) Vasculitis

26

Farida Benhadou and Jean-Claude Wautrecht

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26.1 Introduction [1]

Livedoid vasculitis (LV) is a rare vasculopathic disorder. Different names are used in the literature to define LV and one of them is "atrophie blanche." Atrophie blanche is a confusing term because it is a sign that is frequently observed in chronic venous insufficiency and not specific for LV.

LV can occur at any age but is most commonly a disease of adulthood. LV can be divided into a primary or idiopathic form and a secondary form, which has been associated with other diseases.

Data in the literature concerning LV are limited and mainly based on the review of case reports.

26.2 Histology [1]

Usually deposition of fibrinoid material in dermal vessels with secondary ischemic change of the overlying epidermis leading to ulceration.

26.3 Pathogenesis [1, 2]

Not fully elucidated. Several hypotheses have been proposed:

- Defective endothelial cell synthesis of tissue plasminogen activator and/or prostacyclin
- Dysregulation of coagulation and fibrinolysis
- Dysfunction of platelets or erythrocytes
- Vasospasm and changes in hydrostatic pressure

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26.4 Clinical Presentation

26.4.1 Signs and Symptoms [1, 2, 3]

- Persistent livedo with purpuric macules and papules that progress to small, tender, irregular, and extremely painful ulcerations.
- In our experience, we have observed in the early stage of the disease that the patients are experiencing severe pain even before the development of the ulceration.
- Ulcerations may recur and heal with stellate, ivory-white atrophic plaques, sometimes with surrounding hyperpigmentation and telangiectases.
- Atrophie blanche represents the end-stage lesions and is characterized by irregular, white/ivory, depressed scars.
- Seasonal exacerbations are described.
- Neurological symptoms are rarely described (mononeuropathy multiplex) [1, 2, 3].

26.4.2 Location

- Lower legs, ankles, and/or dorsal surface of the feet

26.4.3 Possible Associated Conditions [4, 5]

- Connective tissue diseases (systemic lupus erythematosus)
- Cryoglobulinemia
- Antiphospholipid antibody syndrome
- Vasculitis (polyarteritis nodosa)
- Abnormalities of the coagulation system (protein C deficiency, abnormalities of the tissue plasminogen activator system, antithrombin III deficiency, elevated homocysteine levels, prothrombin G201210A gene mutation, and factor V Leiden)
- Venous insufficiency

26.5 Diagnosis [2, 3]

- Clinical presentation and evolution help for the diagnosis.
- Skin biopsy has to be performed in case of doubt:
  - *Early stage*: Fibrin deposition in the vessel wall and/or lumen in early lesions. A lymphocytic infiltrate and infarction with hemorrhages may be present.
  - *End stage:* Epidermal atrophy with sclerosis of the dermis and a minimal cellular infiltrate. Vessel walls may have segmental thickening and hyalinization of the intima. Recanalized thrombotic vessels may be noted. Superficial or deep vessels may be involved.

26.6 Treatment [6, 7, 8, 9, 10, 11]

Many treatment modalities have been attempted to control the disease process.

Unfortunately many cases remain difficult to treat. Suggested therapeutical options are often based on the experience from a few case reports.

26.6.1 General Management

- Be sure of the diagnosis!
- Diagnose and treat the associated conditions (connective tissue disease, venous insufficiency, etc.)
- Avoid pain (analgesics).
- Adapt topical wound care.
- Avoid infection.
- Check risk factors for wound healing impairment (malnutrition, smoking, etc.).
- Compression therapy can be suggested.

26.6.2 Therapeutic Modalities

- Antiplatelet agents (aspirin, dipyridamole)
- Fibrinolytic agents (danazol, tissue plasminogen activator)
- Anticoagulant agents (subcutaneous low molecular weight heparin or antivitamin K agents)
- Vasodilating agents (nifedipine, nicotinic acid)
- Pentoxifylline (enhances the blood flow and decreases the blood viscosity)

- Doxycycline is used for its anti-inflammatory properties
- Immunosuppressive therapies (prednisone, methotrexate, ciclosporin, etc.)
- PUVA therapy
- Intravenous immunoglobulins
- Hyperbaric oxygen therapy (Figs. 26.1, 26.2, 26.3, and 26.4).

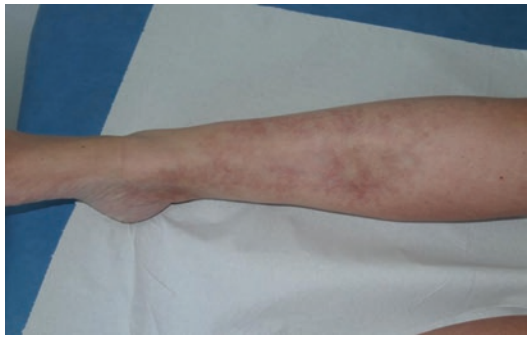

Fig. 26.1 Livedo

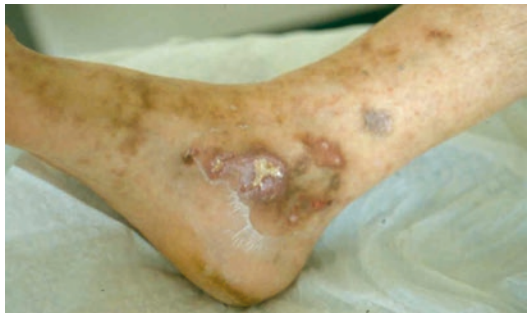

Fig. 26.2 Ulceration and livedoid aspect

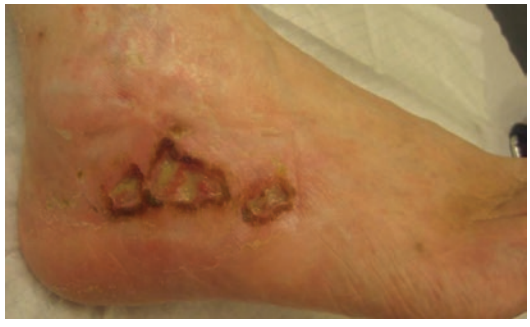

Fig. 26.3 Chronic ulcerations

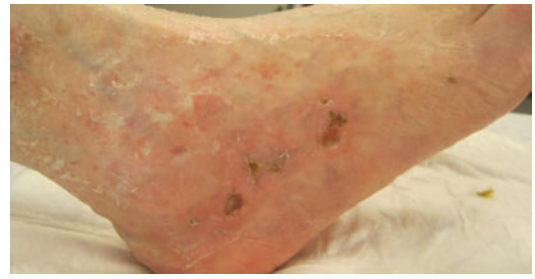

Fig. 26.4 Healing with white atrophic surrounding plaques and telangiectases

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Pyoderma Gangrenosum

27

Hiroshi Yoshimoto

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27.1 Introduction

Pyoderma gangrenosum (PG) is a very rare ulcerative neutrophilic inflammatory skin disease. The clinical manifestations of PG are pain, tenderness, an erythematous nodule, or a sterile pustule in the early stage, which progress to deep ulcers with a purulent base and undermined margin [1]. The ulcers heal with characteristic cribriform scars; however sometimes multiple relapses occur. The patients with PG have frequently an associated systemic disease including inflammatory bowel disease, arthritis, hepatitis, or malignancy [3, 6].

The cause of PG remains unknown, although suggested causes include immune-complex-mediated neutrophilic vascular reactions [7].

PG has no definite diagnostic criteria and is a diagnosis of exclusion. The diagnosis of PG is based primarily on the clinical history, clinical manifestation, and biopsy result. Although the histopathology of PG is nonspecific, the pathological findings are useful in differential diagnosis [6].

It is difficult to get cured completely by local wound management alone. If the patients have a systemic disease, the systemic disease should be preferentially treated [7]. The severe PG is commonly treated with steroids or other immunomodulators. More recently, tumor necrosis factor-alpha blockers and other biologic agents have been used with some success for PG patients [2, 5].

Therefore, the diagnosis of PG can be difficult, and misdiagnosis might lead to serious complications [4].

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27.2 Etiopathogeny

The cause of PG remains unknown, although suggested causes include immune-complex-mediated neutrophilic vascular reactions [7].

The incidence of PG is very low. PG commonly affects women aged 30–50 on the lower limbs, although it occurs in all age groups and any other site including the peristomal area. The histopathology of PG is nonspecific, and the ulcers of PG show necrotic tissue surrounded by neutrophil infiltrates with monocytes and giant cells. About 50 % of PG patients have an associated systemic disease including inflammatory bowel disease, arthritis, HIV infection, hematologic disease, hepatitis, and malignancy [6].

27.3 Clinical Detailing

The clinical manifestation of PG are pain, tenderness, an erythematous nodule, or a sterile pustule in the early stage, which progress to deep ulcers with a purulent base and undermined margin. The ulcers heal with characteristic cribriform scars; however sometimes multiple relapses occur (Figs. 27.1 and 27.2) [3].

Pathergy is a specific but not sensitive finding of PG. The lesion sites expand radically, especially if the borders of the lesion site are traumatized by debridement or by other mechanical trauma [3]. No laboratory finding is diagnostic of PG. PG has no definite diagnostic criteria and is a diagnosis of exclusion. The diagnosis of PG is very difficult and based primarily on the clinical history, clinical manifestation, and biopsy result while being careful about misdiagnosis (Table 27.1). [1, 2, 6]

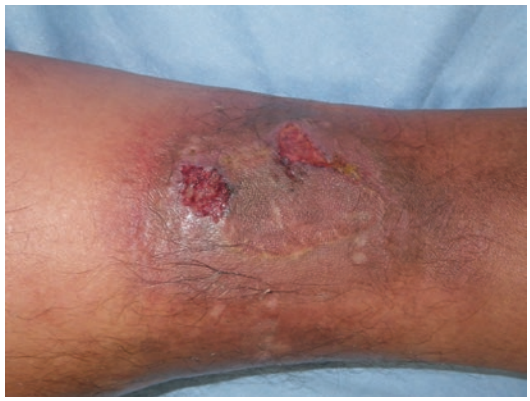

Fig. 27.1 A right leg ulcer in a 20-year-old male that originated from initial abrasion. He has no systemic disease

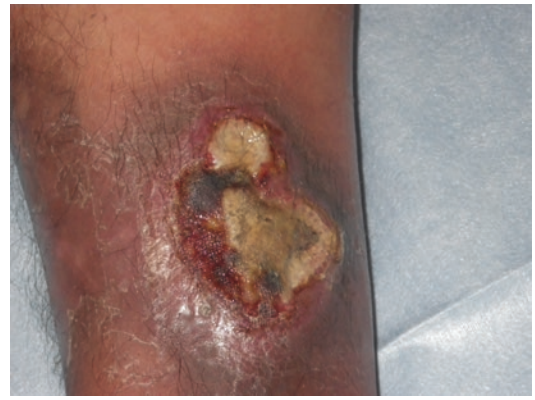

Fig. 27.2 The ulcer expanded with a purulent and necrotic base even though ointment was used

Table 27.1 Causes of ulcers mimicking PG

Infection
Fungal
Mycobacterial
Necrotizing fasciitis
Vascular occlusive disease
Antiphospholipid-antibody syndrome
Venous stasis ulceration
Vasculitis
Wegener's granulomatosis
Polyarteritis nodosa
Neoplasms
Lymphoma
Leukemia cutis
Drug reactions
Hydroxyurea induced ulcer

27.4 Treatments

If the patients have a systemic disease, the systemic disease should be preferentially treated. It is difficult to get cured completely by local wound management alone. Topical treatments are chosen depending on the purpose such as the prevention of secondary bacterial infection or the promotion of reepithelialization. Some topical

Table 27.2 Systemic treatments for PG

Nonbiological treatments
Prednisone, cyclosporine, dapsone, thalidomide, methotrexate, tacrolimus, mycophenolate mofetil, azathioprine, granulocyte apheresis, intravenous immunoglobulin
Biological treatments
Infliximab, entanercept, alefacept, adalimumab, efalizumab

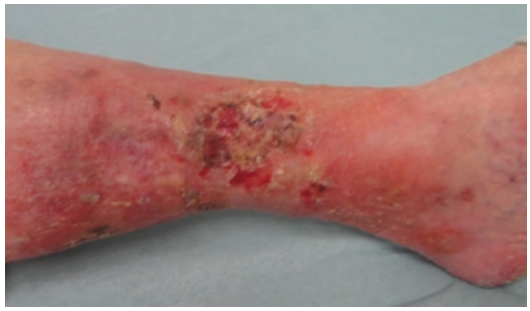

Fig. 27.3 A left leg ulcer in a 58-year-old female with systemic lupus erythematosus (SLE): bizarre configuration of ulceration rims, undermined edges, and soft edematous ulcerated area (This photo is provided by Dr. Fujioka)

agents such as tacrolimus, strong corticosteroids, and cyclosporine have reported efficacy in small case series. PG is commonly treated with systemic corticosteroids and/or cyclosporine [7].

Other immunomodulators have reported efficacy in case reports (Table 27.2).

Tumor necrosis factor-alpha blockers have reported to be very effective in the treatment of PG patients with inflammatory bowel disease or rheumatoid arthritis. Infliximab (tumor necrosis factor-alpha blocker) is the only systemic agent to have demonstrated efficacy for PG in a randomized, double-blind, placebo-controlled trial [5]. The patient's level of pain and signs of inflammation help guide response to treatment. The inflammatory component of PG is assessed by the border elevation and lesion expansion. We must give a diagnosis and choose treatment carefully since PG has no definite diagnostic criteria and no standard protocol for treatment (Figs. 27.3 and 27.4).

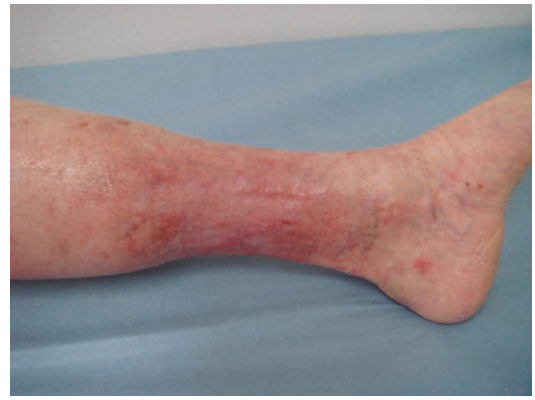

Fig. 27.4 There is no recurrence on 8 months after skin graft. SLE has been treated with prednisone 5 mg/day (This photo is provided by Dr. Fujioka)

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Cryoglobulinemia

28

Salvatore Panduri, Valentina Dini,
and Marco Romanelli

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28.1 Physiopathology

Cryoglobulinemia (CR) is a disease characterized by the presence, in the serum, of abnormal proteins that precipitate reversibly at low temperatures, and generally the cryoglobulins lead to a systemic inflammatory syndrome characterized by myalgia, arthralgia, purpura (Meltzer's triad), neuropathy, and glomerulonephritis [1]. According to immunochemical characteristic, cryoglobulins have been classified into 3 distinct groups:

- *Type I* with monoclonal immunoglobulin (Ig) (IgG, IgA, IgM): this type is associated with lymphoproliferative malignancies or hematologic disorders.
- *Type II* with monoclonal or polyclonal Ig.
- *Type III* with polyclonal immune complex.

In 25 % of cases, an involvement of the skin is present, and the most frequent cutaneous manifestations are palpable purpura, Raynaud's phenomenon, cutaneous ulcers, skin rash, livedo reticularis, and acrocyanosis. Only in 2 % of cases with skin involvement is it possible to observe digital ischemia and gangrene. Renal, neurological, and joint involvement occur in 21–38 % of the patients [2]. The cause of the precipitation of the immunoglobulins is still unclear, but it has been hypothesized that abnormalities of the carbohydrates decrease the solubility of the cryoglobulins [3]. It has been suggested that various interactions between immunoglobulins at low temperatures cause the precipitation of this

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protein [4]. Mixed cryoglobulinemia type II or III represents the most common manifestation of CR. There are only few cases in the literature of type I cryoglobulinemia. Mixed cryoglobulinemia is frequently associated with hepatitis C virus (HCV) infection and this creates a doubt on the existence of essential cryoglobulinemia. The clinical manifestations of type I cryoglobulinemia are essentially due to self-aggregation through complement fraction fragment of monoclonal immunoglobulin that cause hyperviscosity, thrombosis, ischemia, and vasculopathy, involving the skin and kidney. The clinical presentation of type II or III is determined by the cryoglobulinemic vasculitis (leukocytoclastic vasculitis) which is able to determine various cutaneous lesions and multisystem involvement [2].

28.2 Diagnosis

- *Laboratory:* Determination of the cryoglobulins (blood drawn into warmed syringe, red blood cells (RBC) removed via warmed centrifuge, plasma refrigerated in a Wintrobe tube at 4° for 24–72 h and then centrifuged, and cryocrit determined).
- *Semiology:* The course is characterized by cyclic eruptions induced by cold or fluctuations of the activity of underlying disease (Table 28.1). The skin involvement in type I is represented by livedoid vasculitis, cold-induced acrocyanosis, leg ulcers, and cold urticaria. Types II and III are associated with vascular palpable purpura and leg ulcers (Figs. 28.1 and 28.2) [3].

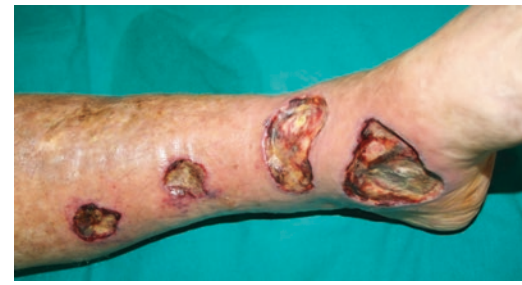

Fig. 28.1 Multiple punched-out ulcers, extremely painful, on the lower leg. Necrotic tissue and adherent fibrin on the wound bed in the absence of arterial disease

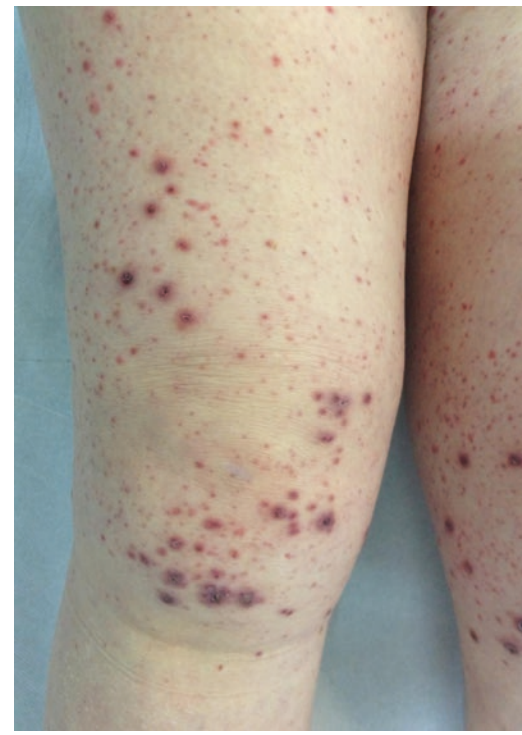

Fig. 28.2 Palpable purpura with hemorrhagic crusts

Table 28.1 Skin manifestations

Ischemic necrosis (40 % in type I, 0–20 % in mixed types)
Palpable purpura (15 % in type I, 80 % in mixed types)
Livedoid vasculitis (1 % in type I, 14 % in type III)
Cold-induced urticaria (15 % in type I, 10 % in type III)
Hyperkeratotic spicules in areas exposed to cold
Scarring of the tip of the nose, pinnae, fingertips, and toes
Acrocyanosis
Nail-fold capillary abnormalities

- *Biology:* Presence or absence of disorders related to underlying conditions.
- *Histology:* In cryoglobulinemia type I, it is evident that there is the presence of an eosinophilic pink coagulum filling dermal venules. In mixed cryoglobulinemia, there are the classical aspects of leukocytoclastic vasculitis (fibrinous degeneration of the vascular

endothelium along with other signs of vasculitis: nuclear dust, perivascular hemorrhage, and vascular destruction).

28.3 Treatment

28.3.1 Systemic Treatment

The therapy is often directed to the underlying condition.

- For patients with chronic HCV infection, antiviral therapy is indicated [5].
- In patients with organ involvement or recalcitrant disease, immunosuppressive or immunomodulatory therapy is indicated: steroids, plasmapheresis, and cytotoxic agents.
- Rituximab, a mouse/human chimeric monoclonal anti-CD 20 antibody, in monotherapy is more effective than standard immunosuppressive therapy over the long term, where therapy with antiviral agent is not indicated [6].

28.3.2 Local Treatment

- Corticosteroids (purpura)
- Moist wound dressing
- Compression bandages
- Bed rest

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Hand Necrosis

29

Nicolas Cuylits, Farida Benhadou,
and Véronique del Marmol

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29.1 Introduction

Loss of fingers represents an important aesthetic and functional handicap. Finger ischemia is a rare pathology but can have several different etiologies and need to be closely managed to limit the extension of necrosis. The management of finger ischemia is dependent on the etiological factors and type of necrosis. This is why a close collaboration between the surgical and medical specialties is mandatory for limiting extension of necrosis and amputation of the fingers. When necrosis occurs and is delimiting, optimalization of clinical assessment and conservative treatment often decreases the need of surgical shortening of the finger and can sometimes save some important functional parts of the hand. We will discuss in this chapter the way to diagnose and how to manage necrosis of the fingers.

29.1.1 Vascularization

The hand and the wrist are supplied by four arteries linked together at the level of the carpus by four anastomotic arcades. Those arteries are the radial, ulnar, anterior, and posterior interosseous arteries. Each long finger is vascularized by a pair of digital arteries running about 1 mm under the skin on the ulnar and radial side of the finger. Those arteries are connected by means of several constant anastomoses able to compensate interruption of one digital artery. The thumb is also

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supplied by two additional short dorsal arteries which can offer additional supply in case of ischemia. A dense capillary network nourished by those arteries is responsible of the excellent finger vascularization [1].

29.1.2 Mechanisms

The digital vascularization can be altered in different conditions.

The two main mechanisms of digital ischemia are due to an occlusive vascular process (thrombi, emboli, inflammation, vasospasm, external compression, etc.) and/or a decreased blood supply process (hemodynamic shock, trauma, etc.). The occlusive vascular process results from an obstruction of the digital arterial lumens leading progressively to the interruption of the digital blood flow and finally to the ischemia of the extremities. A diameter reduction of 60 % or a cross-sectional area reduction of 70 % represents a hemodynamically significant lesion, and these lesions produce a pressure drop across the stenotic area. The distal arterial bed is supplied by collateral blood vessels. In patients with acute arterial occlusions, collateral blood vessels are not formed, and perfusion decreases rapidly below a critical threshold level, which results in persistent pain and tissue necrosis [2].

29.1.3 Etiologies

Digital ischemia is an uncommon disorder reflecting diverse etiologies.

The main etiologies of digital ischemia have been classified in Table 29.1.

Each etiology will be discussed in the appropriate chapter. [3, 4, 5, 6]

29.1.4 Clinical Presentation of Digital Ischemia

The diagnosis of digital ischemia is easy at the stage of gangrene.

The clinical process is divided into three steps:

Table 29.1 Etiologies of digital ischemia

Autoimmune diseases	**Infection**
Scleroderma and CREST syndrome	Hepatitis B and C
Lupus and antiphospholipid syndrome	HIV
Sjögren-Gougerot syndrome	Endocarditis
Sharp syndrome	Mycoplasma
Rheumatoid arthritis, Still's disease	Rickettsiosis
Dermatomyositis and polymyositis	
Primary biliary cirrhosis	
Inflammatory bowel disease	
Vasculitis	**Inflammatory arteritis**
Periarteritis nodosa	Horton
Micropolyangiitis	Takayasu
Wegener's granulomatosis	Kawasaki
Hypersensitivity vasculitis	Buerger
Rheumatoid purpura	
Cryoglobulinemia	
Atherosclerosis and aneurysms	**Arteriopathy**
Emboli	Hypothenar hammer syndrome
Atheromatosis	Vibration syndrome
Cholesterol emboli	Radiotherapy
Calciphylaxis	Fibromuscular dysplasia
Cardiac embolism process	**Endocrinopathy**
Heart failure	Cushing
Endocarditis	Thyroidopathy
Cardiac rhythm trouble	Pheochromocytoma
Valvulopathy	
Myxoma	
Myeloproliferative syndrome and hematologic disorder	**Cancers**
Vaquez's disease	Solid cancers
Essential thrombocytosis	**Decreased blood flow**
Myeloid chronic leukemia	Trauma
Lymphoid chronic leukemia	Hemorrhage
Myeloma	Compression (carpal tunnel syndrome, thoracic outlet syndrome, etc.)
Waldenström	Heart failure
B lymphoma	Septic and hemodynamic shock, etc.
Hypereosinophilic syndrome	
Thrombophilia	
Cryoproteinemia	**Toxic**
Cryofibrinogen	Vinyl chloride

Cryoimmunoglobulin	Chromium
Cold agglutinin	Arsenic
	Epoxy resin
	Trichloroethylene
	Benzene
	Silice
	Silicone
Toxicomania	**Drugs**
Tobacco	Bleomycin
LSD	Vincristine
Cocaine	5-FU
	Cisplatin
	Tamoxifen
	Sympathicomimetics
	Vasoconstrictive drugs
	Ergotism
	Bromocriptine
	Beta-blockers
	Ciclosporine, etc.

1. The early phase: pallor, poikilothermia, livedoid aspect, pulpar petechiae, periungual infarction, and splinter subungual hemorrhages
2. The state phase: digital ulceration
3. The late phase: distal gangrene

The associated symptoms caused by the ischemia are the pain and the paresthesia.

The distal gangrene is a risk of complication including cutaneous and bone infection.

We can distinguish two classical types of digital necrosis presentations, the dry necrosis and the wet necrosis.

The dry necrosis (Fig. 29.1) is more often observed after arterial blood flow occlusion and is characterized by red-black dry necrotic tissue surrounded by painful red borders. The dry necrosis tissue spreads slowly and is often free of microbial infection resembling mummified flesh.

The wet necrosis has a less mummified aspect compared to dry necrosis due to microbiological load.

The wet necrosis results from a microbial critical colonization *(Clostridium perfringens, Bacillus fusiformis*, etc.), which causes tissue to swell and emit a fetid smell. Wet necrosis usually develops rapidly due to blockage of venous and/or arterial blood flow. The affected part is saturated with stagnant blood, which promotes the rapid growth of bacteria and can lead to soft tissue infection and sepsis.

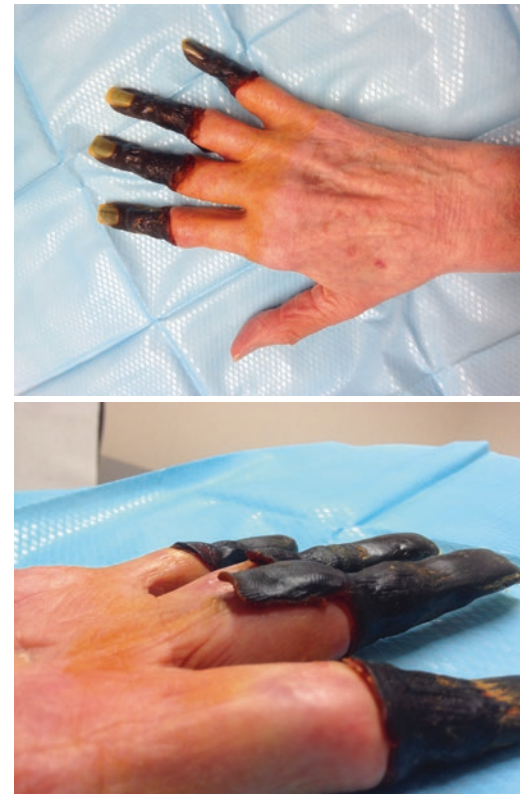

Fig. 29.1 Typical severe dry necrosis

29.1.5 Diagnosis

The diagnosis is based on the clinical presentation as described above in a specific context.

The most important point is to investigate the etiological factors by doing a complete anamnesis and examination of the patient. Appropriate tests will be recommended according to the clinical findings.

- The *anamnesis* will highlight some important points:
  - Circumstances of occurrence (acute or chronic, trauma, etc.)
  - Aggravating factors (cold, etc.)
  - Medications
  - Smoking habits
  - A history of Raynaud's phenomenon
  - Exposure to chemicals or physical agents
  - Personal and familial medical history
  - History of surgical operation, interventional procedure, or intravenous use

  - The profession and occupational activities
  - The presence of systemic symptoms (cancer, vasculitis, endocrinopathy, etc.)
- The *clinical examination* will look for:
  - Ischemia signs (see above)
  - The extra-digital signs correlated with the underlying conditions: signs for arthritis, vasculitis and connectivitis (scleroderma, lupus), signs of infection, signs of endocrinopathy, signs of cardiopathy, etc.
- The *clinical testing:*
  - The venous refilling time
  - Arterial pulse
  - Allen's test
  - The blood pressure (right and left arms)
  - Cardiac auscultation
  - Phalen and Tinel maneuver
- The *complementary* testing:
  - Blood tests (hematology and coagulopathy, renal function, inflammatory syndrome, thyroid tests, antinuclear factors, lipids, serology, proteins and cryoprotein, etc.).
  - Capillaroscopy if Raynaud's phenomenon or suspicion of connective tissue diseases.
  - Hand radiography if suspicion of CREST syndrome, rheumatoid arthritis, or calciphylaxis.
  - Chest X-ray if scleroderma or compressive process is suspected.
  - Cardiogram if arrhythmia.
  - Echo-Doppler of upper limbs.
  - If asymmetric necrosis, an arteriography is recommended.
  - The presence of systemic symptoms and clinical signs will help you to choose the appropriate tests [2].

29.1.6 Management

Up to date, the literature dealing with the clinical management of the necrotic finger is very poor.

Five important points have to be considered in the management of digital necrosis:

1. The etiological factors have to be identified as possible.
2. The local perfusion has to be improved:
   - Vasodilators
   - Antiaggregants and anticoagulants
   - Hyperbaric oxygen
   - Surgical arteriolysis
3. The pain has to be controlled.
4. The infection has to be avoided.
5. The local treatment has to be adapted in each case.
   - *If dry necrosis*: As surgical amputation means often mandatory shortening, directed healing under the mummifying part gives the best length conservation. For this reason, dry dressings are recommended in an effort to keep the mummified part dry. The line of separation usually leads to a complete separation, with eventual falling off of the gangrenous tissue if it is not removed surgically; it is also called autoamputation. Splinting is only recommended if finger retraction is occurring. Active finger motion is started early in all cases. Autoamputation is a long process and is often not accepted by the patient. Anyway, waiting for a clear delimitation of the mummifying part often allows to limit the surgical shortening if the patient asks for it.
   - *If wet necrosis*: The prognosis is poor compared to dry necrosis due to the risk of infection and sepsis. Application of antiseptic dressing is recommended. The affected tissues have to be surgically removed. It is sometimes possible to convert the development of wet necrosis to dry necrosis by application of drying dressings (betadine gauze, alcohol-based dressing, etc.)
   - In case of open ischemia post trauma, the risk of infection is high and should be managed by early surgical debridement and covering with a flap. The only exception should be the very distal tip amputation without bone trauma. This situation can be managed conservatively.
   - The necrosis occurring in the context of a medical pathology should be managed as much conservatively as possible. All effort should be made to keep finger length.
   - Management of digital necrosis is summarized in Fig. 29.2 [7, 8, 9].

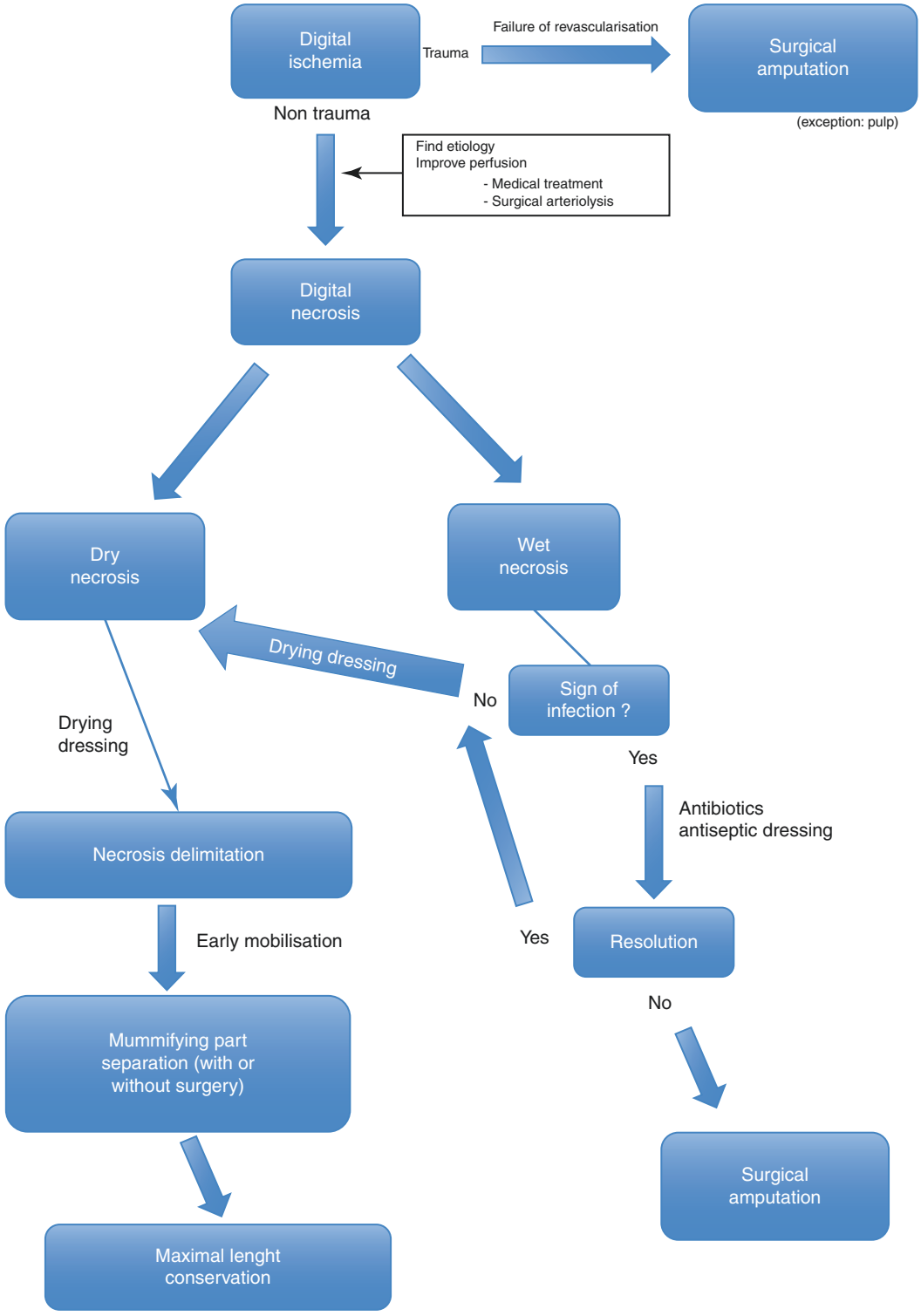

Fig. 29.2 Management of digital necrosis

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Part V

Infectious Origin

Fusarium solani

30

Raphael Masson

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Fusarium solani is a filamentous ubiquitary yeast belonging to the family of *Fusarium* which groups several species. It is a pathogen of plants touching immunodepressed patients [1]. The prognosis is severe [2]. Known risk factors are neutropenia and trauma. Entering ways are the skin (cellulitis), nails (onychomycosis), lungs (sinuses, lungs), or eyes (keratitis) [3]. Dissemination is done by blood and induces fever in most of the cases.

A skin necoritc aspect is observed in immunodepressed patients, looking like ecthyma gangrenosum disseminated [4].

Bad prognosis factors are persisting neutropenia and corticosteroid long-term treatments [5, 6].

The check-up should include hemoccults and biopsies of the involved tissues for analysis of cultures and histopathological samples.

The sensibility to antifungal therapies of *Fusarium solani* is demonstrated by CMI >8 to itraconazole, voriconazole, and posaconazole. CMI 50 and CMI 90 for amphotericin B are, respectively, at 1 and 4 which makes amphotericin B the best activity in vitro over this yeast [6]. But CMI is not correlated to efficacy of antifungic agensts and voriconazole may be an option in the treatment of invasive fusarioses [7].

The therapeutic strategy is based on correcting the risk factors, a surgical debridement associated to an antifungic treatment.

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Necrosis and Infection

31

Farida Benhadou and Véronique del Marmol

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31.1 Introduction

Skin infection leading to cutaneous necrosis is a rare condition. The presence of an immunosuppressant state or an impaired vascular network is a risk factor associated with infection spreading and skin necrosis.

Numerous pathogens can cause skin necrosis, and some of them are associated with a high level of mortality.

This chapter will review the various reported pathogens implicated in skin necrosis.

31.2 Bacteria

Necrotizing fasciitis, also known as the flesh-eating disease, is a progressively destructive bacterial infection of the skin, the subcutaneous tissues, and the deep fascia and carries a mortality rate of about 30 %. Group A streptococcus, *Staphylococcus aureus*, *Clostridium perfringens*, *Bacteroides fragilis*, *Bacillus anthracis*, and *Aeromonas hydrophila* are the most reported bacteria causing necrotizing fasciitis [1].

Acinetobacter baumannii often with a multidrug-resistant phenotype is responsible for an increasing number of necrotizing fasciitis cases. *Acinetobacter baumannii* is a ubiquitous pathogen commonly found in water, soil, and the healthcare environment. Skin and soft tissue infections associated with Acinetobacter species are likely to be underrecognized. Clinicians should be aware of its

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potential as a multidrug-resistant pathogen causing hospital-acquired skin and soft tissue infections, particularly when associated with previous trauma or the use of invasive devices [2].

Another rare life-threatening infection is purpura fulminans characterized by cutaneous hemorrhage and necrosis associated with systemic symptoms. It usually occurs in children, but it has also been noted in adults. Infections reported to cause purpura fulminans include *Neisseria meningitidis*, *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Haemophilus aegyptius*, *Staphylococcus aureus*, group A and other B-hemolytic streptococci, and *Pseudomonas aeruginosa*. Cases secondary to Candida and Rickettsia infection have also been reported [3] (Figs. 31.1 and 31.2).

Ecthyma gangrenosum (EG) is a well-recognized but rare case of cutaneous infection most often associated with a *Pseudomonas aeruginosa* bacteremia. Fungal and bacterial organisms, such as *Escherichia coli* and *Citrobacter freundii*, have been identified less often as the cause of EG. EG usually occurs in immunocompromised patients and is almost always a sign of pseudomonal sepsis. The characteristic lesions of EG are hemorrhagic pustules that evolve into necrotic ulcers. This clinical entity should be considered when otolaryngologists are asked to evaluate necrotic cutaneous lesions of the head and neck [4].

Syphilis is caused by a bacterium called *Treponema pallidum*. Syphilis remains a major health problem, and in spite of excellent methods for diagnosing and treating syphilis, the disease is still widespread. Syphilis is called the big faker because of its numerous and atypical clinical presentations. Cases of extensive necrotic plaques have been reported in patients with an HIV coinfection [5].

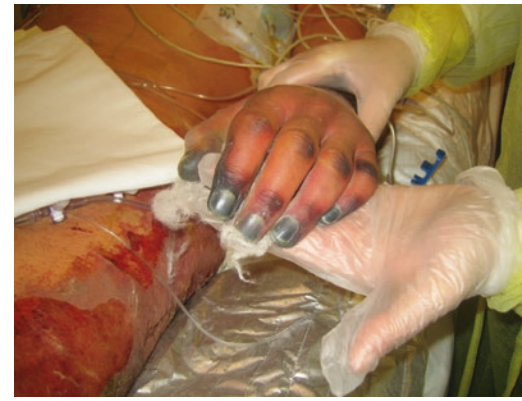

Fig. 31.1 Acinetobacter baumannii colonization and impaired blood flow

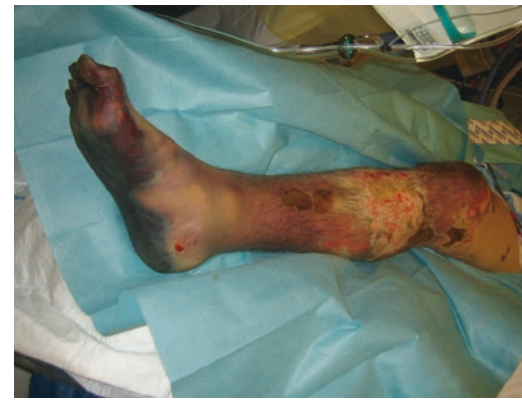

Fig. 31.2 Acinetobacter baumannii colonization and impaired blood flow

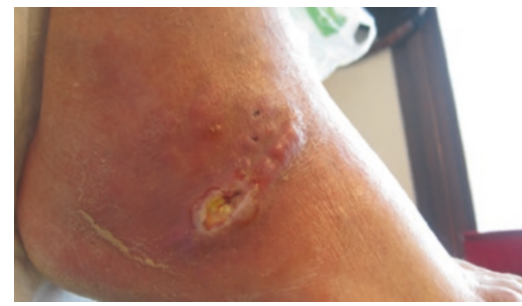

Fig. 31.3 Ulceration caused by mycobacterial infection

31.3 Mycobacteria

Mycobacteria affecting the skin like *Mycobacterium tuberculosis* or *marinum* are more frequently associated with chronic ulcers than with extensive skin necrosis (Fig. 31.3).

Mycobacterium ulcerans is the causative agent of Buruli ulcer. Buruli ulcer is a chronic debilitating skin and soft tissue infection that can lead to permanent disfigurement and disability. The bacterium is most prominent in tropical regions of Africa, Asia, Australia, and South America.

Infection occurs through unknown environmental exposure; human-to-human infection is rare. The frequent clinical presentation is a deep, rapidly developing chronic ulcer associated with necrosis of subcutaneous fat. Bacteriological identification is not always possible. The pathogenic effect of the mycobacterium ulcerans is due to the production of a necrotizing exotoxin with an immunosuppressive effect. Surgery is usually urgently required. The Buruli ulcer is now identified as a major public health problem in Africa [6].

Leprosy is caused by *Mycobacterium leprae*, an acid-fast, rod-shaped bacillus. The disease mainly affects the skin, the peripheral nerves, mucosa of the upper respiratory tract, and the eyes. It once affected every continent, and it has left behind a terrifying image in history and human memory – of mutilation, rejection, and exclusion from society. Lucio's phenomenon is a variant of type 2 leprosy reaction, and its clinical presentation is characterized by a necrotizing erythema. It is a rare condition that occurs in patients who were never treated or in those who have followed treatment irregularly. Lucio's phenomenon may reach severe proportions and cause death by disseminated intravascular coagulation and/or septicemia [7].

31.4 Viruses

The herpes viruses family and more specifically the herpes simplex and herpes zoster member are associated with cutaneous necrosis. Herpes simplex type 1 most commonly causes cold sores. It can also cause genital herpes. Herpes simplex type 2 is the usual cause of genital herpes, but it also can infect the mouth. Herpes zoster is the causal agent of varicella (chickenpox) and zona. The diagnosis of herpes infection has to be discussed in immunodeficient patients with extensive cutaneous necrosis [8].

Recently, cases of limited cutaneous necrosis have been described in young children who have been exposed to domestic rats. The necrosis was caused by the cowpox virus. Cowpox virus is part of the Orthopox virus genus, like variola virus, and is generally transmitted to humans by infected cats or rodents. The cowpox virus infection should be kept in mind when macular, vesicular, or necrotic cutaneous wounds do not improve with antibiotics [9].

Chronic hepatitis C infection is strongly associated with types II and III mixed cryoglobulinemia and occasionally associated with type I cryoglobulinemia.

Mixed cryoglobulinemia secondary to hepatitis C virus infection can involve the skin, and the development of a necrotizing vasculitis is observed in only 2–3 % of patients with hepatitis C virus-related mixed cryoglobulinemia. The circumstances predisposing the infected patients to develop these manifestations remain unknown [10].

31.5 Yeast

Blastomycosis is an uncommon, chronic, granulomatous disease caused by the dimorphic fungus *Blastomycetes dermatitidis*; blastomycosis has now been reported throughout Africa, in the Middle East, and in some parts of Europe. The skin is the most common site for dissemination, followed by bone, genitourinary tract, and central nervous system. Primary cutaneous blastomycosis is a rare illness occurring only after traumatic implantation of the fungus. The incidence of infection is highest in rural areas and in agricultural workers. Skin lesions in disseminated blastomycosis may be single or multiple, are often symmetrical, and are usually on the trunk rather than on the extremities. The primary cutaneous blastomycosis has a strong tendency for spontaneous recovery. Blastomycosis can be associated with necrotic skin lesions in immunodeficient patients [11].

There are fungal infections (aspergillus, candida, etc.) associated with a high level of mortality; therefore, prompt diagnosis and institution of antifungal therapy are vital, as is appropriate management of the underlying disease process. The mucormycosis usually affects the face or oropharyngeal cavity. The skin and the gastrointestinal tract can be affected. The immunocompromised

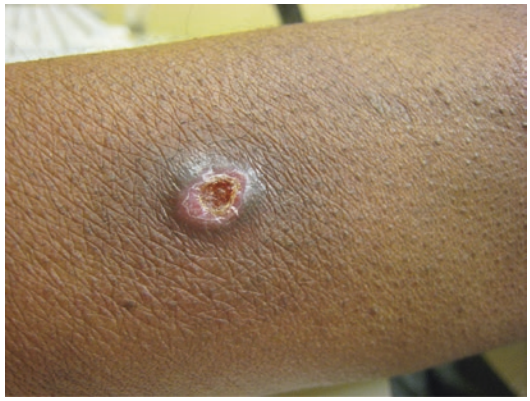

Fig. 31.4 Ulceration caused by candida infection in a renal graft recipient

patients are more prone to this fungal infection. The skin is rarely affected, and its clinical presentation is dominated by an erythema evoluting in a necrosis [12] (Fig. 31.4).

31.6 Parasites

Leishmaniasis is caused by parasitic protozoan parasites transmitted by sandflies. Its clinical presentation is characterized by crusted papules or ulcers occurring several weeks to months after sandfly bite inoculation on exposed skin. Lesions may be associated with sporotrichotic spread and usually heal spontaneously. Leishmaniasis can also cause life-threatening widespread destructive ulcerations [13].

31.7 Pathological Mechanisms

Systemic activation of coagulation and dysregulation of the anticoagulation are the main pathways used by the pathogens to cause skin necrosis.

The interruption of the blood flow in the subcutaneous tissue causes ischemia and impedes oxidative destruction of bacteria by polymorphonuclear cells.

The pathogens can directly invade the blood vessel walls and injure endothelial cells, causing endothelial proliferation and decreasing the vascular lumen. Many factors help in the development of skin necrosis like decreased blood flow in the case of vasculopathy or diabetes, and an immunodeficiency gives the opportunity for the pathogens to proliferate.

Some pathogens are associated with skin necrosis secondary to the vasculitis process like the hepatitis C and the cryoglobulinemia vasculitis. The mechanisms used by the pathogens to induce skin necrosis are numerous and not completely understood.

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Fournier Gangrene

32

Tristan L. Hartzell and Dennis P. Orgill

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32.1 Introduction and History

Fournier gangrene is a necrotizing soft tissue infection of the male perineum, although similar infections have been described in women. It is a type of necrotizing fasciitis, distinguished by its location of origin and the vast majority of cases being mixed infections of aerobic and anaerobic bacteria. It is characterized by a rapidly spreading soft tissue infection that travels along perineal subcutaneous fascial planes and obliterates perforating skin vessels but spares underlying muscle. High mortality rates have resulted in a heightened awareness by surgeons with a low threshold for intervention.

Severe, life-threatening soft tissue infections have been recognized throughout history. Hippocrates first described necrotizing fasciitis in the fifth century BC. It was not until 1764, however, that Baurienne first described a case of scrotal gangrene, characterized by a fast spreading necrotizing infection. The disease ultimately took its name from Jean Alfred Fournier, a French venereologist who described five cases of perineal gangrene in clinical lectures in 1883 [1]. Even in this early practice of medicine and identification of a new disease process, academics recognized that diabetes and trauma were leading causes of Fournier gangrene. Fournier specifically described the ligation of the prepuce to control nighttime enuresis and archaic birth control regimens to prevent an adulterer from impregnating his married mistress as causes [1]. Herod the

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Great and Segundo Ruiz Belvis, a Puerto Rican abolitionist and independence leader, are suspected to have died from Fournier gangrene.

The number of annual cases of Fournier gangrene is difficult to ascertain, owing to inaccurate reporting, incorrect identification, and the many misnomers. Approximately 750 cases have been reported in the literature [2], and the prevalence has been estimated to be as high as 1 case in 7,500 persons [3], although these numbers may be extremely inaccurate since Fournier gangrene is not a reportable disease.

The mortality rate has been reported to be between 14 and 80 % [4]. The rate is on the high end in those who are older, have a rectal focus, and have diabetes [3]. The cornerstones of treatment continue to be early recognition, aggressive antibiotic coverage, prompt surgical debridement, and modern supportive care.

32.2 Physiopathogeny

Fournier gangrene is no longer considered idiopathic in origin, as 95 % of cases have a clearly identifiable cause [3]. For most cases, the triad of disruption to the skin barrier, location of the disruption in the perineum, and a decreased host response to bacterial invasion are present. The embryology and anatomy of this region that creates multiple fascial planes that dissect reasonably easily, combined with the bacteriology of the perineum, undoubtedly contribute to the incidence of this disease.

Fournier gangrene starts as a routine infection in the anorectum, the urogenital tract, or the skin of the perineum caused by trauma, pressure necrosis, or conditions such as inflammatory bowel disease, rectal fistula, or hidradenitis suppurativa. In contrast to classical group A streptococcus necrotizing fasciitis with a rapid onset in immunocompetent patients, Fournier's gangrene has an indolent onset becoming fulminate due to a compromised immune system. Diabetes mellitus is by far the most common predisposing disease; however, numerous other predisposing comorbidities have been cited including chemotherapy, obesity, malignancy, alcoholism, intravenous drug use, malnutrition, cirrhosis, steroids and other immunosuppressant medications, cirrhosis, HIV infection, and Crohn disease [3].

In general, Fournier gangrene develops when an imbalance occurs between host immunity and virulence of the offending organism. The bacteria gain portal of entry from trauma (or one of the etiologic factors mentioned previously), the immunocompromised state of the individual allows these microorganisms to freely proliferate, and eventually the virulence of the bacteria leads to their rapid spread along fascial planes in the perineum (Fig. 32.1). Determining what virulent factors distinguish a routine, contained infection from uncontrolled necrotizing fasciitis has been the goal of researchers for decades.

Originally, Meleney reported in his 1924 series of Chinese men with necrotizing infections that streptococcal species were the responsible genus for this virulence [5]. Since this report,

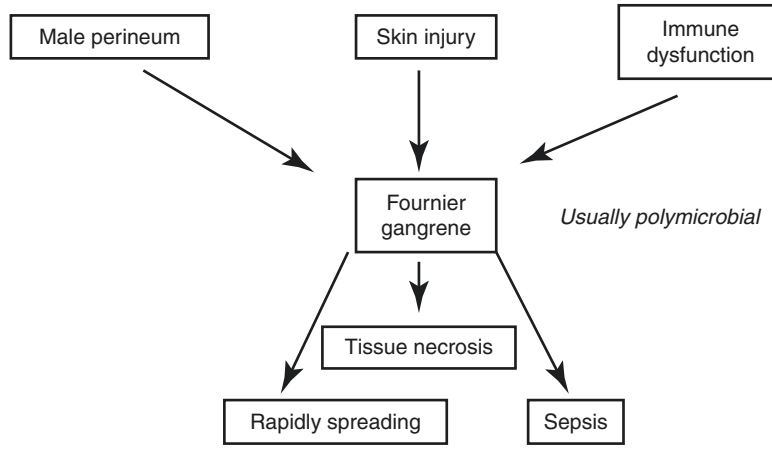

Fig. 32.1 Pathophysiology of Fournier gangrene

most cases of Fournier gangrene have been found to be polymicrobial and when streptococcal species is isolated, it is cultured alongside 2–5 other bacteria. Staphylococcal species, enterobacteriaceae species, anaerobic organisms, and fungi are some of the more frequent causative organisms identified. In Fournier gangrene, it is believed that all of these organisms work in concert to create the final clinical picture. Macroscopically, necrotizing fasciitis produces rapid liquefactive necrosis of the subcutaneous fat and connective tissue, destroying skin perforators while sparing the overlying skin. This is in opposition to cellulitis and erysipelas, which affects the superficial layers of the skin and the lymphatics but spares the fat and fascia. With necrotizing fasciitis, liquefaction of fat leads to the development of a plane between the fascia and subcutaneous tissue that can easily be finger dissected. It also leads to massive edema and the pathognomonic "dishwater pus." Veins traversing the inflamed fat thrombose and a vicious cycle of inflammation and necrosis propagates.

Researchers believe that a polymicrobial infection with a synergy of enzymes produces the macroscopic picture responsible for Fournier gangrene. For example, one organism may carry an enzyme that inflames vessels and leads to their thrombosis. Local tissue oxygen tension is decreased. This then allows an anaerobic bacterium to further propagate. This facultative anaerobe may have an enzyme such as collagenase in its arsenal that then digests fascial barriers and allows the infection to rapidly spread. Destructive proteases further destroy local tissue. A gram-negative bacteria then begins to propagate, releasing exotoxins and creating a cytokine storm and sepsis. Eventually, what started as a simple, indolent infection has become florid necrotizing fasciitis.

32.3 Diagnosis

A rapid diagnosis of Fournier gangrene reduces morbidity and mortality. However, the diagnosis is notoriously difficult and often missed until very late in the hospital course. Since there is no definitive test for Fournier gangrene, it is mandatory that the overall clinical picture be carefully considered. When there is doubt, early surgical treatment is preferred as the infection can progress to sepsis and death within hours. When unsure, a biopsy from normal looking adjacent tissue, a fascial biopsy, and a gram stain can be performed before beginning with a disfiguring debridement.

A careful history can also aid in the diagnosis. Patients who are diabetics, obese, or immunocompromised should be of special concern. A history of recent trauma to the anogenital region, followed by an indolent infection, can usually be elicited. Patients often report weakness, low-grade fevers, and chills for a prodromal period of 2–7 days.

The examiner needs to be especially cautious in those patients who are unable to communicate pain or hesitant to allow a full examination. One should not hesitate to do an exam under anesthesia if necessary. A massive pannus or mons pubis, with or without underlying phimosis, has had several severe necrotizing infections in our experience.

Nonspecific signs of Fournier gangrene include tenderness, swelling, erythema, and pain. Unfortunately, these signs mimic non-life-threatening infections such as cellulitis and erysipelas. In our experience and in the literature [3, 4], the most common distinguishing feature is severe pain and tenderness in the genitals. This pain is out of proportion to the exam findings. As the infection advances this pain progresses to paresthesias and numbness, indicating destruction of the cutaneous nerves. Similarly, with advanced infection the skin changes appearance from red, hot, and swollen with ill-defined borders to pale, mottled, blistered, and gangrenous with sharp lines of demarcation. Hemorrhagic bullae are a late finding, but suggestive of the disease. The odds ratio (OR) of bullae for necrotizing fasciitis compared to a cellulitis was found to be 3.5 with a 95 % confidence interval (CI) of 1.0–11.9 [6].

Subcutaneous emphysema is an often sought finding of necrotizing fasciitis and Fournier gangrene. However, the diagnosis must not be excluded if there is no crepitus on exam or air on radiograph. The majority of cases of Fournier gangrene we have treated have not had subcutaneous emphysema. This finding is only seen when gas-forming organisms are present.

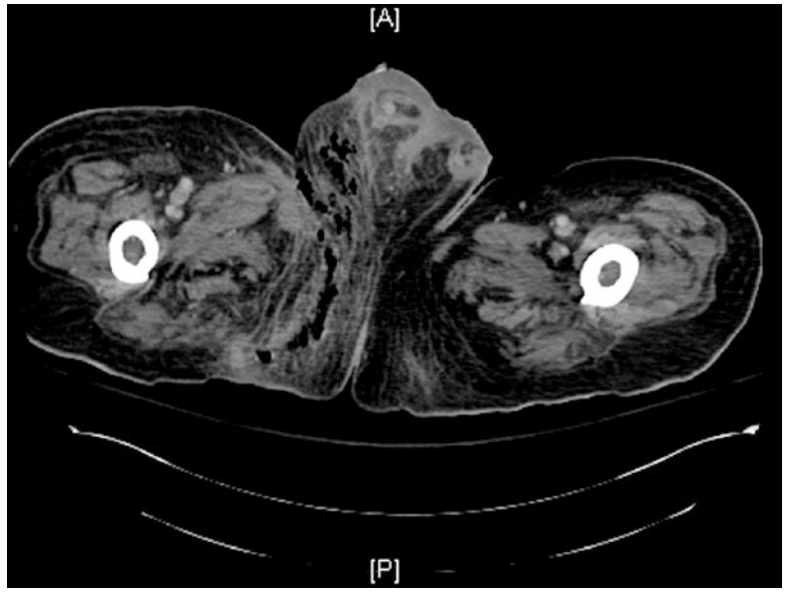

Fig. 32.2 Chronic stage IV right ischial pressure sore that progressed to Fournier gangrene. The patient had radical debridement of his right scrotum, right orchiectomy, and lower right anterior abdominal wall

The role that imaging such as x-ray, computed tomography (Fig. 32.2), and magnetic resonance imaging plays in the diagnosis of Fournier gangrene is debatable. They should only be considered as an adjunct to the clinical exam in doubtful cases and should not be used to determine the extent of surgical debridement. In addition, performing these studies prolongs the time to treatment. If imaging studies are performed, it is important to reiterate that the clinical exam should supersede image finding. Gas seen on scans is usually an indication for operative intervention; however, in patients with chronic pressure sores, gas can be seen in the absence of Fournier gangrene.

Ultrasonography has also been used in Fournier gangrene, mainly to assess blood flow to the testes. However, in our experience it is very difficult to perform this test, as the patients cannot tolerate the pain from direct pressure on the involved tissue.

If a frozen biopsy is needed to assist in the diagnosis, the pathognomonic findings of Fournier gangrene are (1) inflammation and necrosis of the fascia, (2) fibrinoid coagulation of the nutrient arterioles and veins, (3) polymorphonuclear cell infiltration, and (4) microorganisms within the deep tissue. The skin is often minimally involved in the disease process until very late.

32.4 Treatment

Fournier gangrene requires both emergent medical and surgical treatment. Patients with Fournier gangrene should receive immediate, empiric antibiotic therapy and emergent surgical debridement of the involved tissue. Aggressive measures should be taken to ensure normal end organ perfusion. It is critical that these three measures be taken before pursuing unnecessary diagnostic maneuvers:

1. Resuscitation
2. Parenteral broad-spectrum antibiotics
3. Surgical debridement

A multi-specialty approach is mandatory, with the involvement of surgeons, infectious disease experts, and intensivists. The hospital course is often prolonged and nosocomial complications are frequent. Urinary or rectal diversion may be necessary and, if so, should be done early.

The current antibiotic regimen of choice varies by region and hospital. The antibiotic spectrum should cover streptococcus, staphylococcus, the Enterobacteriaceae family, and anaerobes. Common first-line antibiotics for suspected polymicrobial Fournier gangrene are:

1. Ampicilin-sulbactam or piperacillin-tazobactam plus clindamycin plus ciprofloxacin

2. Imipenem/cilastatin or meropenem
3. Cefotaxime plus metronidazole or clindamycin

It is essential that anaerobes be covered.

Clindamycin merits special mention in the antibiotic treatment of Fournier gangrene. It works by inhibiting bacterial protein synthesis, specifically decreasing the production of such proteins as SpeB [7]. Furthermore, its mechanism of action makes it not subject to the inoculum effect that occurs when large numbers of bacteria become slow growing and decrease expression of penicillin-binding proteins [7]. In animal models, clindamycin has been shown to be much more effective in the treatment of necrotizing streptococcal infections compared to penicillin and erythromycin, even when the treatment is delayed [8].

Ultimately, antibacterial coverage is tailored to culture results. With the initial debridement, a gram stain, KOH stain, and culture must be sent. In addition, blood cultures should be done. If the patient defervesces and the clinical picture improves, the results from these tests can then be used to narrow antibiotic coverage. Most consider Fournier gangrene a deep infection and treat it with antibiotics for 4–6 weeks [9].

Antifungal agents are not used empirically in Fournier gangrene, as many are nephrotoxic. However, if the initial KOH stain shows fungi, amphotericin B or caspofungin should be instituted.

Many adjuvant medical therapies have been explored for the treatment of Fournier gangrene. Two of the more commonly discussed are intravenous immunoglobulin (IVIG) and hyperbaric oxygen (HBO). IVIG is postulated to work by neutralizing streptococcal toxins, mitigating the exaggerated cytokine response from them. Several authors have advocated for its use based on their experience in small series [10, 11]. HBO has also been advocated based on the results from small series [12, 13]. It is important to note that HBO is not without risk and has been reported to cause reversible myopia, barotraumas, pneumothorax, and cramps. Also, it should never take precedent over proper surgical debridement. Better studies are needed before IVIG and HBO can be fully endorsed in the treatment of Fournier gangrene.

The unique role of medical comorbidities in Fournier gangrene merits special discussion. As mentioned previously, conditions such as diabetes, alcoholism, and immunosuppression are often predisposing diseases in Fournier gangrene. Strict glucose control and nutritional supplementation are two of the more vital adjuvant interventions.

While the medical management is important, ultimately the most critical part of treating Fournier gangrene remains surgical debridement. It must be swift and decisive. Any delay in surgery will increase mortality. As soon as Fournier gangrene is suspected, the patient must be brought emergently to the operating room for an aggressive and extensive debridement. Signs suggestive of Fournier gangrene are necrosis of the superficial fascia and fat, thrombosis of superficial vessels, and foul-smelling drainage. In early Fournier gangrene the fascia appears edematous, while later in the disease it becomes more gray and dusky.

With Fournier gangrene, tissue should be resected beyond the involved borders to healthy, bleeding edges. If the tissue edge is not bleeding, the vessels are likely thrombosed due to the inflammatory, necrotic process. It is our experience that with Fournier gangrene there is easy separation of the subcutaneous tissue from the fascia by blunt dissection. The margin of resection must extend beyond this easily separated plane. The deep fascia and muscle is spared in true Fournier gangrene; however, it may be involved due to the inciting event, such as a rectal fistula or anogenital trauma. If necrotic, it also must be aggressively resected to healthy muscle. Similarly, the testicles are often not involved in the necrotizing process. If they are exposed, though, they should be buried in a subcutaneous pocket or placed in a moist dressing to prevent desiccation. If necrotic, one should not hesitate to do an orchiectomy.

Reconstructive concerns are secondary. It must not be forgotten that this is a life-threatening condition. Before leaving the operating room at the initial debridement, the wound

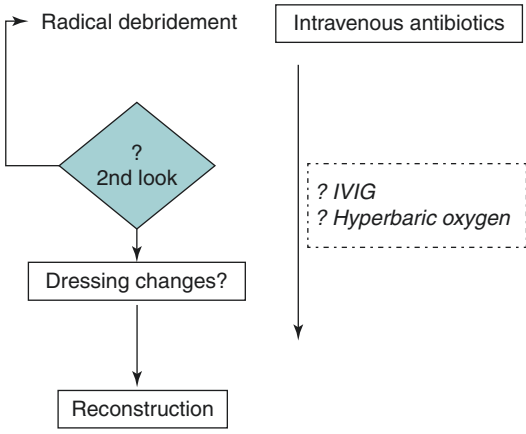

Fig. 32.3 Basic treatment algorithm of Fournier gangrene

should be reinspected for any remaining signs of gangrene. A dilute Betadine- or Daikin-soaked dressing is often used to cover the initial wound at this stage.

"Second-look" surgeries are often necessary within 12–24 h of the initial debridement (Fig. 32.3). Less urgency is often placed on these "second-look" surgeries. However, it must be remembered that this is the same rapid, aggressive, disease process and it merits the same expediency as the initial presentation. Multiple "second-look" procedures may be necessary. Based on our experience, we make every effort to resect all actively infected and necrotic tissue from the start. We do not plan on "second-looks" and have found that many times with an aggressive, proper debridement, the infection can be contained in the initial operating room visit. Our ideal treatment regimen is one thorough debridement followed by the placement of a vacuum-assisted closure (VAC) device. In general, healthy granulation tissue on the first VAC change is an excellent sign that adequate debridement has occurred.

Finally, if perineal involvement is extensive, the surgeon can consider diverting the fecal stream to prevent fecal contamination of the wounds. Modern rectal devices often avoid the need for colostomy. Urinary diversion can usually be accomplished with a urethral or suprapubic catheter.

32.5 Reconstruction

The reconstructive process begins with the preparation of the wound bed. To maximize success, the systemic condition must be addressed. Hemodynamic stability must be achieved and severe anemia corrected. Similar to patients with large burns, nutritional support is mandatory from the first day of admission. A tremendous amount of protein and fluid is lost from these large, inflamed wounds and it is easy for the patient to spiral into a catabolic state. Enteral feeding tubes may be necessary.

While the patient is being systemically optimized, dressing changes to the involved area are being done. The surgeon should not be rigid about one type of dressing, but rather flexible in dressing choices depending on the wound status. A typical regimen is to begin with dilute Betadine dressings for several days. Once the infection is clearly resolved, this is transitioned to a wet to dry saline-soaked dressing with or without topical antibiotics. The wound should be kept moist but not overly so. Desiccation leads to decreased epithelial cell migration and excess moisture contributes to tissue maceration. Subsequently, a hydrogel dressing may be employed to promote granulation. Another alternative is vacuum-assisted closure (VAC). The VAC device has been shown to reduce the days of hospitalization, decrease patient discomfort and pain medication use, and allow for more prompt reconstructive surgery in patients with Fournier gangrene [14]. The VAC device has become very popular in the management of these large wounds and we tend to employ it in all of our patients once the infectious process is under control. When a clean and well-vascularized wound bed is achieved, surgical closure can then be considered.

The workhouse of Fournier gangrene reconstruction is the split-thickness skin graft. Cadaver allografts can be considered if the surgeon is uncertain about the cleanliness of the recipient site. If these grafts take, the sites can easily be grafted with autografts in 1–2 weeks. While primary closure, local tissue rearrangement, and local flaps (such as the medial thigh myocutaneous flap [3]) may be employed for some

wounds, most patients with Fournier gangrene receive a skin graft. Prior to any of these operations, the surgical bed is further prepared in the operating room. Any remaining necrotic tissue is removed and microbial colonization is reduced with debridement and irrigation. Areas of hypergranulation are also debrided. The wound edges are excised to remove fibrotic tissue and obtain a uniform, level edge.

Split-thickness skin grafts are meshed to allow better contouring to the wound and expansion of the skin. We mesh at 1:1.5 or 1:2 for most wounds. The skin graft is secured with staples or absorbable sutures. Some surgeons use fibrin glue to assist with immobilization. A bolster dressing or VAC device is placed over the graft. Those wounds where infection remains a significant concern can be moistly dressed with 5 % mafenide acetate solution. If a bolster or VAC device is placed, it is removed at 4–7 days or earlier if indicated.

Postoperatively, the patient must be rehabilitated from a demanding hospital course. The patients are usually extremely debilitated and benefit from physical and occupational therapy. They frequently develop lower extremity edema and may benefit from compression garment therapy. The debilitated patient may also require recovery in an inpatient rehabilitation facility. Long-term deficits should not be ignored. One study found that nearly 50 % of men who had penile involvement had pain upon arousal, related to scarring and limited mobility of the genitalia [15]. Consultation with a psychiatrist is often important as well to assist in managing the altered self image.

Conclusion

Fournier gangrene is a rare but serious infection that has a high mortality rate. Early diagnosis is critical. Patients presenting with pain out of proportion to the exam, spreading erythema, systemic laboratory abnormalities, and clinical deterioration should raise significant suspicion. Once suspected, the treatment must be prompt and definitive. Broad-spectrum antibiotic therapy should be administered and the patient brought immediately to the operating room. The surgical debridement should be aggressive until healthy, bleeding tissue is encountered. Reconstruction concerns are secondary and the surgical intent should be to rid the necrotizing infection definitively, rather than plan on needing "second-looks." Dressing care can transition to a VAC device which assists in creating an ideal wound bed for skin graft, primary closure, or local tissue rearrangement. Much remains to be discovered in the pathogenesis of Fournier gangrene; however, unique virulence factors and the abnormal interactions with the immune system have been recognized. It is hoped that one day these insights will contribute to a reduction in the mortality rate of this aggressive disease.

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Part VI

Surgical Context

Skin Necrosis Over Osteosynthetic Material

33

C. Rodaix

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33.1 Introduction

Skin necrosis is a frequent complication in the management of traumatized extremity, particularly in the case of open fracture.

The treatment of open fracture is not the purpose of this article and will not be discussed here.

A prolonged period of hardware exposure ultimately leads to contamination, and then the goal of treatment is to prevent infection of hardware and underlying bone.

The traditional management of soft-tissue defects and exposed hardware includes irrigation and debridement, intravenous antibiotics, and likely removal of the hardware. Obviously, preservation of the hardware would be the optimal goal to maintain stability and optimal reduction [1].

Skin necrosis covering osteosynthetic material can be divided into two groups: on one hand that which happened early after the surgery because of soft-tissue injury (contused or crushed) or too tensile strength in stitched and on the other hand that when a deep infection induces skin necrosis, early or later after the surgery.

In all cases, skin necrosis had to be removed, and bone and hardware had to be covered with soft tissue.

33.2 Postoperative Skin Necrosis

In this case, skin necrosis is initially a soft-tissue complication but can lead to a bone infection.

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This is often seen in lower limb trauma with open or closed fracture. Skin necrosis appears because of a combination of soft-tissue injuries (direct contusion, soft-tissue degloving, displaced fracture fragments, articular dislocation, compartment syndrome), vascular injuries (hematoma, ischemia), early infection, and surgery (strength stitches, skin undermining, surgical approach).

33.2.1 Debridement

Those wounds require aggressive irrigation and debridement. This involves excision of all necrotic, devitalized, and contaminated tissue and bone as well as incisions for additional exposure and drainage [2] and had to be repeated every 24–48 h to ensure all necrotic and devitalized tissue had been removed.

The aim of debridement is to prevent the risk of bacterial proliferation and to remove debris and necrotic tissue.

Many different techniques are available. Mechanical methods include ware-jet dissection (Versajet hydrosurgery system [3]) or coblation technology (ArthroCare). Consensus on irrigation technique and additives (bacitracin, antiseptics, surfactants, or non-sterile soap) still remains to be determined. Other additions to wound care including the use of silver dressings [4] and NPWT (negative-pressure wound therapy) have proven successful in helping reduce infection rates. The use of NPWT has decreased the need for further debridements to every 48–72 h.

33.2.2 NPWTi

A modification of the NPWT system that adds automated intermittent wound irrigations was introduced nearly a decade ago. Instillation with normal saline can speed up wound fill with higher-quality granulation tissue composed of increased collagen compared with traditional NPWT [5]. The instillation of an antimicrobial solution (antiseptic or antibiotic) into an infected wound can help decrease the bioburden and create a more favorable environment for wound healing [6]. In addition, analgesics may be mixed with some solutions to treat the pain that may be associated with NPWT therapy [7].

Table 33.1 Indications for NPWT with instillation

Wounds with persistent infection, especially after a trial of traditional negative-pressure wound therapy (NPWT)
Infected wounds with a foreign body in place (orthopedic hardware and total joint arthroplasty)
Exposed biologic or monofilament polypropylene mesh
Stalled wounds
Painful wounds
Wounds with significant biofilm present
Patients whose wounds are at a high risk of resulting in a major amputation due to the advanced nature of the wound and associated patient comorbidities
Wounds with a viscous exudate
Necrotizing fasciitis
Complex sternotomy wounds
Acute osteomyelitis
Chronic osteomyelitis after adequate debridement

NPWT with instillation is particularly indicated to manage patients with infected orthopedic wounds (open fractures, osteomyelitis). Debridement of the infected and devitalized tissue and bone is important prior to the initiation of the NPWTi especially for chronic infections where the presence of a biofilm may make penetration of antibiotics tissues and bones into and treatment of chronic infection more difficult.

The types of wound commonly treated from NPWTi are listed in Table 33.1.

33.2.3 Hardware Removal

In their review, Viol et al. [1] identified 6 parameters with prognosis relevance for the management of exposed hardware before soft-tissue coverage and proposed an algorithm for treatment management (Fig. 33.1): location of the hardware, infection, type of bacteria, duration of infection, duration of exposure of hardware, and hardware loosening.

Absolute indications for hardware removal are the presence of hardware loosening, exposure of hardware for more than 2 weeks, and infection of hardware proved by positive cultures.

Hardware removal is recommended in case of clinical signs of deep infection (the presence of

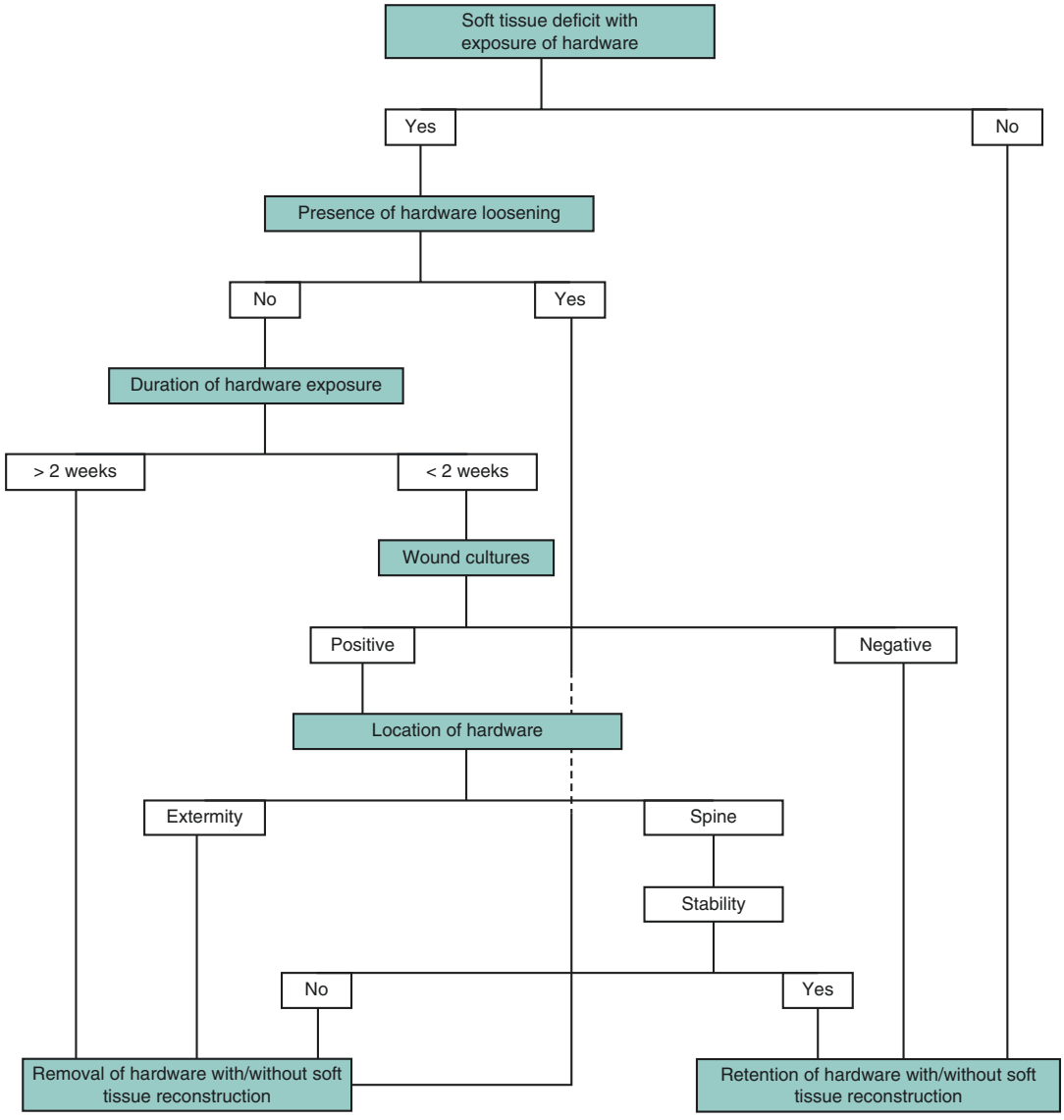

Fig. 33.1 Algorithm for management of soft-tissue defects and exposed hardware according to the literature

purulent fluid and exposed hardware) and at the lower extremity when axial stability can be maintained with an external fixator device.

Osteosynthetic material for fractures or arthrodesis may be left in place for longer periods despite infection because the goal is bony consolidation, although the healing time may be prolonged. This is especially true for the spinal column, where the removal of hardware is only possible if stability is maintained.

Superficial infection without exposure of hardware can be treated without removal of the hardware but may nevertheless require additional soft-tissue reconstruction [1].

33.2.4 Soft-Tissue Reconstruction

In the case of exposed hardware as in open fracture, the concept of early coverage is important [8]. Patzakis et al. [9] have shown that only 18 % of infections after open fractures are caused by an organism initially cultured from the traumatic wound, suggesting many of the infections after open fractures are

nosocomially acquired. For this reason, early coverage should be protective against infection.

Godina [10] found that early flap cover in primary trauma with a soft-tissue defect was associated with a lower rate of failure of the flap, a lower rate of postoperative infection, a shorter time to bone healing, and a shorter mean length of hospital stay.

The local wound environment is usually ischemic and contaminated, with a soft-tissue defect, and the use of free muscle flaps conveys a considerable advantage in such conditions because of their rich vascular supply and superior resistance to infection.

The ideal timing for free-flap reconstruction of these injuries has been controversial.

In the case of open fracture, free flaps transferred after 7 days had a significantly increased rate of infection and venous thrombosis [11]. Rates of flap take-back and osteomyelitis were significantly higher in patients who had metalware exposed for greater than 7 days compared to those who underwent free-flap coverage within 1 day of skeletal fixation.

Nowadays, local flaps decrease the need for free flaps in the reconstruction of the lower leg, and they are less expensive and time-consuming.

33.2.5 Alternatives to Flap Cover

Acellular skin substitutes (or artificial dermis), initially developed for acute burns, came to be used in the treatment of chronic wounds.

Because of the risk of infection and often poorly vascularized tissue, care must be taken in indications, and NPWT is often required to improved local environment.

Of course skin substitutes as skin grafts must be used after removal of the hardware.

33.3 Delayed Skin Necrosis

Deep infection as osteitis, particularly in the case of internal fixation or arthroplasty, can lead to superficial wound and skin necrosis.

The definition of deep infection requires clinical signs and positive cultures. Radiographic signs of hardware loosening or bony infection seem to be not reliable enough to make decisions regarding the removal of hardware.

Management of infected prosthesis is quite the same with or without soft-tissue defects and early coverage is the rule.

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Necrotic Complications After Skin Grafts

34

Xavier Santos and Israel Iglesias

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34.4 **Graft Rescue** 205

34.1 Introduction

Skin grafts are used in a variety of clinical situations. The essential indication for the application of a skin graft is wound closure. Skin grafts are usually the initial treatment of choice for many open wounds that cannot be closed primarily. Skin grafts are generally avoided in the management of more complex wounds. Anfractuous wounds; exposed bones, tendons, nerves, or vessels; and deep pressure ulcers normally require the use of flaps for stable wound coverage. Skin grafts have limited success in wounds with a compromised blood supply, such as irradiated wounds or ischemic ulcers.

Skin grafts can include either a portion of dermis (split-thickness graft) or the entire dermis (full-thickness graft). Split-thickness grafts can tolerate less vascularization of the recipient site but have a greater amount of contraction. The donor site generally heals spontaneously, through epithelialization from cells of hair follicles and sweat glands. Large areas of split-thickness grafts can be taken to cover big defects such as in large surface area burns. Full-thickness grafts require a better vascular bed for survival but undergo less contracture. Thus if the recipient site is not well vascularized, full-thickness grafts have a greater chance to become necrotic. Full-thickness graft donor sites must be closed primarily. Thus full-thickness grafts are only used to close small wounds, especially in the face because of better color matching and less contraction.

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A skin graft is essentially a skin transplantation. The graft is completely severed from its blood supply, drainage system, and sensory innervation. The graft is placed onto a vascular bed so that it will become vascularized and sensate. So the survival of the graft completely depends on the recipient site. A skin graft becomes partial or totally necrotic when it fails to be vascularized from the recipient site. Necrosis of the transplanted skin is a complication of the procedure and can be related to the grafting technique, to the conditions of the recipient site, or to both of them.

34.2 Graft Survival

The process of graft survival has not been completely understood although it is accepted that it includes two phases: serum imbibition and revascularization.

Serum imbibition describes a well-understood series of events. After a graft is harvested, the graft vessels go into spasm, evacuating any old blood and serum. Once laid onto the recipient site, the graft passively absorbs the underlying serum. The graft becomes edematous and can increase in mass by as much as 30 %. Metabolism in the graft converts to anaerobic metabolism and the pH in the graft falls to 6.8. Metabolism waste products from anaerobic metabolism may stimulate the revascularization process. The graft remains edematous and in anaerobic metabolism for approximately 48 h until revascularization occurs and the graft is able to unload its waste products.

Throughout the phase of serum imbibition, endothelial ingrowth from the host into the graft is occurring. Thus, vascular flow through the graft can be established as quickly as possible. Serum imbibition phase and revascularization phase can be thought of as overlapping rather than as mutually exclusive.

The phenomena occurring during the *revascularization phase* have been a matter of research for more than one century. In 1874, Thiersch proposed the theory of inosculation. This theory states that the cut vessels from the host bed line up with the cut ends of the vessels of the graft and form anastomoses. The process begins immediately, and vascular connections have been demonstrated as early as 22 h after grafting. At the beginning of the twentieth century, some authors proposed another theory. These works indicated that the original vasculature in the skin graft degenerates. Endothelial cells and capillary buds from the host invade the graft, restoring blood flow. Again, the process begins immediately, and as early as 9 h after grafting, inflammatory cells can be seen invading the graft. By the fourth postoperative day, flow through the graft has been reestablished. More recently, a third theory, first proposed by Henry, has evolved to describe skin graft revascularization. This theory states that the original vasculature of the graft does indeed degenerate. However, the acellular basal lamina persists, providing a conduit for the ingrowth of the new vascular tree from the host bed. Histologic studies have identified acellular patent vascular channels in the skin graft 48 h after grafting, which later become endothelialized from the invading host capillary buds.

There is strong evidence supporting all three of the proposed theories, and it is possible that graft revascularization involves all three processes. Inosculation may be responsible for early graft revascularization, allowing the graft to unload metabolic waste from the phase of serum imbibition. Concomitantly, the capillary buds and vascular endothelium developing in the bed invade the graft in both a random pattern and through patent vascular channels.

It is widely believed that a split-thickness graft can survive longer without revascularization than a full-thickness graft can. Split-thickness grafts contain fewer cellular elements than full-thickness grafts do. Also, a thick dermis acts as a barrier to diffusion of serum during the phase of serum imbibition. A thin split-thickness graft can survive longer during serum imbibition because there are fewer cellular elements to nourish, and there is a shorter distance of diffusion through the dermis. Thus in managing a wound with marginal vascular bed, a thin graft is more likely to survive than a thick graft.

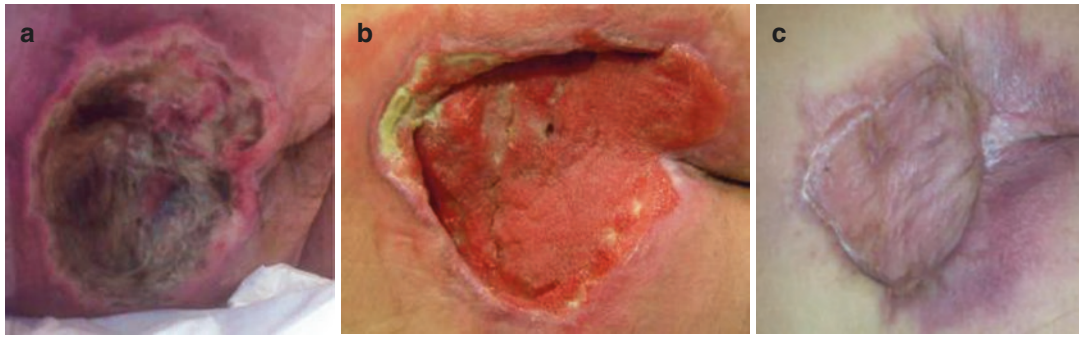

Fig. 34.1 Sacral pressure ulcer with necrotic tissues and exposed bone (**a**). Vascularized bed with granulation tissue developed after surgical debridement and negative pressure therapy (**b**). Closure with split-thickness graft (**c**)

34.3 Graft Failure and Necrosis

Any development that disrupts the process of serum imbibition or revascularization will result in failure of the skin graft and necrosis of the transplanted skin. This failure of graft taking can be related to recipient site circumstances, intraoperative or postoperative complications, or technical errors. If a skin graft fails to be revascularized, the transplanted tissue will develop total or partial necrosis. It is important to make a correct indication for skin grafting with respect to the wound bed, graft thickness selection, meticulous technique, and adequate postoperative care.

34.3.1 Recipient Site

The process of skin graft take depends on a healthy and vascularized bed. One of the most common causes of skin graft failure is an inadequate bed. Exposed tendon, bone, and cartilage will not support a skin graft and can be considered a contraindication to skin graft application. Fat, peritenon, perichondrium, and periosteum are poorly vascularized, but they will support split-thickness skin graft. However, conservative treatment with dressings and/or negative pressure therapy can stimulate development of granulation tissue, creating a vascularized bed, which improves the chances of skin graft take. In those cases in which a well-vascularized bed cannot be achieved (arterial ulcers, radiated bed), skin grafting will drive to necrosis of the transplant. In such situations, a well-vascularized flap must be the election.

The presence of necrotic tissues is an absolute contraindication for skin grafting. Necrotic tissue must be surgically removed and the wound treated in an adequate way to allow development of healthy granulation tissue. Once a well-vascularized bed is present, a split-thickness graft can be used to close the wound (Fig. 34.1).

34.3.2 Barriers Between Bed and Graft

Any barrier between the graft and the recipient bed can prevent revascularization of the graft. The most common barriers are blood, serum, and purulent material. Hematoma, seroma, and infection can lead to either partial or complete skin grafts necrosis.

To prevent blood depots between the graft and the bed, careful hemostasis must be performed in the wound bed before the graft is placed. A useful preventive maneuver is to make small cuts in the graft to allow blood drainage (Fig. 34.2).

If in the postoperative period fluid collections develop under a skin graft, they can also be evacuated through small cuts in the graft, often saving a portion of the skin graft. It is better to cut a small hole in the graft over a hematoma than to dislodge surrounding adherent graft to express the fluid through the graft periphery. If eschar is present, it should be debrided because eschar offers an excellent medium for bacteria.

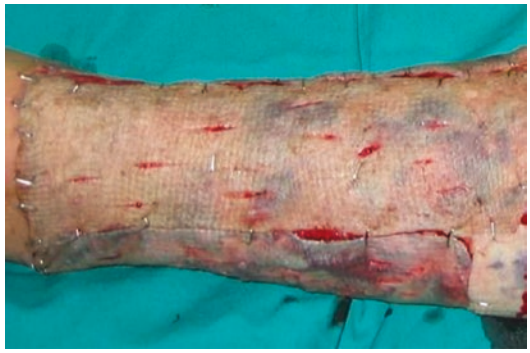

Fig. 34.2 Small cuts in a graft to allow drainage of blood

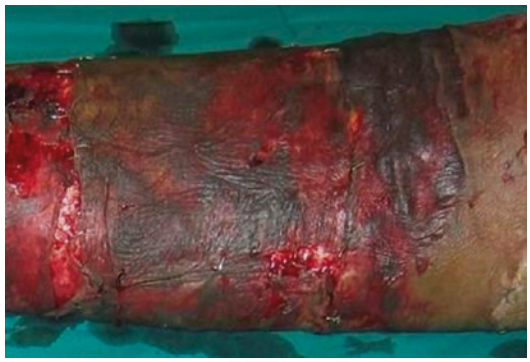

Fig. 34.3 Blood collection under a split-thickness graft that leads to necrosis of the graft

If large collections of blood accumulate between the graft and the bed, the more probable outcome will be the necrosis of the graft (Fig. 34.3).

To prevent fluid collection under the graft, it is recommended to apply a compressive dressing. Pressure should help to stop bleeding and seroma formation. In small grafts, it is very useful to apply a bolus or tie-over dressing to keep the contact between the graft and the bed and prevent fluid collections. To use a bolus dressing, the graft must be fixated with a permanent suture which is intentionally cut long. This leaves strands of suture that will be used to hold the dressing on. Once the sutures are placed, petrolatum gauze, vaselinated gauze or Mepitel® is applied on top of the graft. Fluffed gauze or cotton balls are gently pressed onto the graft. The suture strands are then tied together so that they hold the dressing firmly onto the graft (Fig. 34.4). Apart of minimizing the risk of fluid collections under the graft, the bolus dressing prevents shearing forces from disrupting the graft.

In larger grafts, the dressing should apply gentle pressure on the graft to promote graft adherence without causing pressure necrosis. Cotton balls or fluffed gauze is pressed onto the wound to conform to the underlying bed. On an extremity, a circumferential wrap can be applied snugly across the wound to ensure contact between the graft and the host bed.

34.3.3 Graft Shearing

One of the most common causes of graft failure is shearing of the graft. The small capillaries that invade the graft are fragile and can be disrupted with a minimum of force. Grafts can be devascularized during a dressing change or during movement in the early postoperative period. Consequently, grafts to the extremities are usually immobilized, and all dressing changes are performed with utmost care for the underlying graft. A nonadherent dressing must be applied over the graft. The silicone mesh dressings like Mepitel® have proved to adhere only to intact skin but not to the wound or the graft itself. The nonadherent properties of these types of dressings prevent the skin graft from being debrided off the wound at the time of the first dressing change.

If a portion of the graft appears to be sheared at the time of dressing change, it should be replaced and newly immobilized. In some cases, these displaced parts of the graft will take. If not, they should be removed with scissors, and if the defect is small, it will be re-epithelialized from the edges of the remaining graft.

34.3.4 Infection

Infection can cause destruction and necrosis of the graft without the formation of purulent drainage. It is generally accepted that a wound with more than 10^5 organisms per gram of tissue will not accept a skin graft. Some organisms, *Pseudomonas* being the most common, can destroy a skin graft with little or no purulence

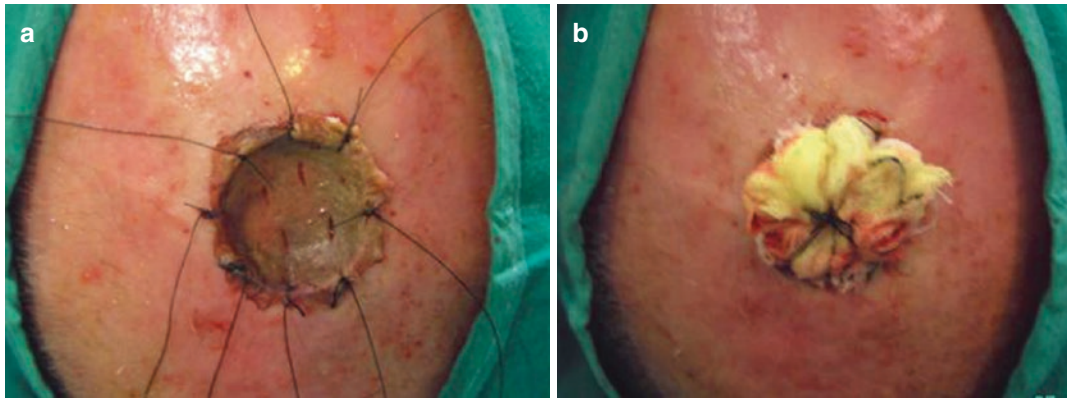

Fig. 34.4 Split-thickness skin graft to close the defect after excision of a basocellular carcinoma in the scalp (**a**). Bolus dressing to keep the graft in place (**b**)

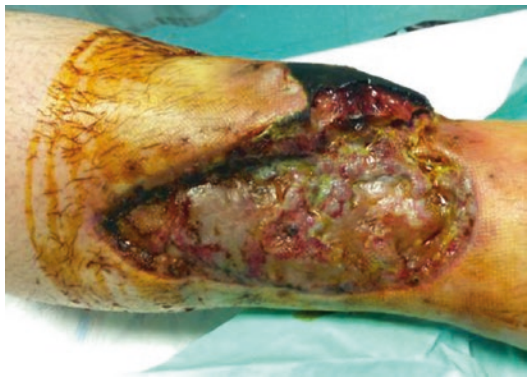

Fig. 34.5 Total destruction of a skin graft by *Pseudomonas* infection

(Fig. 34.5). The infection does not have to be limited to the wound. In fact, some authors recommended that a patient be completely free of infection before skin grafting. Systemic infection can lead to poor wound healing and ultimately partial or total graft failure.

To prevent infection, apart from systemic antibiotics, local antiseptics should be used in the dressing. Nitrofurazone cream or povidone-iodine gel can be used on top of the graft before the compression dressing is placed.

Once an infection has destroyed a skin graft, the wound must be managed with extensive debridement, local and systemic antimicrobial treatment, and prevention of new grafting until the wound is clinical and microbiologically free of infection.

34.3.5 Poor Systemic Conditions

Unfavorable systemic conditions can lead to poor graft take and necrosis of the transplanted skin. Malnutrition, diabetes, vasculitis, malignant disease, steroids, and chemotherapeutic medications have all been shown to impair wound healing and to impair graft take. Radiation injury impairs the recipient bed and can lead to total or partial skin graft failure.

34.3.6 Technical Errors

Technical errors during grafting are a relatively uncommon cause of graft failure today. Grafts can be applied upside-down or they can be handled roughly, leading to total or partial necrosis. Dermatomes can be too hot after sterilization and burn the graft during the preparation phase.

First dressing change should be done at postoperative fifth day. If it is done earlier, there is a significant chance of shearing and disruption of the small capillaries penetrating the graft.

34.4 Graft Rescue

When there is a partial graft failure not caused by infection, there are some chances to rescue the already taken graft. The necrotic portion of the graft should be removed with scalpel or

scissors. If the defect is not too large, it will re-epithelialized from the edges of the defect. Adequate nonadherent dressing should be applied to allow this process. If the defect is large, it should be regrafted.

When the cause of graft failure is infection, the more probable outcome will be the total loss of the graft. In such cases, the wound should be managed as an infected one and when sterile regrafted.

Arterial Leg Ulcers

35

Josef Aschwanden, Jurgen Hafner,
Vincenzo Jacomella, and Severin Läuchli

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35.1 Introduction

Leg ulcers are not a diagnosis but a symptom of many different diseases. In this chapter we will describe leg ulcers caused by arterial disease. However, many other causes should be considered in refractory ulceration on the lower extremity such as venous disease, neuropathy, and miscellaneous causes like vasculitis, malignancy, and autoimmune disease and even rare causes like pyoderma gangrenosum [1], thromboangiitis obliterans, or arterial-venous malformation. Martorell hypertensive ischemic leg ulcers [2] as part of the arterial causes are not discussed here as they are described in another chapter. Very often the ulcers of the lower leg result from a combination of factors [3]. Therefore, it is important to rule out arterial insufficiency even when other causes or clinical signs are present. For example, about 15 % of all leg ulcers are of a mixed arterial-venous origin [4–6]. We postulate that every patient with ulceration on the lower leg should receive an arterial workup, not only because a concomitant arterial disease may delay healing but also because of the underlying systemic process (arteriosclerosis) for which the patient might profit by an appropriate systemic therapy [7, 8].

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35.2 Epidemiology and Classification

Chronic ulceration of the lower leg can result from several underlying factors as mentioned above. The most common cause is venous insufficiency in about 75 %, followed by ulcers of mixed venous and arterial (15 %) and those of primarily arterial (4 %) origin [4, 5]. Arterial leg ulcers are caused by an oxygen deficit in the tissue resulting from reduced tissue blood perfusion due to occlusion of the arterial lumen. The most common cause for this occlusion is peripheral arterial occlusive disease (PAOD) due to an arteriosclerotic process. Generalized arteriosclerosis is therefore the most common cause not only of cardiovascular and cerebrovascular disease but also of peripheral vascular disease. The prevalence of PAOD in the general population varies between 7 and 21 % [9]. It is related to age, gender, and the definition of PAOD (by the cutoff value of the ankle-brachial index (ABI) and/or the presence of symptoms). The Fontaine stages classify the clinical appearance of PAOD (Table 35.1). Before progressing to a clinically symptomatic stage such as intermittent claudication or even critical limb ischemia, PAOD is typically asymptomatic for several years. Approximately 23 % of all patients are asymptomatic, and this is probably one reason that PAOD stage I seems to be underestimated [8]. Sometimes symptoms can also be masked by reduced walking distance due to other reasons or by polyneuropathy secondary to diabetes. In stage II, rest pain is normally missing. Stage III ischemic rest pain is typically a nocturnal pain. Approximately 15–20 % of patients with intermittent claudication will progress to critical ischemia. The distinction between arterial insufficiency and critical ischemia is not clearly outlined in the literature, and critical limb ischemia occurs only in a minority of patients with PAOD [10]. *The Second European Consensus* [14] has 1996 outlined criteria for the diagnosis of chronic critical limb ischemia: recalcitrant rest pain or distal necrosis of more than 2 weeks' duration in the presence of (A) a systolic ankle pressure (AP) 50 mmHg or less, (B) a systolic toe pressure of 30 mmHg or less, or (C) a transcutaneous oxygen pressure (tcPO2) of 10 mmHg or less. In the last few years, the threshold for critical ischemia has been raised several times. Necrotic ulceration occurs in stage IV, usually on the toes or the back of the feet, but can also occur in stage II after trauma or in combination with chronic venous disease and is then generally considered a "complicated" stage IIB. In fact, the majority of arterial ulcers occur in "complicated" stage IIB on the lateral lower leg and do not match the criteria for critical ischemia. The angiosome concept is one possible explanation for the occurrence of nonhealing ulcers above the threshold of critical ischemia. It was first described by reconstructive plastic surgeons in 1987 [11]. They divided the tissue in specific three-dimensional sectors of the body supplied by specific arteries and veins, named angiosomes. Each angiosome therefore consists of a topographically specific arteriosome and correspondening venosome supply, which build block systems of perfusion. Neighboring angiosomes are linked by numerous communicating vessels, so-called choke vessels. In ischemic conditions these interconnections between adjacent angiosomes create a very effective compensatory system in non-atherosclerotic and non-diabetic limbs [12]. In atherosclerotic or other changes of the large collateral vessels, such as those typically accompanying diabetic arterial disease below the knee and end-stage renal disease (ESRD), this natural "rescue system" between adjacent angiosomes may be jeopardized.

Table 35.1 Fontaine classification for PAOD

Stage I	Asymptomatic
Stage II	Claudicatio intermittens
	Walking distance:
IIA	>200 m, with no disablement
IIB	< 200 m with disablement
Stage III	Resting pain
Stage IV	Peripheral necrosis/gangrene

35.3 Clinical Findings

The typical localization for arterial leg ulcers is the lateral malleolar region for PAOD stage IIB (Fig. 35.1), whereas distal arterial necrosis

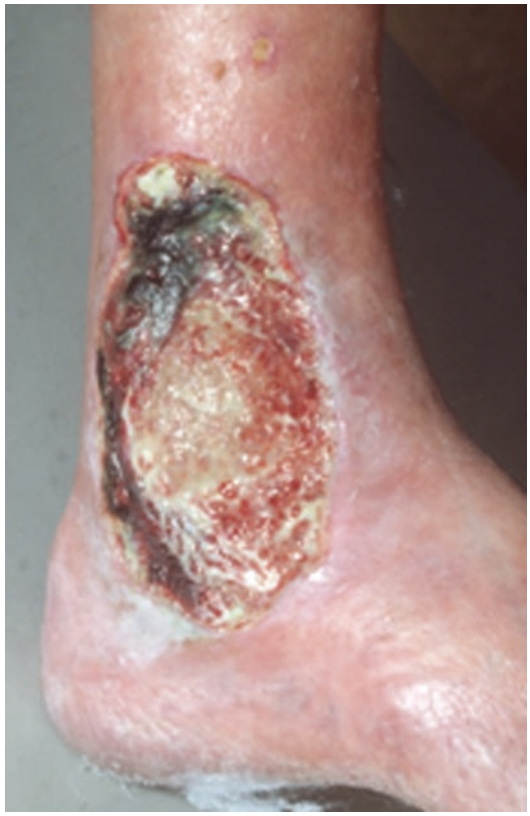

Fig. 35.1 Typical arterial leg ulcer on the lateral malleolar aspect of the lower leg (PAOD complicated stage IIB)

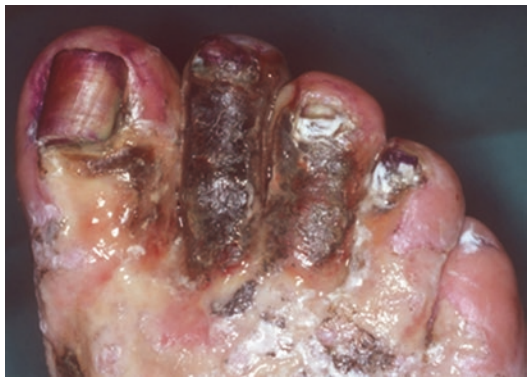

Fig. 35.2 Distal arterial necrosis due to PAOD stage IV

(PAOD stage IV) is usually localized in the foot and toe region (Fig. 35.2). Arterial leg ulcers often have irregular edges and/or a "punched-out" appearance. The ulcer base is usually poorly developed with a grayish granulation tissue. Signs of chronic venous disease are missing except in mixed ulcers. Painful and necrotic areas are the typical appearance for all ischemic ulcers.

Table 35.2 Doppler ankle-brachial ratio [21]

0.91–1.4	Normal, if under exercise no ABI loss
0.5–0.85	PAOD, claudication (mild to moderate disease); a wound can heal
<0.5	Severe PAOD, threat of tissue and limb loss
>1.4	May be due to diabetes, Mönckeberg disease, renal disease

35.4 Diagnosis

The first test to rule out arterial insufficiency should be the palpation of the pedal pulses. It should be mentioned that the dorsalis pedis pulse is missing in about 10 % of individuals and the palpation of the posterior tibial pulse may be difficult due to swelling or the presence of ulceration caused by a concomitant chronic venous insufficiency. If a pulse is palpable, we can assume that the ankle pressure is >100 mmHg [13] and wound healing should be possible. If no pulses can be detected, noninvasive vascular testing should always be performed.

As a fast and simple test, the ankle-brachial index (ABI) can be measured very easily with a cheap and simple continuous wave (CW) Doppler probe (8–10 mMHz). The ABI is defined as the systolic ankle pressure divided by the systolic arm pressure and is considered an accurate and reliable marker of symptomatic and asymptomatic PAOD (Table 35.2). Significant arteriopathy is normally defined as an ABI <0.91 and an ABI <0.5 as severe arterial insufficiency [23]. The ABI measurement can therefore identify patients at risk of any systemic atherothrombotic events even in an asymptomatic stage. Identification of asymptomatic PAOD also leads to intensified targeted prophylactic anti-atherothrombotic treatment that can reduce morbidity and mortality as mentioned above [8].

To recognize critical ischemia the measurement of ankle systolic pressure is the most accurate test. If the pressure is below the level of critical limb ischemia as defined with an ankle systolic pressure <50 mmHg [14], leg ulcers will

only heal in 20 % of cases, and aggressive revascularization therapy should be performed [15]. In contrast, a systolic pressure over 70 mmHg can nearly exclude arterial insufficiency as a cause for the ulcers. If the arteries are not compressible, i.e., the ABI is higher than 1.4 or the difference of the measured pressure between ankle and arm exceeds 75 mmHg, calcification of the arteries should be considered. In these cases, a toe systolic pressure or a tcPO2 measurement should be performed. In cases of Mönckeberg mediocalcinosis, the pole test technique can also give further information concerning the critical ischemia of the lower limbs. A toe systolic pressure lower than 50 mmHg or a tcPO2 lower than 30 mmHg is diagnostic for critical ischemia (Table 35.3). If the tcPO2 is over 30 mmHG, a wound can heal. Ultrasonic duplex scanning or arteriography can localize the arterial lesion but cannot make any statement about the severity of the arterial disease. In contrast, it is a very good surveillance tool after an invasive intervention or as first-step screening in order to evaluate an invasive procedure. The gold standard to investigate PAOD is still angiography, especially when an intervention is planned. Recently, magnetic resonance angiography has emerged as a noninvasive imaging modality without the risks associated with conventional angiography (e.g., arterial puncture, plaque embolization, and contrast-induced nephropathy).

Table 35.3 Use of noninvasive vascular tests to predict the presence of underlying severe arteriopathy [22]

Noninvasive ascular testing	Findings	Severe arteriopathy
Pedal pulses	Present	Unlikely
	Absent	Possible[a]
Ankle systolic pressure	>70 mmHg	Unlikely
With ulcer	< 50–70 mmHg	Possible[a]
Without ulcer, with rest pain	<30–50	Likely
Toe systolic pressure	>50 mmHg	Unlikely
	≤50 mmHg	Likely
tcPO2	>30 mmHg	Unlikely
	<30 mmHg	Likely

[a]Proceed with further, noninvasive vascular tests to confirm or rule out severe arteriopathy especially if clinical evolution is poor

35.5 Treatment

The arteriosclerotic process as a systemic problem needs an interdisciplinary approach. The common arteriosclerotic risk factors should be treated aggressively (Table 35.4). Whenever possible, revascularization should be attempted by angioplasty or vascular surgery. This is the only effective therapeutic option to allow wound healing when ischemic necrosis is present. Furthermore, it often provides the most efficient pain relief. If revascularization by interventional or surgical means is not possible, intravenous application of iloprost can ameliorate the situation, but this is often limited by side effects (e.g., hypotension, headaches). Exercise also plays an important role in improving the maximal walking distance and thus increasing the blood perfusion. Adjuvant medical treatment with antithrombotic or rheological agents can improve the outcome [16].

For the local therapy, the common principles of modern wound care should be applied. Sharp surgical debridement is of foremost importance to remove the bioburden which can delay wound healing. However, as arterial ulcers often reach to deeper structures, it should be performed by surgeons or wound care experts with adequate training. Enzymatic debridement or biosurgery with maggots can be viable alternatives. Local wound infection can be treated with wound antiseptics or silver dressings; if signs of systemic infection are present, systemic antibiotics have to be utilized.

The choice of wound dressing must take into consideration the amount of exudation and necrosis and the phase of wound healing. Generally, occlusive dressings should be avoided, as their main mode of action, a local increase of CO2 tension, is not desirable for ischemic ulcers and the detection of wound infection could be delayed. Semiocclusive dressings can be utilized with

Table 35.4 Risk factors for arteriosclerosis and PAOD

Hypertension
Diabetes
Elevated cholesterol, especially low-density lipoprotein
Smoking

caution, if granulation tissue exceeds necrotic areas and there are no signs of wound infection. The type of wound dressing does not significantly influence healing times [17, 18]. Therefore, the choice of wound dressing should be guided by patient-centered concerns such as exudate management and pain control [19]. Wound pain is one of the main concerns of patients [20]. Dressings that avoid desiccation of the wound and which do not traumatize the wound when the dressing is changed are therefore ideal.

Arterial leg ulcers can show a very protracted healing time, especially if surgical or interventional revascularization is not possible. In these cases, advanced methods often have to be utilized, such as acellular matrices, keratinocyte cultures, or growth factors. In many instances, split thickness skin grafts can improve the wound pain immediately and accelerate healing, even if the wound bed does not show sufficient granulation for a full graft take.

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Skin Necrosis of Diabetic Foot and Its Management

36

Joon Pio Hong

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36.1 Introduction

The chapter describes the statistics related to diabetic foot ulceration, pathology of necrosis formation, types of necrosis, and the current surgical management of diabetic foot skin necrosis.

According to the statistics given in the USA, approximately 3–4 % of individuals with diabetes currently have foot ulcers or deep infections and 25 % will develop foot ulcers sometime during their life [24, 30]. Their risk of lower leg amputation increases by a factor of 8 once an ulcer develops. It is estimated that the age-adjusted rate of lower extremity amputation in diabetic patients is 15-fold that of nondiabetics [20]. Intractable diabetic foot ulcers can bring not only decreased physical, emotional, and social functions but huge economic impact to the patient [1, 25, 27]. Furthermore, the 5-year mortality after major amputations may range from 39 % to as high as 80 % [24, 21]. The necrosis is often seen in the late stages of the diabetic foot. The presence of skin necrosis is a serious implication leading to the loss of limb. Their respective indications vary depending essentially on criteria like the hardness of the black cover and the extent of necrosis in depth, the extent of necrotic tissue over the skin.

In neuropathic foot, infection is usually the cause, whereas it can be solely due to ischemia alone with slow onset of mummification like dry necrosis.

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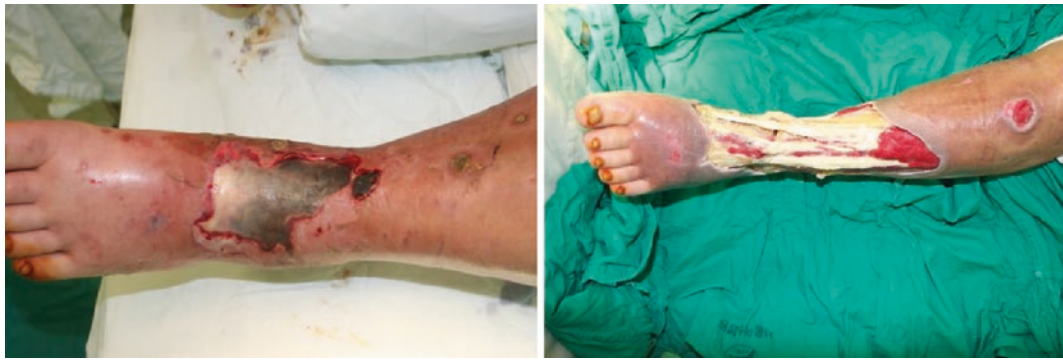

Fig. 36.1 Patient with wet necrosis extending to the deep fascia tissue and debridement was performed. Note the extent of necrosis after the debridement of all necrotic tissue

36.2 Risk Factors for Diabetic Foot Skin Necrosis

Risk factors involved for ulceration are peripheral neuropathy, vascular disease, limited joint mobility, foot deformities, abnormal foot pressures, minor trauma, history of ulceration or amputation, and impaired visual acuity [12]. Superimposed with infection in neuropathic or neuroischemic types will lead to wet necrosis, whereas occlusion of arteries will lead to dry necrosis. The dry necrosis frequently coincides with the angiosome territory of the macrovascular supply [3].

36.3 Clinical Presentation

36.3.1 Detecting Early Change

Early signs of necrosis may begin with sudden change in color of the skin. Previously pink skin may change to a blue or purple color when hit by infection. Skin turning from pink to pale white may be from lack of circulation. Sudden change of ulcer character may also imply potential change to dry or wet ischemia. A close follow-up should be scheduled as sudden change may occur within hours. Special attention should be made to patients under immunosuppressive therapy.

36.3.2 Wet Necrosis

Wet necrosis is due to severe infection and ulceration. This is the most frequently seen necrosis of the diabetic foot. Untreated infections and recent traumatic wounds may lead to necrosis. One must stay alert during the follow-up for patients especially being treated with immunosuppressive drugs after kidney transplants. Clinical characteristics suggesting serious infection may be ulcers penetrating to subcutaneous tissues, involvement of deep tissues, extensive cellulitis expanding more than 2 cm from ulceration, and local signs such as severe inflammation, crepitus, bullae, swelling, discoloration, and necrosis [19]. Deep tissue specimens should be sent to identify pathogen. Patients should be hospitalized for possible surgical intervention, fluid resuscitation, treatment with antibiotics, and control of diabetes (Fig. 36.1).

36.3.3 Dry Necrosis

Dry necrosis is a black, hard, mummified tissue often with clear demarcation from the surrounding tissue. It may have infection but usually is from severe ischemia resulting from vasculopathy. In cases where peripheral artery disease progresses slowly among ischemic-neuropathic diabetic foot patients, it gradually develops vascular compromise of the skin, and thus perception of ischemic

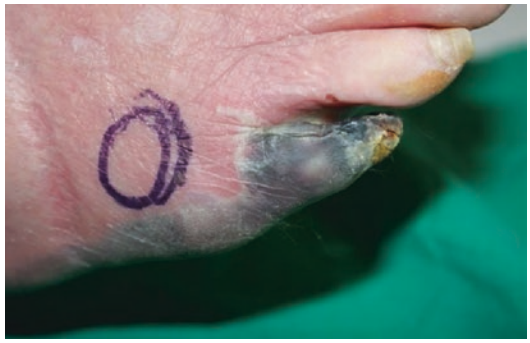

Fig. 36.2 Dry necrosis with relatively well-demarcated wound

pain is reduced [11]. The result is that the prevalence of claudication in the diabetic population with PAD is lower than the prevalence of critical limb ischemia (CLI) in this population. Thus eye inspection becomes a very important tool to diagnose the dry necrotic change among this group.

In diabetic patients with acute ischemia, sudden onset of pain is noted with pallor and coldness of the foot followed by mottling of the skin and shiny appearance of the texture.

Regardless of the duration of the peripheral artery disease, intervention of the artery is required to reperfuse the ischemic skin. Failure to reperfuse the foot will end in dry necrosis and loss of the tissue. Intervention angioplasty or bypass surgery should be applied accordingly to ensure better outcome after removal of dry necrotic skin [9]. Otherwise, further complication and increase in necrosis may occur in resection without vascular intervention. One must also be aware of the reperfusion injury after intervention. Once reperfused, inflammation will ensue and the wound around the dry necrosis will turn wet and increase the risk for infection. Debridement must follow reperfusion (Fig. 36.2).

36.4 Treatment and Reconstruction

When considering the diabetic foot for reconstruction, there are multiple issues to be addressed. These issues can be effectively approached though a multidisciplinary approach. The first step is to control the systemic aspect of diabetes. Then malnutrition, chronic renal disease, and hypertension have to be addressed properly and treatment schedules made before and after surgery especially hemodialysis and perioperative blood sugar control. While the systemic condition of the patient is being optimized, specific attention can be directed to the foot ulcer. Depending upon the general condition, peripheral vascular status; bone pathology; wound depth, location, and duration; involvement of chronic osteomyelitis; and patient motivation, wounds can be treated with debridement and other related surgical procedures. Another important issue concerns the vascular pathology of the patient. The vascular surgery consultation is warranted when the patient is symptomatic with ischemic pain or a nonhealing ulcer. Neuropathic ulcers require debridement of nonviable or infected tissue, combined with local wound care and off-loading. If the diabetic wound is not improved by such procedures or aggressive wound care, foot salvage procedures can be considered. A robust predictor of healing is 53 % change in wound area of diabetic foot ulcers [28]. In our center we monitor the change in wound size and depth, and when wound healing is stalled despite good standard of care such as off-loading, infection control, edema control, and advanced dressings, then additional treatment with hyperbaric oxygen, cell therapy, growth factor treatment, and negative pressure wound therapy is considered. But depending on the complexity of the wound, some of these secondary modalities are used primarily as well. Again, wound healing progress is closely monitored, and stalled healing despite of these multimodal therapies may become one of the indicators for reconstruction. Figure 36.3 shows the spectrum of care for diabetic foot ulcers from general care to reconstruction or amputation.

36.4.1 Debridement

The first step of treatment for diabetic foot wound is to evaluate, debride, and treat infection [3].

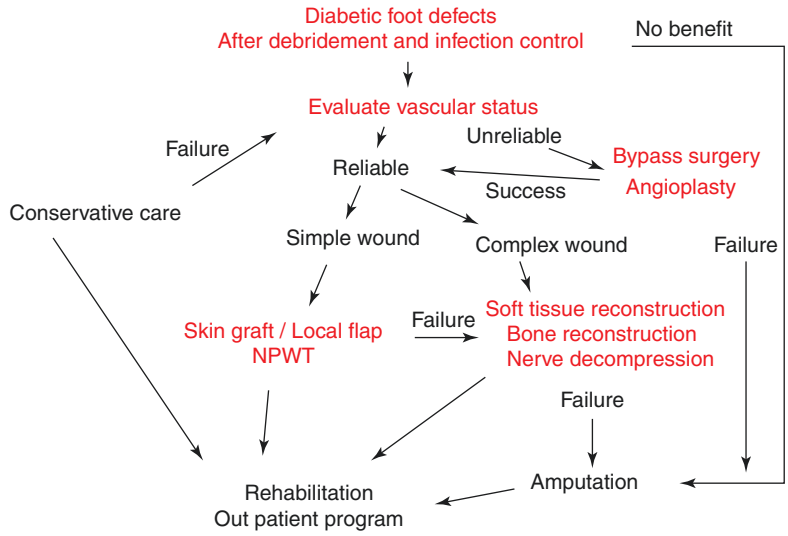

Fig. 36.3 Algorithm for diabetic foot reconstruction after debridement of necrotic diabetic wound

Missing timely management will lead to amputations and longer hospital days [26]. If symptoms and signs of infection are clinically suspected, proper treatment must be provided without delay. If superficial infection is suspected without systemic infection, antibiotic treatment along with non-weight bearing of the foot should be ensued. Optimal management of diabetic foot infection can potentially reduce incidence of major limb amputations and other related morbidities. All nonviable and infected soft tissue and bone should be excised during debridement. Milking along the proximal tendon can be helpful to identify and limit ascending infection. Tissue culture should be sent. Sufficient irrigation should follow after debridement to reduce bacterial count [4]. Recent advance in technology introduced a hydrosurgery system that allows to debride while preserving viable tissues and irrigate simultaneously, allowing reduced surgical time [15, 16]. Biodebridement such as maggot therapy has also been useful in clearing the necrotic tissue [10]. Application of negative pressure wound therapy has also played a role in reconstruction as they are used as an indicator and a wound preparation method of achieving clean wound with reasonable vascularity.

The understanding of vascular distribution of the foot, angiosome, helps to plan not only reconstruction but debridement [8]. When planning for reconstruction, one can avoid violating the angiosome territory when designing a local flap that may lead to flap breakdown [2]. Also by performing debridement according to the angiosome territory, one may enhance flap survival by increasing the chance for marginal vascularization from healthy surrounding angiosome territory.

Repetitive debridement should be performed as part of wound preparation for reconstruction while monitoring C-reactive protein for possible hidden infections and using it as an index for possible infection after reconstruction.

36.4.2 Vascular Intervention

In our surgical algorithm, all patients considered for microsurgical reconstruction undergo a noninvasive CT angiogram to evaluate the vascular status. The CT angiogram provides information regarding general vascular anatomy of the lower extremity and shows atherosclerotic change of vessels which is useful information when choosing recipient vessels. The overview is important as collateral vessels may be the main trunk to the distal limb. Without this information, one may elevate the flap harvesting the main arterial source to the distal limb and cause limb ischemia. If vascular status is in doubt, then revascularization by angioplasty or bypass surgery is referred. Although preoperative angiograms may indicate

intact anatomy of the artery to the foot, actual findings upon surgery can be different. In order to confirm the distal vascular flow, we use ultrasound duplex scans. A study by Kim et al. showed correlation of peak blood flow velocity over 40 cm/s to flap survival [18]. However, in an ongoing study at our center, we hypothesized that the preoperative measurement of flow will not influence the survival of the flap, but the perioperative flow will play a more important factor. For now, ultrasound duplex scan provides information in the selection of recipient vessels or to refer for vascular intervention when no recipient vessels can be identified. The transcutaneous oxygen measurement (TcPO2) also plays a role in our protocol. Measurement over 30 mmHg in normobaric oxygen is a relative predictive factor for successful healing, whereas pressure less than that of 30 mmHg is likely to follow an unfavorable course [7, 14]. The wound, if measured under this level after vascular intervention, was treated with hyperbaric oxygen. If peri-wound $TcPO_2$ measurements were over 30 mmHg, then further treatment including reconstructive procedures was planned; otherwise, amputations at according levels were performed. The ankle-brachial index (ABI) is not used as it is not reliable in diabetic patients due to the high incidence of calcified vessels causing falsely elevated values [13].

In diabetic patients, the most significant atherosclerosis occurs in the crural arteries often sparing the arteries of the foot [31]. Bypass to the dorsalis pedis or posterior tibial artery of the foot or angioplasty with or without stent placement procedures results in high success to restore perfusion pressure to the distal circulation of the foot reestablishing palpable pulse. The timing of when to perform reconstruction after vascular intervention is not clear. Reports have shown successful free flap transfer with simultaneous vascular reconstruction to salvage the limb [23]. But early bypass failures within 30 days are reported to be high [6, 29]. In our experience, partial flap loss or total loss was suddenly noted after 2–3 weeks in the cases combined with simultaneous or reconstruction following few days after vascular interventions. This may suggest that there should be a sufficient stabilization period after vascular intervention.

Reperfusion is most essential prior to microsurgery reconstruction. If vascular intervention fails and wound progresses, amputation is warranted.

36.4.3 Reconstruction Using Free Flaps

Once an adequate debridement and reasonable vascular perfusion are achieved, in extensive and complex diabetic foot defects, reconstruction should be considered. In my experience, local flaps such as reverse sural, medial plantar, or lateral supramalleolar for large defects have not been as successful as free flap reconstruction. Especially when reconstructing diabetic foot with reduced vascular flow, the utilization of local flaps may breach the distal flow of the small collateral vessels. One must consider current vascular status as well as future flow where small collateral vessels may play an important role for distal circulation. In this sense my choice for moderate and large defects is the reconstructive microsurgery to transfer free flaps. Inclusion criteria from a meta-analysis of free tissue transfer in 528 diabetic patients in 18 studies suggest (1) lower limb defect which has not displayed any signs of granulation or healing despite adequate debridement or necrotic tissue and conservative treatment, (2) no significant renal function impairment, (3) no significant systemic illness likely to be exacerbated by multiple operations and prolonged rehabilitation, (4) previously ambulatory with the aim to restore a functional limb, (5) likely to engage with the significant physiotherapy required for return to normal living, and (6) peak flow velocity of >40 cm/s in the recipient artery. We generally agree with the suggested inclusion criteria except for the significant renal disease. In our experience, we have not found an increased risk for failure despite the fact that uremia may cause a decrease in cell-mediated immunity and impair wound healing [5, 22, 32]. But we did report a significant risk of 4.857 times higher odds for flap failure in patients using

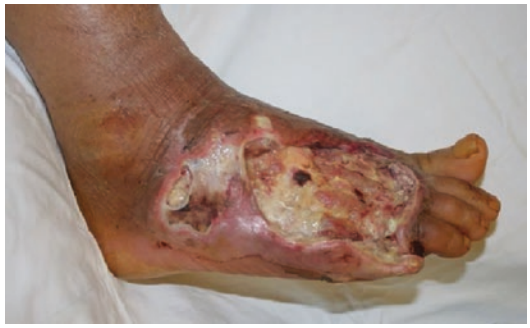

Fig. 36.4 Necrotic diabetic foot with neuroischemic wound. Poor vascular supply of the anterior tibial artery was noted. Endovascular intervention was performed successfully increasing the flow to the feet

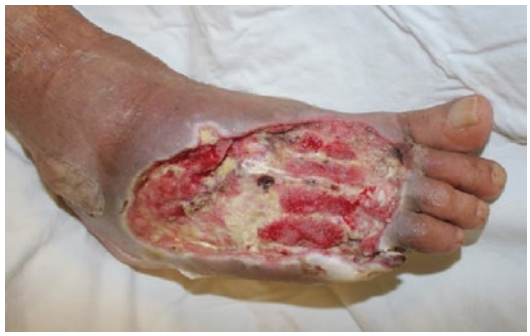

Fig. 36.5 Complete debridement with respect to angiosome territory. The patient then underwent NPWT (CuraVAC®, Daewoong Pharmaceuticals, Seoul, Korea) for 10 days to prepare the wound for microsurgical reconstruction

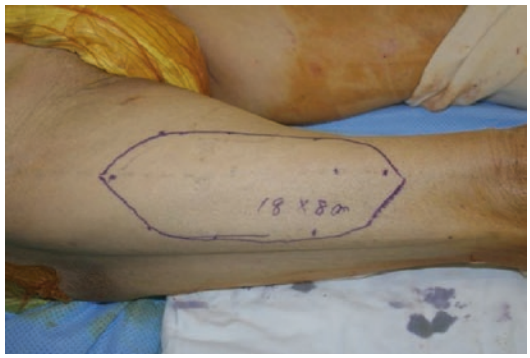

Fig. 36.6 Anterolateral thigh flap was used to reconstruct the feet

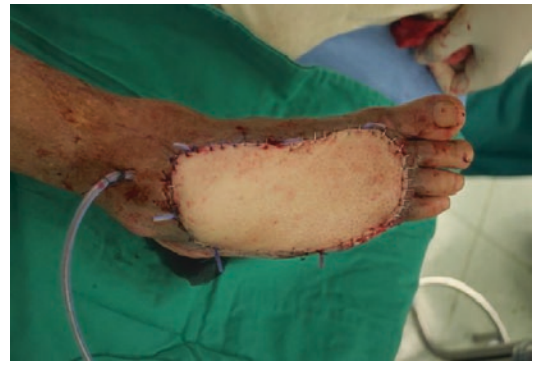

Fig. 36.7 The anterolateral thigh flap artery was anastomosed to the dorsalis pedis end to side fashion

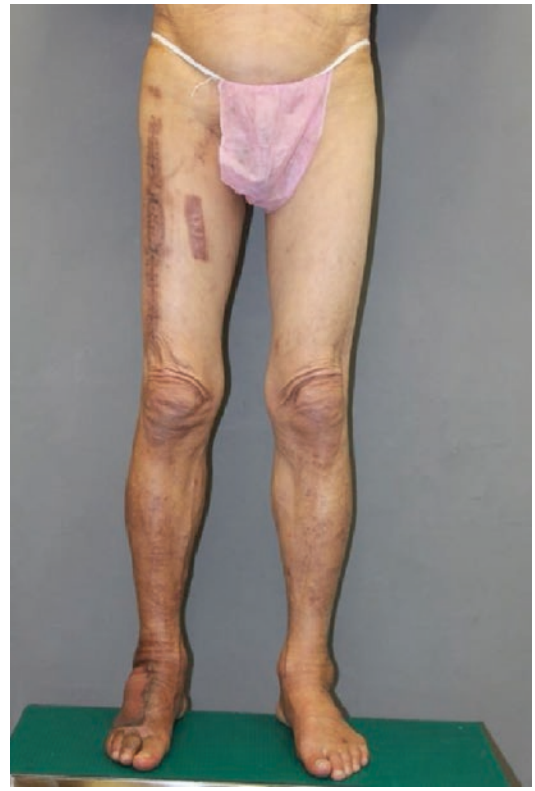

Fig. 36.8 The patient at a 2-year follow-up shows good contour and function of the foot without signs of recurrence

immunosuppressive agents after renal transplant ($p < 0.041$) [22].

I would rather prefer to present the contraindication rather than the indications for flap reconstruction as microsurgery technique evolves using small recipient vessels rather than major vessels for reconstruction [17]. The most important factor may be the perfusion of the recipient vessel. If any small vessel is seen with good pulsatile flow, it would be indicated for

microsurgery. Thus an absolute contraindication would be no flow to the foot without any sign of perfusion from any distal small vessels [22].This supermicrosurgery and freestyle reconstruction approach, however, will require a refined skill along with a paradigm shift for reconstruction (Figs. 36.4, 36.5, 36.6, 36.7, and 36.8).

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Exposed Necrotic Tendons

37

Luc Téot

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37.1 Introduction

Tendon necrosis may be observed in several types of wounds, traumas or chronic wounds like pressure ulcers, diabetic foot ulcers or arterial leg ulcers, as a consequence of skin necrosis. The origin is multifactorial, exposure to air and desiccation of poorly vascularised structures being the most frequently encountered situation and infection and degloving being also observed. The deep parts of the tendons often remain vascularised enough to be appropriately debrided and covered either with a negative pressure therapy or directly using a dermal substitute and skin grafting. Flaps are sometimes preferred, but direct skin grafting is not recommended as it leads to adherences. Immobilisation of the tendon is the key element to prevent infection to spread along the tendon sheets and develop tunnels and allow covering structures to heal. Tendon necrosis should be considered as an emergency in order to preserve the functional results.

37.2 Clinical Features

Three different stages of severity are observed (Fig. 37.1a–c). The tendon may be simply exposed, the paratenon becoming necrotic on its exposed aspect, or partially necrotic, or completely destroyed.

Stage 1: The paratenon is exposed and looks inert, dry and more or less hard. A few opening may

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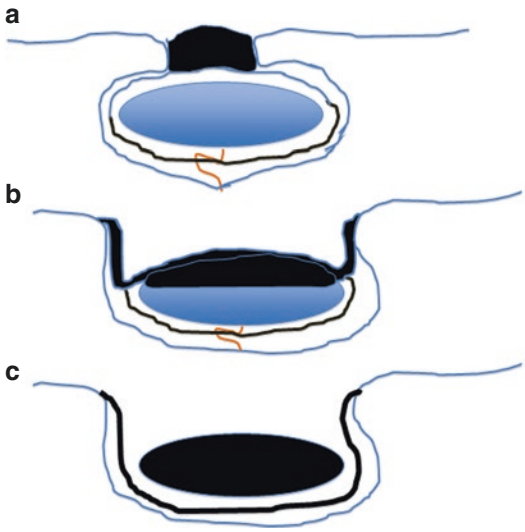

Fig. 37.1 (**a**) Partly exposed tendon. (**b**) Half of the tendon is devascularised, the deep part remains in contact with the depth. Some vascularisation remains. (**c**) The whole tendon is completely detached. Vascularisation comes the edges, the risk of necrosis is high

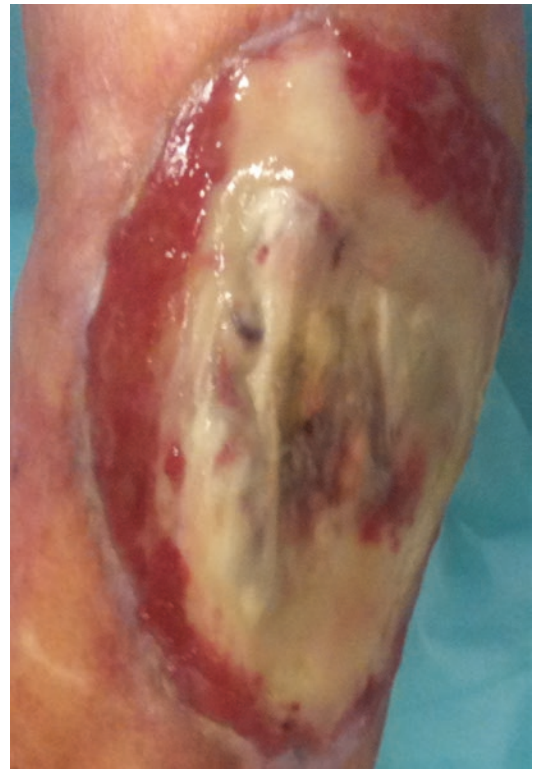

Fig. 37.2 Exposed infected tendon. Half of the structure is devascularised, soft and adherent. This portion should be debrided to the deep dense fibers

be observed, giving access to the tendon itself. When properly managed, the paratenon may recover, be revascularised by the surrounding living structures.

Stage 2: The paratenon is lost and the tendon is directly exposed, some areas presenting a dead fleshy aspect, tendon fibres being easily dissociated with a single gauze. It is not easy to differentiate the still living areas from the dead parts, but the mechanical resistance to dissociation and hardness of the tendon fibres specifically differ (Fig. 37.2). Risks of complete loss of the tendon are important as infection of the exposed tendon may extend under the tendon sheets up and down and develop a large infected pocket. Modern management including negative pressure therapy after a surgical adapted debridement will enhance the progression of the granulation tissue coming from the edges and the deep part of the wound. The tendon will progressively be incorporated into this granulation tissue, and a coverage technique using either dermal substitute or flap will allow tendon salvage.

Stage 3: Clinically the tendon looks dry and hard having lost suppleness. No more connexion with the underlying structures is observed, the tendon lying inert over the wound (Figs. 37.3 and 37.4). Tunnels on each extremity are long and pus may be present. The tendon should be removed on the whole exposed area including the tunnels.

When not managed properly complications of tendon exposure are multiple. The necrotic extension to the surrounding structure is often observed, infection may progress along the tendon sheet, issuing to secondary at distance infected wounds and complete destruction of the tendon and paratenon.

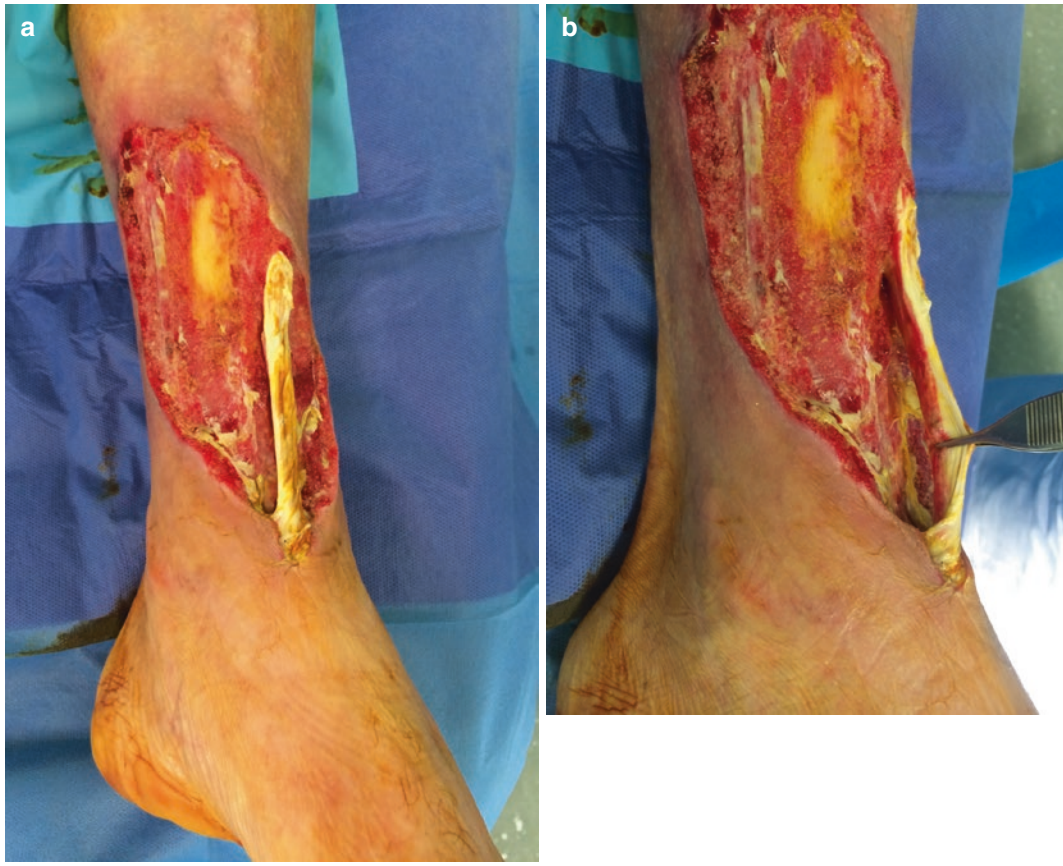

Fig. 37.3 (**a**) White pale devascularised tendon. (**b**) Adherence to the depth is lost. One can observe on the margins microvessels penetrating the deep part of the tendon

37.3 Modes of Treatment

37.3.1 Immobilisation

Immobilisation is a technique to be adapted to the limb segment and the structure to immobilise. Tendons being less rigid than bones, a strict tight immobilisation is not required. On the other hand, the course of a tendon of the foot being comprised between 2 and 4 cm, it is easy to understand that infection will tend to move with the tendon along the sheets and induce secondary infected zones involving the subcutaneous areas and the skin itself. In situations discovered lately, infection runs along the tendons or aponeurosis of the muscles and emerges as a secondary infection at the other extremity of a segment (seen in ischiatic pressure ulcers with a distal emergence of infection at the level of the knee).

37.3.2 Negative Pressure Wound Therapy

NPWT became a key factor to enhance tendon revascularisation and salvage. This technique represents a good alternative to flaps with less

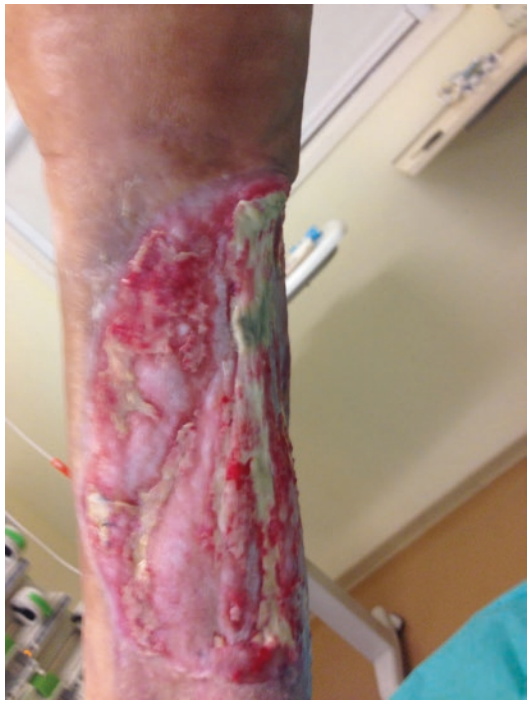

Fig. 37.4 Progressively the tendinous fibers are embedded into the granulation tissue. The surgical coverage may be realised using skin substitutes, skin grafts or flaps

morbidity and more chances to save function, as the negative pressure acts as a regional booster for healing. Granulation tissue formation is increased around the tendon, providing a neovascularisation and preventing spreading of local infection. In an initial series of 16 patients, Lee et al. [1, 2] reported that NPWT facilitates the rapid formation of healthy granulation tissue on open wounds in the foot and ankle region and thus shortens healing time and minimises secondary soft tissue defect coverage procedures, reducing the need for a free flap to one single case. NPWT was also effective on infected patellar tendon salvage. Hong et al. [3] proposed an algorithm of decisions in soft tissue defects including NPWT.

37.3.3 Artificial Dermis

Several authors recently published clinical results concerning the use of artificial dermis in tendon coverage and more largely in soft tissue defects in the upper and lower extremities.

Attinger et al. [4] resume these possibilities as a step-by-step management of complex wounds with debridement, negative pressure wound therapy and coverage using dermal substitutes. These techniques are techniques described in chronic wounds, acute trauma wounds and burns [5, 6] with good results. Products used may either be double-layer dermis, mainly used in US, covered with a silicone film secondarily skin grafted, contrarily to one stage immediately covered with single layers proposed in Europe [7, 8] and Asia [9]. Other dermal substitutes have recently emerged on the market, aiming to the same objective which is to bring suppleness and prevent adherences of skin grafting to the underlying structures.

Dermal substitutes may also be used in the upper limbs [10] with good results in terms of mechanical possibilities of recovering skin capacities.

37.3.4 Flaps

Flaps remain as the most adapted tissue to cover a tendon. This technique leads to few adherences, a soft covering allowing the tendon to glide underneath with few complications, like excess of fat tissue or wrinkling observed when the transferred flap is too deep. Local flaps or regional sural flaps like distally based neurosural flaps [11] can be used, free flaps being used in large defects or in acute wounds for young patients with adapted vascularisation [12].

Flaps are more available in the upper arm where many possibilities of local or regional skin flaps are used and available directly or reversely.

37.4 Causes and Specific Management

37.4.1 Burns

In third-degree burns tendons are often exposed. Both upper and lower extremities can be

touched. Electrical burns may be terribly devastating at the wrist level, issuing to an exposure of all tendons, with a destruction of the paratenon and a progressive lysis of the tendinous structures. Coverage using flaps (oni) may be proposed, but it remains difficult to diagnose clinically tendon necrosis, the flap possibly covering already necrosed anatomical structures. Negative pressure therapy is usually proposed prior to reconstructive or covering surgery, combined to immobilisation of the tendon. A progressive separation between dead and living tissue appears, the tendon being slowly incorporated into a granulation bed. Coverage may then be obtained using a dermal substitute secondarily grafted using a partial-thickness skin graft. Tendon repair will be planned some months after, ideally more than one year in order to prevent recurrence of inflammation which is source of secondary adherences.

37.4.2 Trauma

Traumatic skin avulsion in the upper or lower limbs issues to a direct exposure of the tendon. If properly debrided and immobilised, tendons will be preferably covered using skin flaps as patients are younger and presenting less comorbidities. Microsurgery is often proposed [3].

Chronic wounds like pressure ulcer, DFU and LU may expose infected tendons. The tendon viability is difficult to assess, but the clinical analysis may be distinct if the tendon is still attached to the depth by the paratenon or not. In DFU series of cases using NPWT and dermal substitutes to cover successfully exposed tendons were recently reported [13, 14].

37.4.3 Miscellaneous

Infected postinjection sites with corticosteroids, fat or other augmentation devices may lead to tendon exposure and necrosis. This situation obliges to treat and debride the necrosed structures, heal and cover the wound and plan after several months a reconstructive procedure for tendon repair.

This situation on the dorsum of the hand has been described as a cause of tendon destruction (Casoli) where Integra may be used.

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Dissecting Haematomas in Patients Submitted to Anticoagulation

38

Sergiu Fluieraru

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38.1 Introduction

Large haematomas of the lower limbs are more frequently observed in patients submitted to anticoagulants [1]. Skin necrosis are limited in size, but the blood collection largely extends below the apparent lesion, inducing a vast dissecting collected space with clinical consequences comparable to compartment syndrome, with muscular and tendinous consequences.

38.2 Clinical Signs

The apparent skin lesions are usually reported by the patient to be due to a mild trauma on the leg, a fall, or a consequence of bandaging compression. Pain is moderate to intense, the local colour darkening progressively. The skin lesions are not extending over the skin surface during the next days, with a limited clinical symptomatology. This creeping lesion may induce extensive devascularisation of tendons and muscles located in the leg compartment involved, issuing to devastative loss of substances.

The leg volume slightly increases when the haematoma extends. However, the patients are usually aged and the symptoms are not always recognised, the clinical exam being rarely conclusive, a reason why the diagnosis is often delayed.

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38.3 Anatomical Lesions on the Skin Spreading to the Depth

Skin apparent lesions are relatively limited, usually located over the anterior part of the tibia and sometimes over the medial aspect of the knee joint or the calf muscles. Low impact traumas are most of the time reported by the patients who are submitted to anticoagulants.

Lesions are linked to the dissecting hyperpressure of blood in a non-expandable zone, inducing self-ischaemia of soft tissues like tendons and muscles. This progressive necrosis is often underestimated as the skin itself is not extensively destroyed. It looks like a limited consequence of a localised trauma with a mild haematoma.

Lately inflammation is present, issuing to exudation from the opened necrotic skin, contemporarily with coagulated blood extruding from the wound. Infection is quickly spread, depending on the size of the collection, inducing a potential risk for septicaemia [2].

This life-threatening complication may induce spreading of infection to other tissues like the cardiac valves. The situation may lead to death.

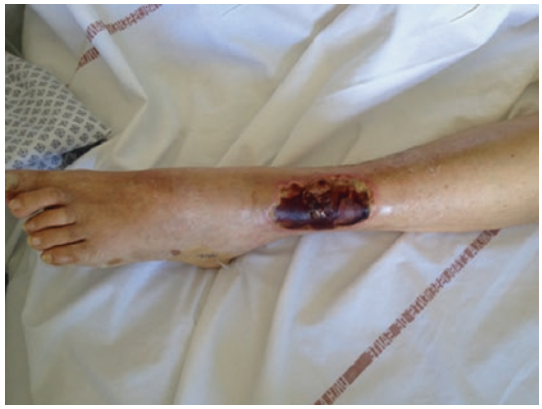
38.4 Complementary Exams

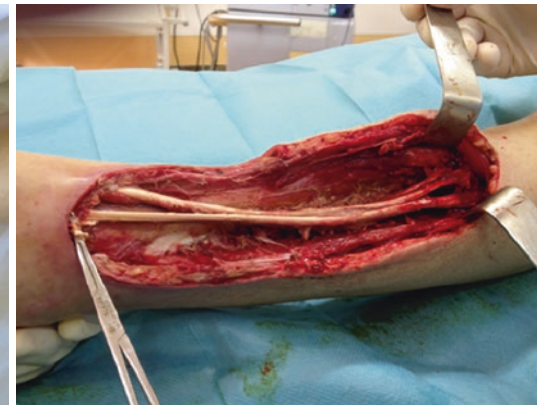
Ultrasonography is mandatory to assess the presence of blood still below the normal skin located around the visible necrotic skin. This collection may be still under liquid form, accessible to syringe aspiration, or under coagulated form, observed after some days. This collection is highly susceptible of becoming infected.

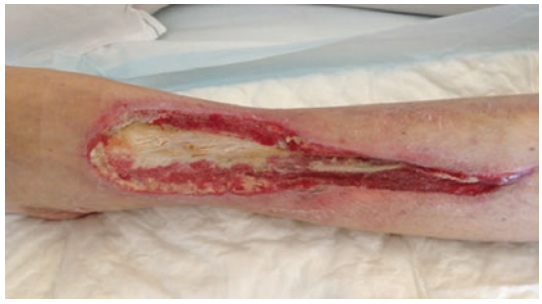
Magnetic resonance imaging (MRI) is sometimes needed to assess the soft tissues involvement, muscles being destroyed partially or completely.

38.5 Surgical Management

Extensive surgical debridement is needed to eliminate the whole infected pocket when the skin is opened. Ultrasonography will define the anatomical limits, and the surgeon will excise the necrotised skin and the surrounding cover. This surgical decapitation is needed to promote granulation tissue formation over a clean wound, without persistent undermining. Negative pressure therapy will rapidly induce a healthy granulation tissue within 2 weeks and allow a surgical coverage using skin grating (Figs. 38.1, 38.2 and 38.3).







Figs. 38.1, 38.2 and 38.3 Extensive necrosis of the anterior compartment of the leg (compartment syndrome), inducing a septicaemia with cardiac valve destruction and thrombosis of the ipsilateral femoral artery. In spite of several attempts of debridement and promotion of granulation tissue, below knee (*BK*) amputation was needed

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Management of the Patient After Flap Failure

39

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39.1 Introduction

The chapter describes how to approach the patient who has suffered loss of a free microsurgical tissue transfer.

The pathophysiologic events eventually leading to perfusion arrest and to subsequent flap loss will be outlined. Subsequently, reasons for failure are analyzed dependent on their origin, either patient inherent and irreversible or due to outer circumstances which are commonly reversible and correctable.

An algorithm will be presented on management of the patient after failure of free tissue transfer. The appropriate decision making depends on a large variety of factors including the persistence and urgence of reconstructive needs of the patient, the underlying cause of flap failure and its reversibility, the changed geometry and size of the defect, presence of recipient vessels, as well as the remaining selection of donor sites.

39.2 Etiology and Pathogenesis

Over the past decades, free tissue transfer has become one of the mainstays in the reconstructive plastic surgeon's armamentarium to solve complex reconstructive problems in the whole body arising from tumor resection, trauma, or congenital defects or malformations [1]. Success rates of free flap transfer have reached an average of 95 % in specialized centers,

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making this kind of procedure a very safe one in recent years [2].

All the more, it is a devastating event for the patient but also for the reconstructive microsurgeon if the rare event occurs and the free flap fails [3, 4].

It is of crucial importance to determine the underlying cause of flap failure as soon as possible because it will affect the future reconstructive strategy and whether to consider a repeat free flap or not to a significant extent.

However, the pathomechanisms of the final steps leading to eventual flap failure are the same in every single case and have their background in the normal physiology of blood flow within a blood flow [5].

When vascular injury occurs at the site of the microvascular anastomosis, the natural reaction is adherence of blood platelets at the site of injury which acts in a thrombogenic way due to denudation of the endothelium. The growing thrombus created by platelets following the thrombogenic stimulus is counteracted by the shear stress caused by the blood flowing physiologically through the vessel at the site of anastomosis. At the moment when a balance between these two processes is reached, a fibrin clot will be generated at the site of platelet accumulation and will stabilize and prevent further prothrombotic platelet adherence. Within a week, the endothelial surface will be restored making thrombotic occlusion of the vessel wall and subsequent flap failure a very unlikely event.

If the described balance is not preserved, the growing accumulation of platelets will eventually lead to occlusion of the microvessel at the anastomosis leading to subsequent flap failure [6].

39.3 Causes of Flap Failure

Causes of flap failure will be discussed as far as they directly relate or impact decision making for the subsequent steps in patient management. This applies particularly when a second free flap is considered to achieve the reconstructive goal (Table 39.1).

Table 39.1 Causes of flap failure

Reversible	Irreversible
Technical problems	Vascular disease
Microsurgical techniques	Atherosclerosis
Reduced blood flow	Radiation injury
Postoperative management/ anticoagulation	Malformations
Patient positioning	Hypercoagulability
Delay in diagnosis	Systemic disease
Delay in salvage	

Modified after Neligan and Wei [7]

39.3.1 Reversible Causes Due to Outer Circumstances

39.3.1.1 Microsurgical Technique and Intraoperative Flap Handling

The initial thought after failure of a free flap procedure will generally lead a self-critical microsurgeon to investigate whether technical reasons are directly responsible for the flap loss [8]. Indeed, many flap losses are attributable to inadequate surgical technique and planning [9, 10]. It is also well known that around 90 % of anastomotic thromboses occur in the venous part and that therefore the venous part has to be considered as the most frequent cause of anastomotic failure [11]. Therefore, immediate revision is mandatory when there is any suspicion of thrombosis postoperatively [12, 13]. Using coupler systems for venous anastomosis is believed to lower the complication rate on the venous side [14].

Risk of vessel injury and increased endothelial lesion followed by excessive platelet adhesion can be minimized by meticulous technique [15].

This includes avoiding to grasp the intima unduly with sharp instruments, avoiding tension at the anastomosis site, or undue clamping of vessels resulting in inner intimal lesions, not

directly visible from the outside. It is advisable that if in doubt, vascular interpositional grafts should be used. Size match of flap vessel and recipient vessel should be ensured to avoid blood flow disturbances. At flap inset, tension on and kinking of the pedicle should be avoided [16]. In our own clinical practice, we found it helpful to protect the microanastomosis from kinking and from direct compression from the outside (such as by hematoma or seroma formation) by covering the anastomotic site with fibrin sealant [2, 17].

39.3.1.2 Postoperative Management

Careful positioning of the patient to prevent compression of the pedicle or the flap itself is crucial for successful outcome of free flap transfers, e.g., in the lower extremity or in the perineal or sacral region.

If in free muscle flaps skin pedicles are used, one has to make sure that the monitor island is sufficiently perfused and reflects the perfusion status of the muscles itself to rule out a false decision making [18].

The use of systemic anticoagulation varies widely, but routine use is not uniformly agreed upon by all microsurgeons [19, 20]. Dextran, aspirin, heparin, and low-molecular-weight heparins are the most commonly used pharmacologic agents. Particular indications such as bypass free flaps have been the subject of a more aggressive anticoagulative regimen. Given that evidence-based recommendations are not available thus far, the German-Speaking Society for Microsurgery has recently published its attempts to formulate potential guidelines for anticoagulation regimen after microsurgical free flap transfer [21].

When a second microvascular free flap is going to be performed to achieve a reconstructive goal following flap failure, systemic anticoagulation is often applied if risk factors persist as unfavorable conditions that are not correctable such as radiation tissue injury or radionecrosis [22]. This holds also true for complex microsurgical procedures including arterial bypasses or arteriovenous loops between flap and recipient site. In such interdisciplinary cases in our institution, we apply oral medication for systemic anticoagulation for half a year.

39.3.1.3 Patient-Inherent Irreversible Causes

These issues need to be considered in particular when evaluating the reconstructive options after free flap loss since they cannot be altered and may pose a limiting factor to secondary free flap reconstruction that has not been considered thoroughly enough at initial evaluation.

39.3.1.4 Vascular Disease

Atherosclerosis is one major threat to successful microsurgical free flap reconstruction. In particular, recipient vessels in the head and neck are and in the lower extremity may often be of poor quality, increasing the risk of anastomosis-related complications, embolism or thrombosis formation. When there is peripheral vascular disease of the lower extremity, free flap surgery itself may threaten survival of an already hypoperfused limb, necessitating the use of combined approaches using a bypass or vessel loop to provide both sufficient recipient vessels and secure perfusion of the compromised lower extremity [23, 24].

A history of diabetes and radiation injury may also severely compromise the quality of flap or recipient site vessels [25], the latter being of particular importance and frequently encountered in autologous breast reconstruction and sarcoma patients. When free flaps are buried, PET scanning may be helpful to determine the necessary measures [26] when Doppler or duplex sonography is not sufficient.

39.3.1.5 Systemic Disease

It is not uncommon that a failed free flap worsens the patient's general condition, giving the patient an even greater risk when secondary free flap reconstruction is considered [27].

Clotting disorders including factor V Leiden, protein C and S deficiencies, and other conditions are not common, but an important cause to consider and identify before further efforts are undertaken to start another reconstructive effort using microsurgery [28, 29].

Myocardial infarction, stroke, respiratory failure, and morbid obesity and malnutrition are other severe conditions possibly precluding microsurgical reconstruction.

In each single case, the reconstructive goals must be reevaluated and potential new factors included in the analysis of patients after free flap failure.

39.4 Reevaluation of Reconstructive Goals

After a thorough assessment of the clinical course has been carried out and the cause for failure of the free flap procedure has been identified, a careful reevaluation of the status quo and the reconstructive goals is warranted.

The following factors must now be considered before the next steps towards a secondary reconstruction are being made, in particular if a second attempt for free flap microsurgical reconstruction is considered: first, the possible limitation of donor sites; second, the new defect that may be potentially larger than the first defect; and third, previously available recipient vessels that may no longer be available. Taking all these factors together, a second free flap may be more technically challenging, increasing the risk for another free flap failure in the same patient. The need and urgence to reach a reconstructive goal by the use of a free flap may vary considerably, reaching from indications mainly for restoration of aesthetic appearance (breast reconstruction, reanimation of the paralyzed face), functional reconstruction (reanimation of the paralyzed face), and limb salvage (lower leg reconstruction) to the essential coverage of vital structures such as major blood vessels [24] (Fig. 39.1).

39.4.1 Repeat Free Flap Procedure

Typical indications for where a repeat free flap procedure is recommended include the coverage of major vessels or vital structures, limb-threatening wounds in the extremity, and timely wound healing for potentially life-saving radiation. In such cases, it may be advisable to not risk another free flap but instead solve the problem with a pedicled flap to cover vital structures if possible [30–32].

Contraindications include deteriorating general conditions and severe uncontrollable local wound infection.

Typical flap choices will usually be the contralateral side of the initial donor site, “easy to perform” safe and standard flaps that the surgeon is experienced and comfortable with, and flaps with long and good-caliber pedicles (Fig. 39.2).

39.4.2 Non-microsurgical Therapy

Several factors may lead to the conclusion that another attempt to microsurgical free flap transplantation may not be the best reconstructive option for a particular option. When the patient’s general condition deteriorates or when there is severe uncontrollable infection, alternative strategies of problem-solving must be implemented. These include local flap coverage, skin transplantation, and healing by secondary intention.

Treatment of free large flaps other than small skin flaps with the use of leeches is not advisable. It leads to anemia necessitating blood transfusions and does not alter the underlying condition. This is different when fingers are replanted, where the application of leeches due to the often immanent problem of lacking venous vessels may help to overcome the initial period of venous congestion in replanted digits [33].

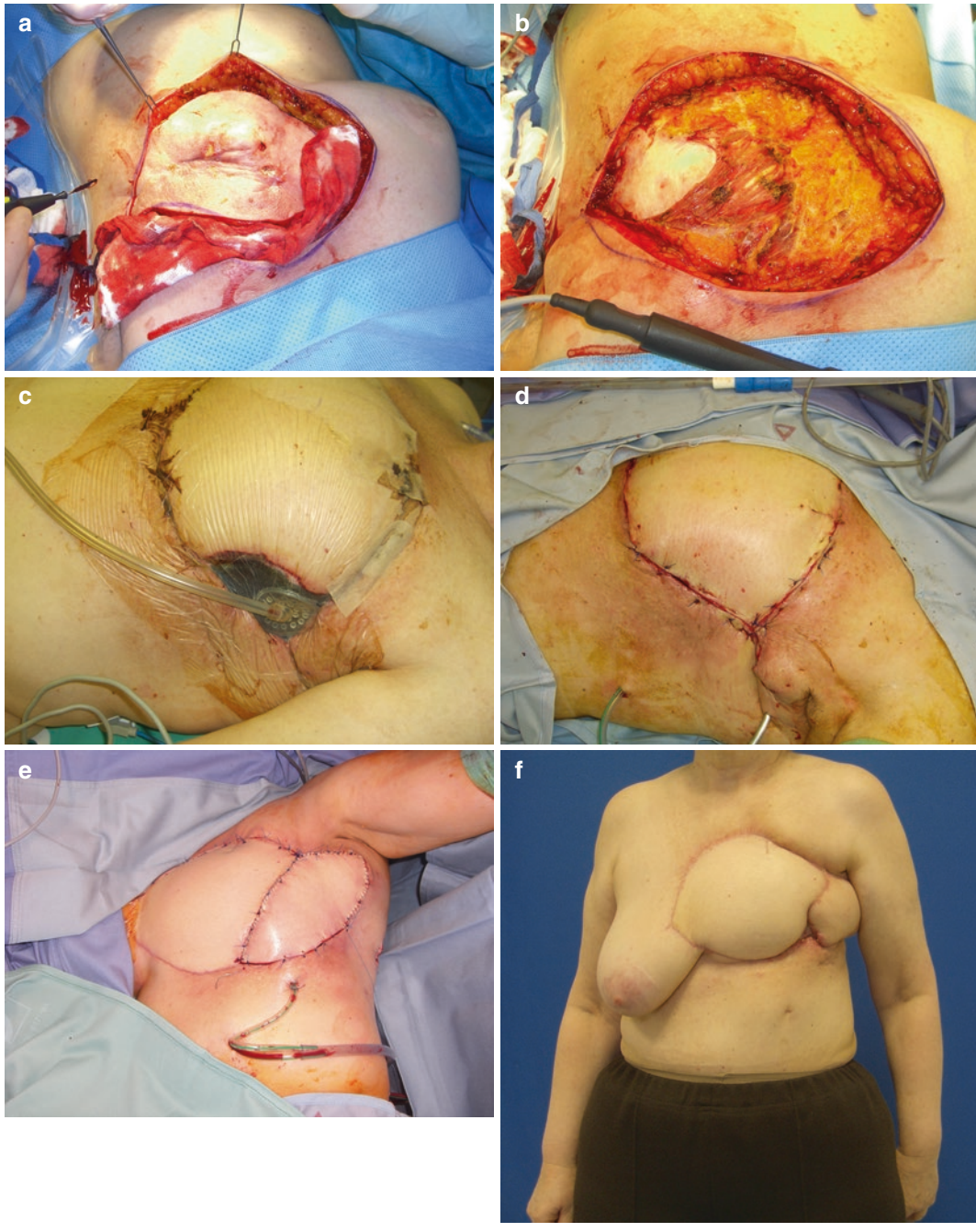


Fig. 39.1 (**a**) Palliative resection in fistulating inflammatory breast cancer after mastectomy and repeated irradiation (first cycle due to breast conserving therapy and second radiotherapy after mastectomy). (**b**) 43 cm×27 cm large defect after palliative resection of fistulating inflammatory breast cancer. (**c**) After inset of extended DIEP flap to cover the large area, partial necrosis in zone IV occurred, necessitating debridement of the tip of the flap. We attempted wound conditioning with topical negative pressure therapy (TNP). (**d**) Secondary closure in the heavily irradiated field was attempted after wound conditioning with TNP. (**e**) Following wound breakdown after the secondary closure, a pedicled latissimus dorsi myocutaneous flap was necessary to achieve stable cover of the large wound area in the irradiated field. Note the fibrotic tissue changes and skin alteration below the latissimus dorsi flap in the upper abdominal wall soft tissue where the drain is placed through the skin. (**f**) Finally the wound was closed with conservative treatment of minor secondary healing in the lower wound margin between the latissimus dorsi and the DIEP flap within the irradiated area in this palliative situation rendering improved quality of life. The patient deceased 1 year later from pulmonary metastasis

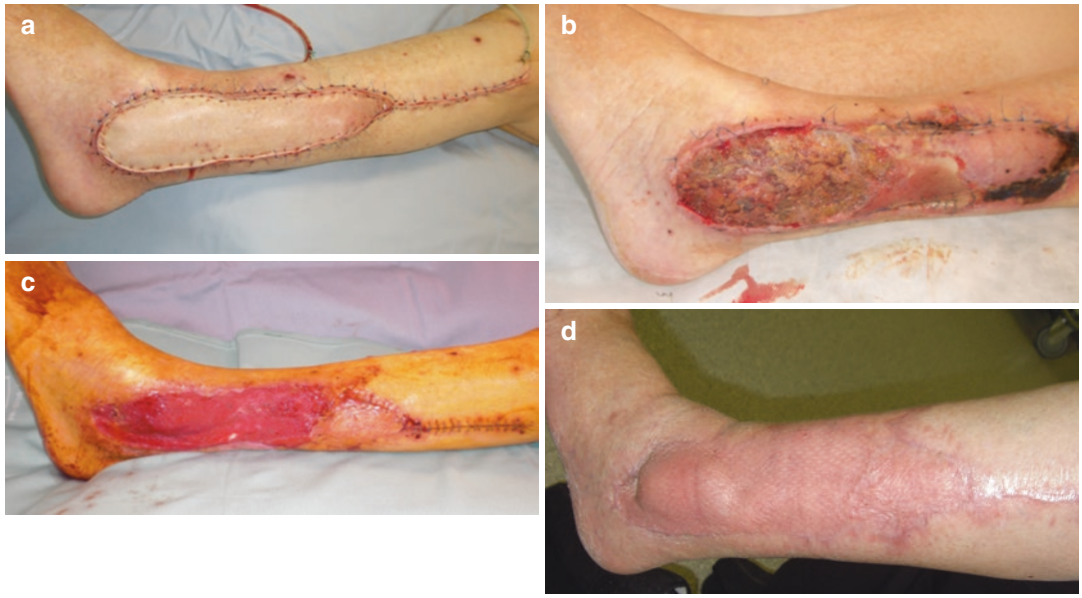
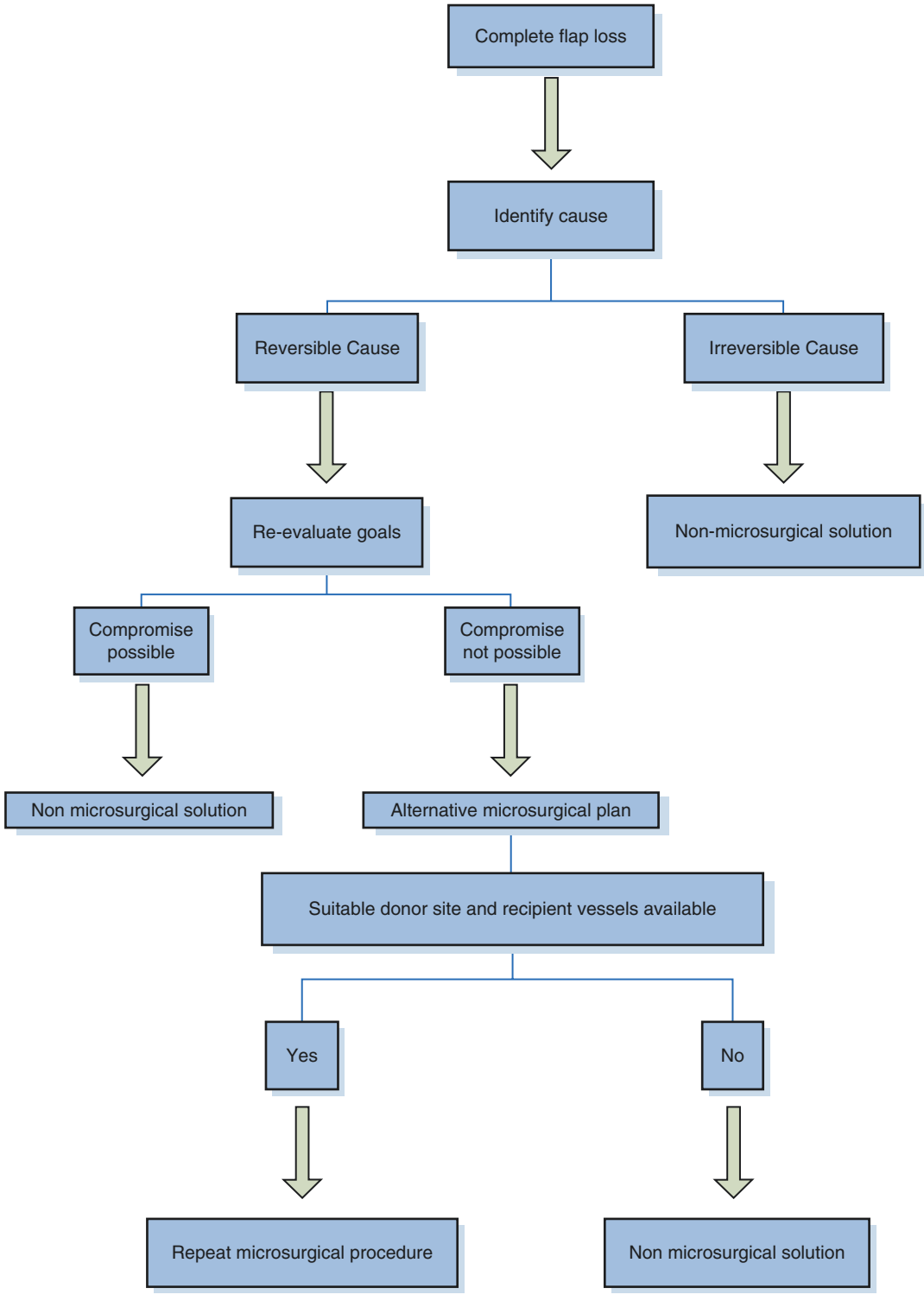


Fig. 39.2 (**a**) The patient initially suffered from a combined pilon tibiale and fibula fracture. After initially successful osteosynthesis, further clinical course was complicated by an unstable scar followed by soft tissue breakdown. After radical surgical debridement and removal of the exposed hardware, a propeller flap based on a perforator from the fibular artery was performed for defect coverage. (**b**) In the postoperative course, malperfusion occurred, mainly in the distal part of the flap. After debridement, the remaining defect was covered with a free gracilis flap which again became necrotic in its distal part. The remaining defect then was covered after a partial debridement of the gracilis flap with a peroneus brevis flap. (**c**) After wound conditioning using negative pressure therapy, a healthy well-perfused wound bed was visible. (**d**) The wound bed was then amenable to split-thickness skin grafting. The further course was uneventful, and the patient had long-term stable soft tissue coverage

Flow sheet – surgical decision making after complete flap loss



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Stonefish Necrosis

40

J.D. Harms, C. D'Andréa, and N. Fartaoui

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The marine environment is rich in poisonous and venomous animals and plants. Among them the stonefish is responsible for wounds with poisoning which sometimes evolve towards necrosis. The geographical distribution of such fish is widespread and it usually lives in shallow water; as a result the stings are not rare among the human population. The wounds of stings are at risk of extensive necrosis.

40.1 The Stonefish [3, 4]

40.1.1 Identification

Stonefishes are of the family of Scorpaenidae (according to ITIS[1]) or Synanceiidae (according to FishBase[2]). There are several species among which *Synanceia verrucosa* (Figs. 40.1 and 40.2) is the one present in La Réunion.

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[1] ITIS: information system taxonomique Integrated (Joined).

[2] FishBase: consortium since 2000 established (constituted) by Africamuseum, Aristotle University of Thessaloniki; Chinese Academy of Fisheries; Fisheries Centre, University of British Columbia; United Nations Organization for the food (supply) and the agriculture (farming), IFM-GEOMAR; National natural history museum; Swedish Museum of Natural History; and WorldFish Center.

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Fig. 40.1 STONEFISH - Olivier Allart from Diony-Bulles (Reunion Island) All the other photos are from myself ; we are not obliged to mention the author either: (photo jdh)

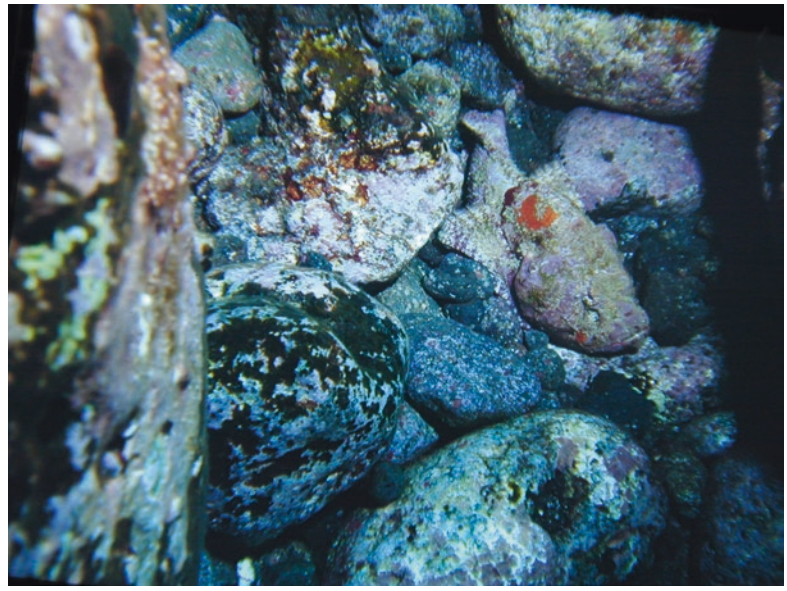

Fig. 40.2 Do you see the stonefish???

40.1.2 Habitat

Stonefishes are found on coral reefs, muddy waters or sandblasters of the Indian Ocean, Red Sea, Indonesia, Australia, New Caledonia and the Pacific [5].

40.1.3 Venomous Apparatus

40.1.3.1 Thorns and Glands with Venom

The stonefish has 13 thorns on its dorsal fin which rise in case of danger. Every thorn is covered with

a verrucose tegumental envelope and has a pair of glands with venom in its base. Every gland has a canal filled with poison and leading to the top of the thorn. If someone walks on or tries to seize the stonefish, its thorns penetrate into the skin and the tegumental envelope is then pushed downward causing the compression of the gland, which if sufficient will launch the release of the poison. The stinging and poisoning is a defensive mechanism.

The venom: its composition is complex: substances such as the histamine, adrenalin, norepinephrine, dopamine as well as enzymes such as hyaluronidase, protease and lipase. The main toxin is the verrucotoxin: it inhibits the calcic canals and it activates the potassium canals. The venom is myotoxic, neurotoxic and haemolytic. It is inactivated in 54 °C [3].

40.2 Stings by Stonefish

40.2.1 General ideas

Stonefishes were notorious for being among the most venomous animals of the world and its stings were thought to be lethal. In fact, the sting by stonefish provokes an extremely intense pain that can possibly result in a faint fit. Also if it happens to a scuba diver, it may cause an accident if the diver is unable to control his ascent (barotraumatism) or to make the required decompression stops (desaturation accident).

40.2.2 Circumstances

The stonefish is a sedentary and benthic fish. It favours rocky areas or lays buried under sand or mud. It feeds on small fishes and shrimps which it swallows with its mouth. The stonefish can survive several hours out of the water and its venom remains active from 24 to 48 h after its death. Stings by stonefishes mostly occur during activities such as bathing, fishing, snorkelling and scuba diving.

40.2.3 Wound Location

The wounds are mainly seen on the feet of people who accidentally walked on a stonefish. They can also be seen on hands due to an attempt to touch or seize the fish.

40.2.4 Clinical Evidence

The pain is immediate and very intense. It can cause a person to faint. The pain is quoted between 8 and 10 on the visual analogic pain scale. It often results in restlessness and aggressiveness.

There are one or several wounds, mostly in the foot or in the hand.

An oedema quickly develops, sometimes limited around the wound, often wider and spreading. Not rarely, it might extend to the whole limb up to its base.

General symptoms are often noticed: sweats, nauseas, arterial hypotension, tachycardia, heart rhythm disorders, myasthenia and pulmonary oedema.

40.2.5 Diagnosis

The diagnosis is easy when the victim saw the fish and clearly identified it. It is often the case with fishermen and scuba divers. In many others cases, it is about a person who was bathing and suddenly felt an excruciating pain without seeing the cause of such pain. Thus, there is a doubt for it could also be a wound by a piece of coral or shell, a sting by another marine animal (*Pteroïs volitans*, ray, poisonous shell, etc.).

The diagnosis is then based on assumption. If the stonefish is not clearly identified, the elements which allow to incriminate the stonefish are:

The pain which is of maximum intensity at once and resists to painkillers, including level 3 analgesics. The pain remains at highest intensity

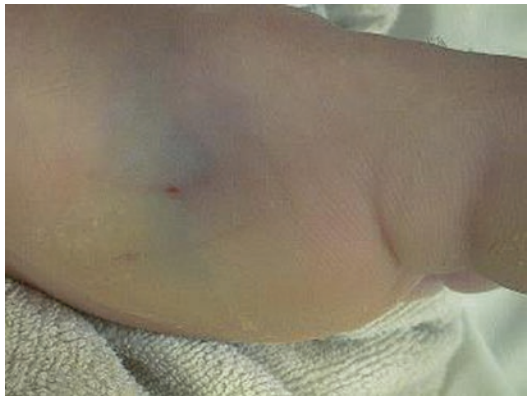

Fig. 40.3 Typical aspect of a sting with punctiforme lesion and bluish halo

during 12–18 h and then gradually decreases within 2–3 days.

The examination of the wound allows identifying the origin of the sting: if there are several stings by several thorns, they are distributed at equal distance. Every sting presents a small wound with clear edges from 1 to 2 mm in length with an inflammatory area and a bluish halo (Fig. 40.3) and sometimes a small blood and fluid flow.

Often the delay is more important and thus the inflammation has further extended with oedema and phlyctenas around the wound.

The association of a sudden, intense pain and these local aspects allows evoking the diagnosis of sting by stonefish.

40.2.6 Severity of the Wound Depends on Several Factors

The size of the fish: the bigger the stonefish is, the more venom is injected and the more serious is the wound.

The wound: the number and the depth of the stings.

The victim: his (or her) age, weight and medical history.

The time period until medical care is given.

40.2.7 Medical Complications

Presence of a foreign body which will have to be removed: a piece of thorn that would have broken into the wound. Medical imaging might be necessary if there is a doubt, though this is rare for the *Synanceia verrucosa* thorns are very resistant.

Superinfection of wounds: the marine environment is rich in bacteria of all kinds and any wound by marine animals may become infected.

Extended infection: the risk of a spread infection is real, possibly leading to cellulitis, fasciitis or gas gangrene.

Thromboembolic complications are also possible.

The necrosis of wounds is the most frequently met complication, though rather infrequent. If necrosis is observed, medical supervision of the wound and its course is required. The bluish halo around the sting usually evolves within a few days towards a small lesion: a superficial necrosis which only requires simple dressing. However, the necrosis sometimes extends reaching the dermis, hypodermis and the muscle and tendon underneath. This necrosis continues to extend in spite of local care, and from the initial, limited lesion the wound extends to its neighbouring structures. This is serious and worrisome for both the patient and physician.

40.2.8 Treatment

Treatment of the pain is from the beginning an absolute priority due to its intensity:

Grade 1 (paracetamol) or 2 (tramadol) analgesics are often ineffective. Morphine must be tried, but in number of cases and in spite of important doses, it remains ineffective too.

Heat is used because the venom is inactivated at 54 °C. It is necessary to dip the limb in a 45 °C water tub and let it soak until the pain decreases. This “hot-water technique” is sometimes very effective, sometimes not. The duration of the soaking is important what exposes the patient to a risk of burn. It seems that the sooner the technique is used, the better the results is. However the disparities observed in the results are important. In all, some disadvise this technique because of the potential burns whereas others use it. In our personal experience, we used it with sometimes dramatic results and often failures or poor improvements, in

particular the outbreak of the pain as soon as the hot water is removed [1, 2].

The equimolar gas oxygen/nitrous oxide (Entonox®) can be used, but it is often insufficient for the relief only lasts while the gas is given and it cannot be given for a prolonged duration. It can be helpful then while waiting for the analgesics to become efficient.

The local injection of lidocaine can be used.

Locoregional anaesthesia is the most effective method for the treatment of the pain. We implemented an epidural anaesthesia using bupivacaïne and continuous administration through a catheter during 12 h for a patient whose pain was unbearable and resistant to the drugs. C. Maillaud in New Caledonia successfully realised several truncal locoregional anaesthesias on patients [6]. This requires anaesthesiologist availability and in our hospital we have set up a protocol for locoregional made by anaesthesiologists in our operating unit preparation room: "single shot" (no indication of nervous catheter) with naropeine in a sciatic block in the lower limb or axillary block infra clavicular/humeral in the upper limb. The patient must stay at hospital for 1 day.

40.2.9 Other Used Treatments

The antivenom serum for stonefish is made by the Commonwealth Serum Laboratories in Australia by immunisation of horse with some venom of Synanceia trachynis and would be effective according to its manufacturer on the venom of *Synanceia verrucosa*. This serum is expensive, it must be kept between 2 and 8 °C and its duration of use is limited. It is not available in Reunion Island but it is in Mauritius. S. Hansrod, in her report of interuniversity diploma of physiology and hyperbaric and underwater medicine, studied the Mauritian experience: the injection of "serum anti-stonefish" would have a very fast effect on the decrease of the pain especially if the intramuscular injection can be prematurely made. The intravenous route can be exceptionally used. The risk of anaphylactic shock and serum disease must be taken into account [1–3].

Steroids as anti-inflammation medication: their efficacy has not been demonstrated by any study, and their effect is not recommended because of the risk of infection.

The antibiotic therapy is often prescribed, especially if one or several wounds were not prematurely disinfected. Amoxicillin/clavulanate potassium or a third generation cephalosporin is prescribed for 3 in 5 days [3].

The tetanus prevention must to be considered and implemented depending on the vaccinal status of the subject.

Low-molecular-weight heparins are prescribed if there is an important oedema or to patients at risk.

The treatment of the wound requires the earliest possible disinfection and dressings.

The surgery is sometimes necessary, secondly, for the treatment of complicated wounds.

The hyperbaric oxygen therapy (HBOT) is used for the treatment of wounds evolving unfavourably as an adjuvant therapy to improve the healing. It becomes essential in case of infection such as cellulitis or gas gangrene [2].

40.3 Our Experience in Reunion Island

In 2008, we made a retrospective study in Reunion Island. We had listed the suspicions of sting by stonefish in the Emergency Unit of the Groupe Hospitalier Sud Reunion from 2000 until 2005: 51 cases had been counted. It was 11 females and 40 males (average age 30, 6 years/extremes: 3 and 63 years). The stings concerned the feet in 78 % of the cases and the hands in 22 %. In all the cases, we found a very intense pain, a local oedema (57 %) or extended (in cases to the whole limb) (16 %), an ecchymosis (16 %), an inflammation (20 %) and an early local necrosis (16 %). Analgesics were used in 70 % of the cases with an association of different grades in 33 % and using morphine in 43 %. The hot-water soaking was used in 65 % of the cases and the local injection of lidocaine in 9 %. An antibiotic therapy was prescribed in 43 % of the cases. The patients were hospitalised in 46 % of the cases. The extension of the necrosis occurred in four cases and the surgery was necessary in two cases. HBOT was used in three cases [2].

40.4 Clinical Cases

Case 1

It is an old report from 2001. A 63-year-old fisherman caught a stonefish of a beautiful size, estimated at 2 kg. By picking it up, his right-hand middle finger got wounded. He came to the emergency unit to consult a physician only the next day. Figure 40.4 was taken on the 13th of February 2001 at his admission in the emergency unit. There is a necrosis of the pulp of the 3rd phalanx, while there was initially a phlyctena. Figure 40.5 was taken on the 21th, and later evolution of the wound is seen on Fig. 40.6: the examination of the wound suggested the necessity of a distal amputation. This patient was treated by dressings and HBOT sessions (Fig. 40.6). The healing of a good quality will be obtained after 5 months of care.

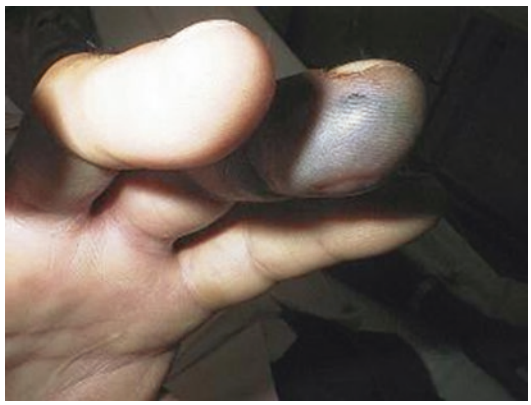

Fig. 40.4 Case 1: Pulpaire necrosis of the finger the day after the sting

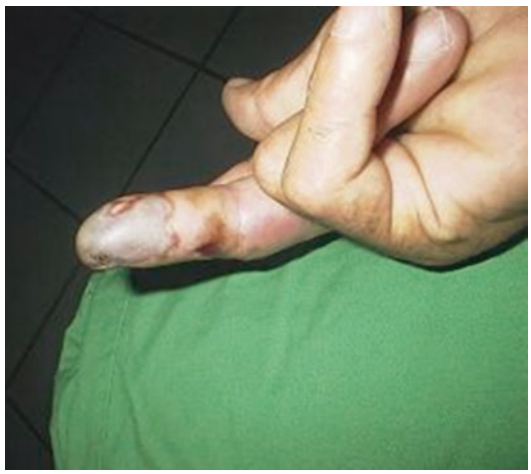

Fig. 40.5 Case 1: Aspect after 3 weeks

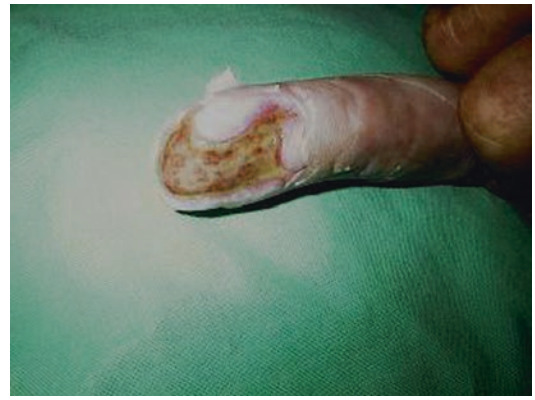

Fig. 40.6 Case 1: Later evolution

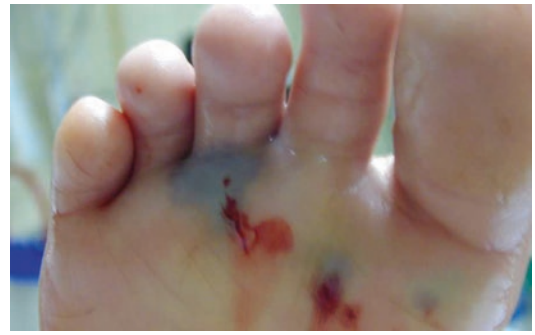

Fig. 40.7 Case 2: Typical early aspect with 3 points of sting

Case 2

It is about a 12-year-old boy who was stung while bathing in a rocky area. We saw him approximately half an hour after the sting (Fig. 40.7). The pain was extreme with a state of agitation. The aspect is characteristic because we see three stings made by three thorns: they are regularly spaced out. We clearly distinguish the stings, with blood and an ecchymosis which is spread on the most external lesion. The internal injury has a small halo: the penetration of the thorn was superficial at this level. The soaking associated with analgesics was effective and the course simple.

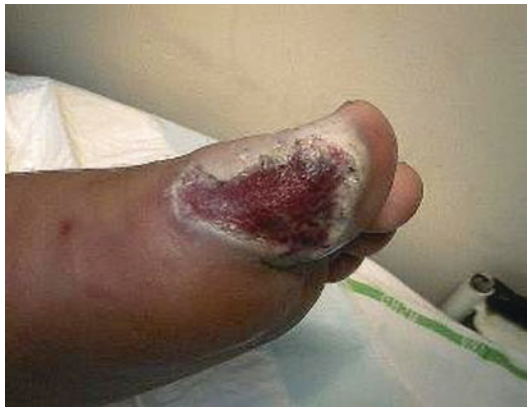

Fig. 40.8 Case 3: Intermediate aspect after use of hydrocolloide dressings

Case 3

An 8-year-old girl was stung and we saw her a month later. Her mother was very worried. We gave her explanations onto the usual evolution of these wounds and our project for dressings with stop of the daily use of povidone-iodine disinfection and use of dressings changed all the 3 or 4 days. The evolution was quickly positive and healing was obtained a month and a half later (Fig. 40.8).

The stings by stonefish are frequent in all the tropical zone of Indian and Pacific seas because of the presence of the fish in shallow water. The severe pain monopolises the immediate care. The risk of evolution in extensive necrosis, difficult and long to be treated, should impose a particular surveillance after initial care.

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Part VII

Techniques Applicable to Skin Necrosis

Dressings for Necrosed Skin

41

Christine Faure-Chazelles

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41.1 Introduction

During the physiological process of healing, the initial stage of debridement and inflammation is realised spontaneously. Moist wound healing favours the activity of proteolytic enzymes and the macrophages phagocytosing dead cells, and it allows absorption of tissue debris. However, this slow natural process may lead to negative consequences for wound healing. The necrotic process stops the formulation of granulation tissue and creates a milieu that favours bacterial development. This necrosis may be black and dry or humid or fibrinous, the colour depending on the accompanying bacterial colonisation. The presence of a biofilm prolongs the inflammatory stage and exposes the wound to recurrent infectious episodes [1, 2]. Modern dressings based on the concept of moist wound healing contribute to the acceleration of autolytic debridement.

This chapter presents the different dressings recognised to be effective during debridement and their mode of use. Depending on the type of necrosis—hard and dry or soft and humid—these recommended dressings are mostly absorbent or mixed hydrating/absorbent. These dressings may be gauzes, sheets or gels [3, 4]. Some dressings with osmotic properties are also used for debridement and are briefly described below.

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41.2 Dressings and Autolytic Debridement

41.2.1 Hydrating Dressings

41.2.1.1 Hydrogels

Hydrogels are mainly composed of water (around 80 %) to which is added, depending on the adsorbing components (carboxymethyl cellulose [CMC], alginate, etc.), hydrating agents (gelatin, pectin, etc.), thickening agents (xanthan gum, guar gum), and bacteriostatic agents (propylene glycol, etc.). Gels are mostly used for debridement, but they also exist in the form of gauzes impregnated with gel and transparent sheets.

The physical properties of hydrogels should combine a relatively low viscosity favouring the maximal coverage of the wound and good adherence, preventing the gel from gliding over the wound. Because of their composition, they hydrate and soften the necrotic plaque to facilitate debridement of hard, dry necrosis (Fig. 41.1a). Gels are presented differently depending on the manufacturer: classic tubes, accordion tubes, and syringes. Unexpected events may be observed, such as maceration of the wound edges in the case of heavy exudation or when the gel is applied in excess (Fig. 41.1b). Good care should be taken to apply a uniformly thin layer of hydrogel over a previously cleaned and dried wound bed. The choice of the secondary dressing is crucial, as it will enhance the moisturising effect of the gel. Any absorbing dressing should be avoided. Facility of use of the applicator is the main element of differentiation among the products currently on the market: a long nose for deep wounds, the sharpness of application, and the ease of use of the product as a whole.

41.2.1.2 Hydrogel-Like Devices

Over the last few years, the classic formulations of hydrogels have changed. Adding antiseptics was proposed, and of the products currently on the market, the following could be mentioned:

- A matrix of hydroxyethyl cellulose polymers, insoluble and hydrophilic, containing 85 % water and octenidine dichlorhydrate, a cationic antibacterial belonging to the bipyridine family [5];
- A solution containing hydrogel, but also polyhexamethylene biguanide (PHMB) together with betaine. PHMB is an antimicrobial belonging to the biguanide family, whose property is to reduce the bacterial load by acting on the phospholipids of the bacterial membrane. Betaine is a tensioactive agent called a surfactant, whose action is to dissolve fibrinous material on the wound surface [6].

One of the main expected actions of these devices is to eliminate and prevent biofilm formation.

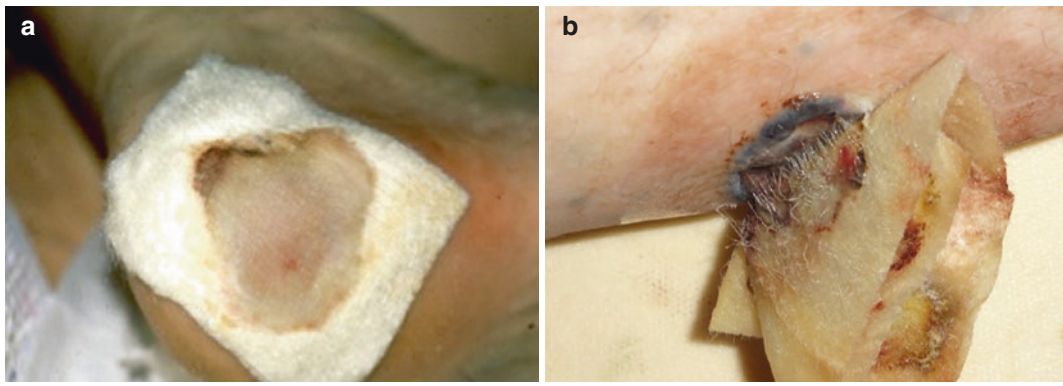

Fig. 41.1 (**a**) Appearance of hydrogel applied on necrotic tissue two days ago. (**b**) During application, the gels sticks to the wound, and the porduct layer should not be applied on the wound edges

41.2.2 Mixed "Hydrating/Absorbent" Dressings

41.2.2.1 Irrigo-Absorbents

Irrigo-absorbent dressings are gaining popularity among debridement dressings, although only one device has been launched under TenderWet [7]. It is a multilayer dressing presenting a shape of a cushion whose centre is mainly composed of polyacrylate particles activated by an adequate volume of Ringer solution. The superabsorbent polyacrylate presents an increased attraction for wound exudate rich in proteins compared with the Ringer solution. The combined action of irrigation is due to the continuous delivery of Ringer and the drainage of exudates. Periwound blanching may be observed when the dressing lies over the wound edges; a water paste or zinc oxide paste can be proposed. The Cleansite study article now in press demonstrates the superiority of the product over normal hydrogel in long-term undebrided chronic leg ulcer.

41.2.2.2 Hydrocolloids

Considered to be active at all wound healing stages, hydrocolloids occupy a relatively modest position in the list of debriding agents. These older devices have been progressively supplanted by more adaptive dressings. Composed mostly of sodium CMC, they jellify when in contact with fibrin or necrosis and provide an optimal level of moisture (Fig. 41.2a). The absorption of exudate occurs slowly and moderately and their use is indicated in the presence of humid necrosis and mainly for superficial wounds owing to the speed of action.

They can be found as fairly thick sheets, opaque or transparent and with anatomical shapes (sacrum, heel, elbow). All are adhesive and do not require secondary dressings. The dressing should lie at least 3 cm over the edges of the wound to obtain maximal adhesion (Fig. 41.2b). In some cases, an adhesive tape can be used to secure the edges of the dressing in place.

41.2.3 Absorbent Dressings

Absorbent dressings are composed of various materials such as alginate, CMC and polyacrylate. Their main characteristic is that they jellify when in contact with exudates without being destroyed. To be active during the debridement stage, the dressing should not dry out between two successive changes. They are available as gauzes or meshes.

41.2.3.1 Alginates

Alginates are polymers of alginic acid obtained from brown algae. They are differentiated from each other by their chemical composition and thus their physical properties. When guluronic acid is predominant compared with mannuronic acid, the dressing will be more rigid. Ca++ and Na+ concentrations and the presence or absence of CMC provide different levels of absorption. The jellification of alginate fibres is concomitant

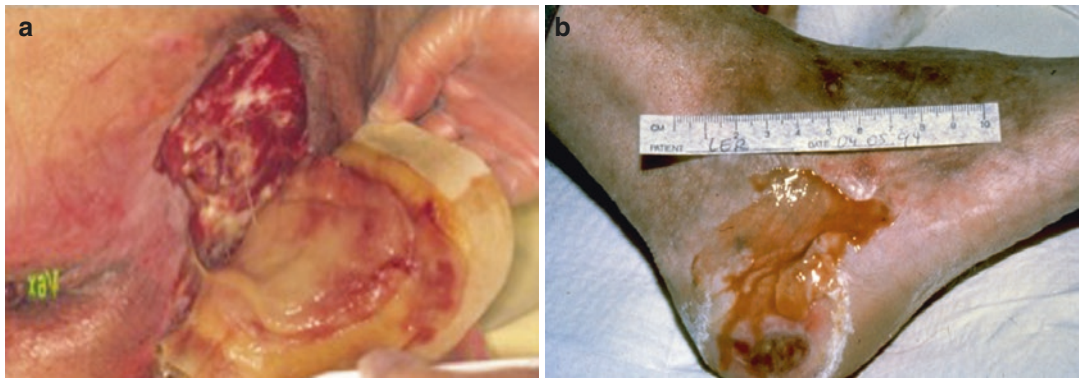

Fig. 41.2 (**a**) Aspect of hydrocolloid after two days. Gelification smells and look like pus. (**b**) Hydrocolloid dressing should ideally be placed 3 cm over the wound edges

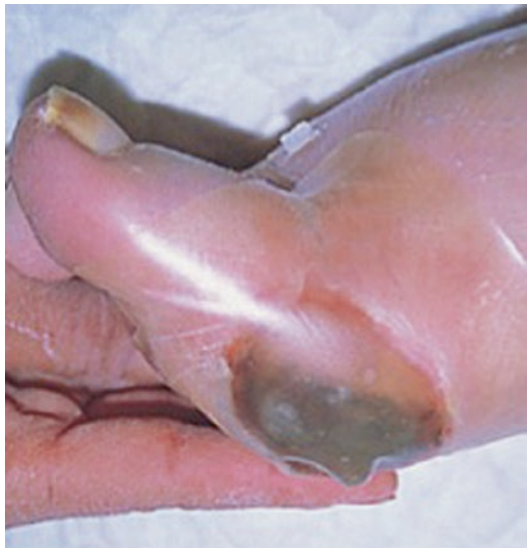

Fig. 41.3 Highly exudating wound covered with an alginate will be changed when saturated

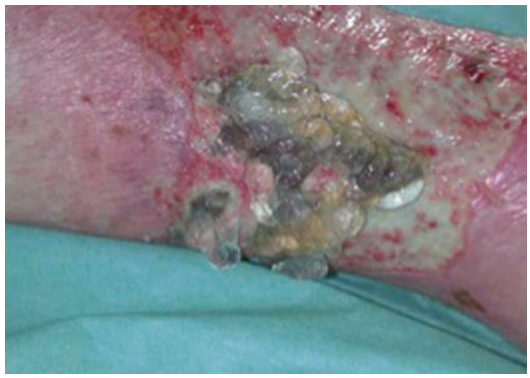

Fig. 41.4 Saline is applied over an alginate in order to facilitate the dressing removal

with the formation of Na alginate, which is soluble in water and highly hydrophilic, and/or with the presence of CMC (Fig. 41.3).

Maintaining the adapted level of moisture without occlusiveness allows better efficacy. Their haemostatic capacity is also an interesting property [8]. In order to facilitate the removal of the dressing, NaCl 0.9 % may be used (Fig. 41.4). Alginates are contraindicated over dry wounds or during the epidermisation stage. Sequential use of alginates during the debridement stage is recommended by numerous guidelines [9].

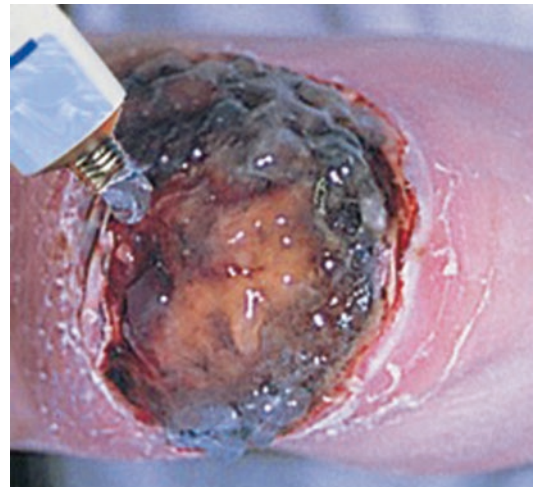

Fig. 41.5 Hydrofiber removal is easy thanks to the CMC gelification

41.2.3.2 Hydrofibres

Hydrofibre technology was introduced in 1999 when launching the product, whose composition has recently changed. This unwoven dressing is composed of sodium CMC and of a vertical and horizontal matrix containing regenerated cellulose. Hydrofibres are characterised by their high degree of hydrophilia combined with a large capacity for absorption. Looking at their composition, they are similar to hydrocolloids as they jellify when in contact with exudates (Fig. 41.5), but they have the capacity to retain moisture inside the matrix (bacterial sequestration) [10]. The recently developed matrix enhances these properties; thus, it is better to cover the dressing with a secondary dressing, allowing some moisture (hydrocolloid, foams). Removal of the dressing is facilitated by hydration.

41.2.3.3 Dressing with Polyacrylate Fibres

There is one unique dressing in this recent category. It consists of a gauze composed of polyacrylate fibres and coated in a micro-adherent lipido-colloid layer (TLC-Contact) (Fig. 41.6a).

The mesh version does not contain lipido-colloid. Together with the hydro-debriding fibres, polyacrylate fibres jellify and adhere to fibrinous residues, absorb them and drain them in order to

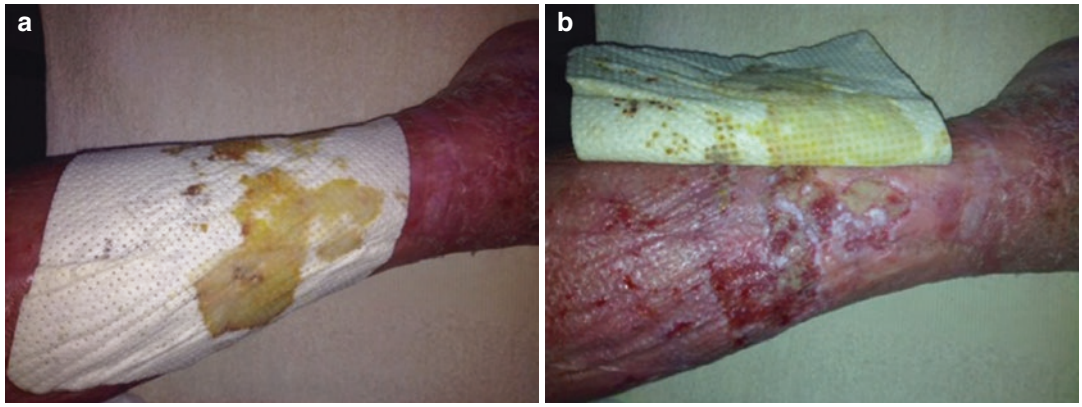

Fig. 41.6 (**a**) Polyacrylate fiber dressing is a fast remover of undesired tissues over a fibrinous leg ulcer. (**b**) When saturated the polyacrylate dressing is mechanically resistant enough to be removed as a whole, without leaving debris over the wound

enhance their elimination: this mechanism favours autolytic debridement (Fig. 41.6b). Resistance to traction is also observed. The clinical study EARTH, whose publication is in process, has confirmed advantage of these dressings in highly exudative, chronic wounds with non-inferiority to hydrofibres [11].

41.2.3.4 Dressings and Osmotic Pressure

Dressings Containing Salts

Salts with 20 % NaCl were added to the initial composition of hydrogels to form a hyperosmotic dressing. This formulation is more adapted to the necrotic plaques, which are black, hard and dry. The periwound has to be specifically checked when using these dressings.

Medical Honey Dressings

Sterile dressings are now available. They have physicochemical and microbiological properties that are comparable to the ancient description of honey when it was used empirically in ancient times [12].

Its high osmolarity favours wound exudation and mechanically induces the elimination of dead tissues and foreign bodies (including microorganisms). This mechanism induces a moist ambience that favours wound healing. This debridement is accompanied by an antibacterial effect on Gram-positive, Gram-negative and Gram-resistant bacteria, whatever their presentation, whether planktonic or biofilm. Honey is either attached to the gauze or present as a paste.

41.3 How to Use These Dressings

Hygiene should be respected during the dressing change. Whichever dressing is used, the protocol is important. The wound should be cleaned carefully (with water and soap), rinsed and dried. The dressing should then be applied respecting the mode of use specified by the manufacturer. Debridement, being an active stage, should be carried out rapidly; the frequency of the dressing change is usually every 2 days. The use of these debriding dressings does not prevent active debridement during the dressing change.

41.4 How to Choose the Dressing

This autolytic debridement is suitable for all types of wound, except for infected or heavily exudating wounds. It acts in a selective manner on the tissues. It is easy to use requiring no training before use, which makes them easily accessible to nurses. The cost is moderate compared with surgical debridement. Its main inconvenience is the slow process, but the absence of

pain and bleeding, preventing microtrauma on the surface of the wound, is an advantage.

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Surgical Debridement

42

Sadanori Akita

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42.1 Introduction

Surgical debridement in chronic wounds plays pivotal roles. Debridement is considered to fasten the wound healing rate and time and reduce the wound area by removing necrotic wound bed, wound edge tissue like hyperkeratotic epidermis, necrotic dermis, foreign debris, and bacterial pathogens, which bring inhibitory effects on wound healing [1]. There is marked cytoplasmic reduction and localization of epidermal growth factor receptor (EGFR) in the epidermis by microarray analysis, which indicates that the nonhealing keratinocytes have attenuated capacity to respond to EGF. Along with epidermal and keratinocyte inhibition, fibroblasts derived from nonhealing wounds demonstrate slower migration [2]. All these information with molecular analysis suggest that proper surgical debridement may be a reasonable solution to overcome this problem. Surgical debridement is considered one of the essential choices in accelerating and optimizing the wound healing; however, the evidences of this technique and rationale should be further discussed in each pathologic condition such as leg and diabetic foot ulcer.

As in all cases of wound healing, the patient should be nutritionally optimized prior to surgical debridement. If any of these criteria are not met, it is in the best interest of surgeon, physician, and patient to delay the wound closure until conditions are reaching more ideal. Both chronic and acute wounds can be improved by debridement.

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A wound that can produce granulation tissue in the absence of bacterial overload is generally ready for subsequent skin grafting, temporally converge with artificial dermis or flap if necessary. In wounds that fail to develop a bed of granulation tissue, bioactive dressings or topical growth factors may be employed.

42.2 Pathophysiology of the Underlying Diseases and Conditions in Surgical Debridement

42.2.1 Burns

In the deep burn (third-degree burn, penetrated through the total skin), it is almost necessary to use surgical debridement of the dead, eschar, and necrotic tissues. In general, the surgical debridement is proceeded until the fresh tissue and bleeding are observed. Thus, surgical debridement may be performed in a multiplane fashion. After complete and thorough surgical debridement, it usually requires the coverage with skin grafting, flap, or alternative bioengineered materials such as artificial dermis.

Skin grafting is most frequently used for skin coverage because it can cover the bigger postsurgically debrided wound beds and is easier to handle. Split-skin grafting is applied in less vascular beds since it has decreased metabolic demand compared to full-thickness grafts. These areas of tenuous vascularity include the paratenon (tendon sheath), periosteum (bone envelope), and perineurium (neural envelope).

Especially in cases of pediatric burn, it is crucial to perform adequate debridement and skin coverage (Fig. 42.1).

In the deep dermal burns (second-degree burn, partial-thickness burns), surgical debridement is normally used together with skin grafting, but controversy is continued. Some deep dermal burn wounds may heal within 2–3 weeks, and it may not require aggressive surgical debridement of such healing wounds; however, current standard techniques and decision making of the burn depth are largely dependent on the clinicians' naked eyes and it is often inaccurate even with experienced surgeons. A porcine contact deep dermal burn, sized 50 cm^2, which requires more than 3 weeks to heal with reepithelialization by proliferation and migration of keratinocytes from the skin appendages in the deep dermis is required and this is best illustrated burn model of either with or without surgical interventions [3].

42.2.2 High-Energy Wound

As often observed in the orthopedic subspecialty, high-energy open fracture accompanies deep infection due to severe damage and remnant necrotized tissues [4]. The negative pressure wound therapy (NPWT) group developed 5.4 % of delayed deep infection, while the control did developed 28 % of deep infection. A high-energy wound is prone to wound infection due to both acute and delayed insufficiency of blood supply and severe tissue damage.

Traumatic wounds are composed of both blunt and penetrating injuries. Usually blunt trauma causes larger area of tissue damage. Crush, degloving, and avulsion high-energy injuries are in this category and the extent of the wounds is not clear all the time. There are "zone of injuries" that may be different from acute diagnosis because aggressive debridement of non-/devitalized tissues, bacterial control, and fluid maintenance may change the wound evaluation.

In such case, temporal coverage with artificial dermis and subsequent judgment may enhance proper healing (Fig. 42.2).

42.2.3 Pressure Ulcer

Pressure ulcers are reflecting patients' systemic health: physical, nutritional, social, and psychological status. The complex pathophysiology suggests that several stepladders of the evolution are required. First, the sustained pressure force or shear force continued over soft tissue in between

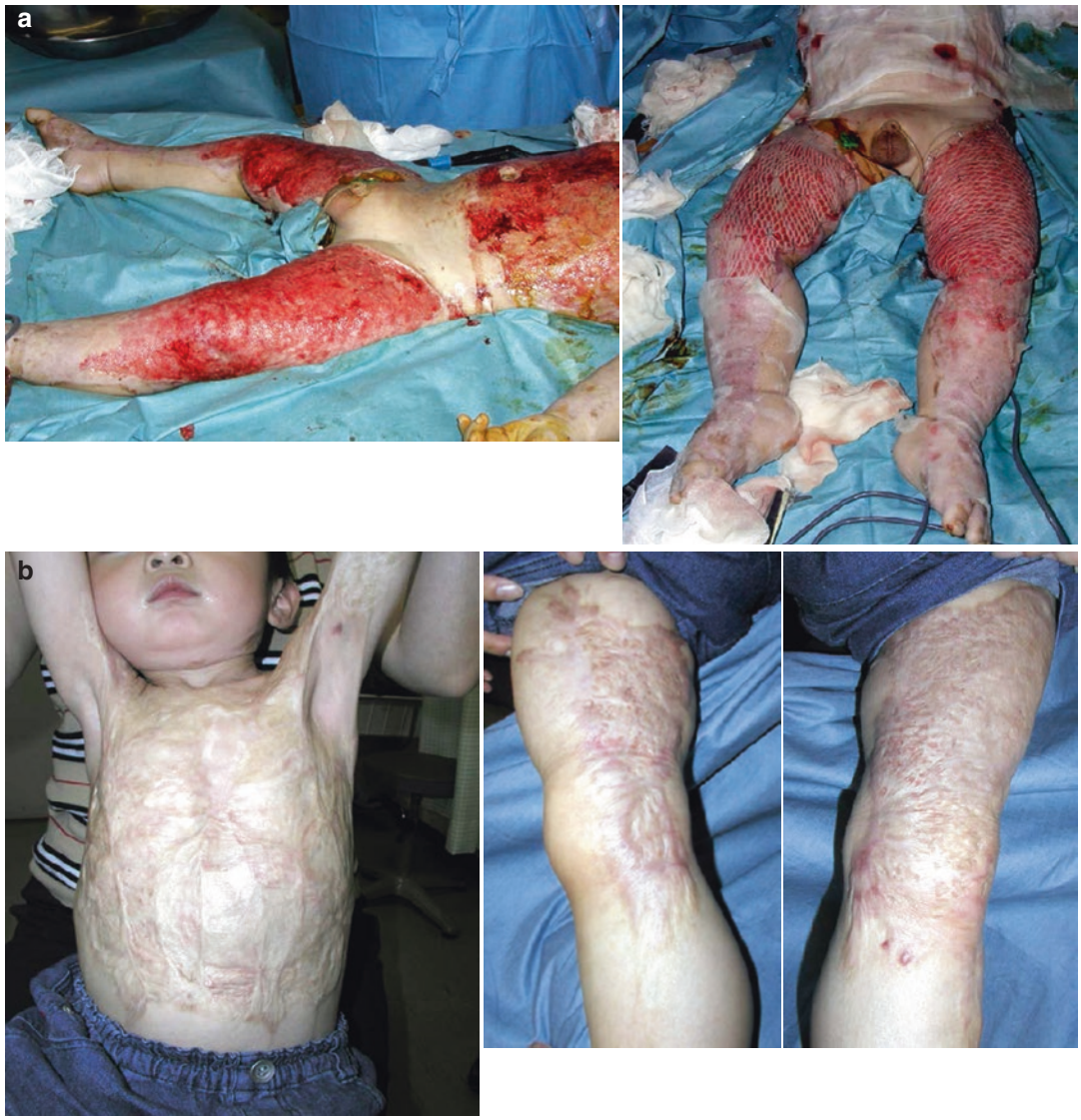

Fig. 42.1 (**a**) A 9-month-old boy, extensive scald burn, debridement and mesh skin grafting. (**b**) A 1.5 years after surgery

body mass, bony process, and surface. Capillary vessel flow reduced, and then blood vessel and lymphatic vessel occlusion and capillary thrombosis followed. Tissues are ischemic in this condition and reactively capillary permeability increased and the fluid is collected in the third space (extravascular space). Pressure-related intact discolored areas of the skin are described as a nonblanching erythema or suspected deep tissue injury. Prevalence of suspected deep tissue injury is more frequent than deeper pressure ulcers such as stage III or IV and increases recently than any other stages of the pressure ulcers [5]. Edematous tissues may result in necrosis, which is irreversible. Once tissue developed necrosis, precisely enough debridement is considered. The deep surgical intervention may start with when to evaluate the necrosis of tissue and how to remove effectively from the healthy surrounding tissue (Fig. 42.3).

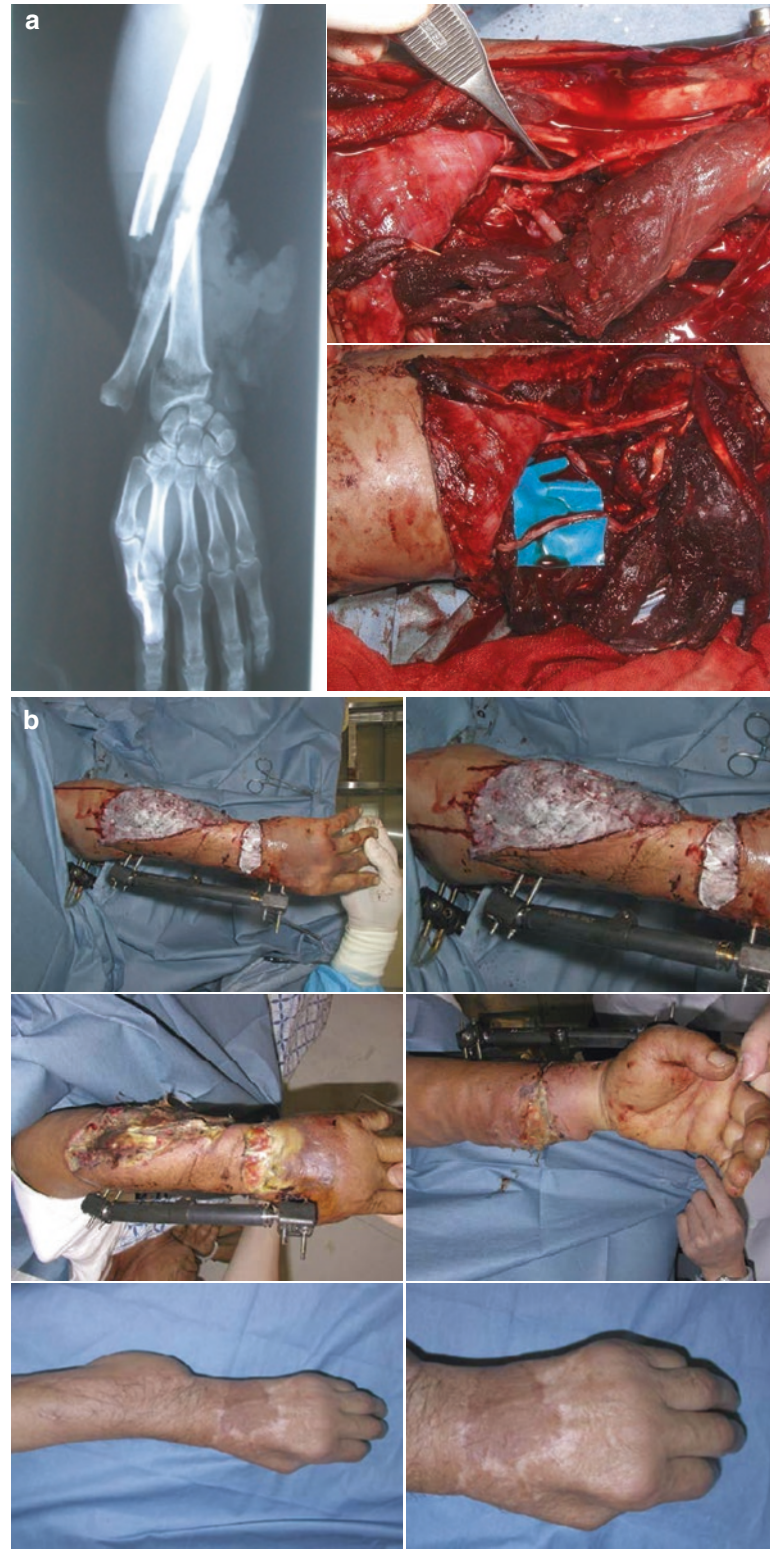

Fig. 42.2 (**a**) A 67-year-old man, high-energy injury, open fractures of the ulna and radius, externally intact but later found thrombus-formed radial artery (*right above*) and severed ulnar artery after microanastomosis. (**b**) External fixation with thorough debridement and artificial dermis (*top*), 10 days later, some tissues are still necrotic and further debridement and flap reconstruction (*middle*), 2 years after reconstruction (*bottom*)

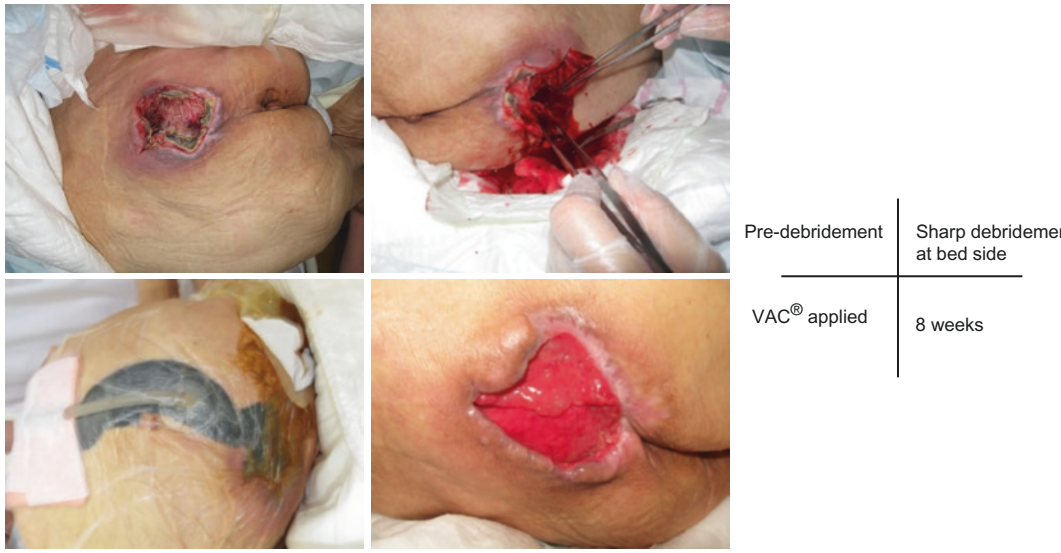

Fig. 42.3 A 87-year-old female, sacral pressure ulcer

42.2.4 Diabetic Foot Ulcer

The etiology of the diabetic foot composes of combined factors including peripheral vascular disease along with sensory, motor, and autonomic neuropathy [6]. Objective evaluation for ischemia and underlying bone infection is mandatory, and surgical debridement with proper wound dressings promotes moist wound together with appropriate off-loading. Surgical debridement is considered standard of care; in theory, it may convert a chronic nonhealing wound to acute wound healing environment through deleting the senescent or non-vital cells, enhancing the wound environment to better respond to local treatment [7]. Histologic assessment from biopsies of the edge of nonhealing chronic wound demonstrates hyperproliferative epidermis with hyper- and parakeratotic elements [2] largely due to repetitive stress in the sensory-disturbed foot. Even though the keratinocytes at the nonhealing edge are activated, wound healing is deteriorated. The keratinocytes at the edge of nonhealing wound demonstrate nuclear localization of β-catenin, which leads to the downstream activation of c-Myc and glucocorticoid pathway and results in inhibition of keratinocyte migration [8]. In microarray analysis of nonhealing ulcers, reduction and cytoplasmic localization of EGFR, which causes the attenuated responsiveness to EGF, are observed. Fibroblasts from the nonhealing wound edges show clear pathogenic phenotype and slower migration [2] (Fig. 42.4).

42.2.5 Leg Ulcer

Though venous ulcerations are always associated with venous ambulatory hypertension, the exact mechanism leading from pathological hemodynamics in venous circulation to the necrotic lesions in the skin still remains undiscovered. It appears that the underlying events are far more complex than expected. Many experiments have shown that the tissue injury in venous ulcer patients was induced by leukocytes. Leukocytes become entrapped in the microcirculation of the legs placed in a dependent position. Later, many authors confirmed that this process was exacerbated in patients with chronic venous insufficiency (CVI). It is speculated that this leukocyte trapping in patients with CVI is increased because in these patients the expression of adhesion molecules in the capillaries of the papillary dermis is increased. In patients with CVI, leukocytes enter into the microvascular regions that are affected by venous hypertension. As the distance over which leukocyte adhesion molecules can interact

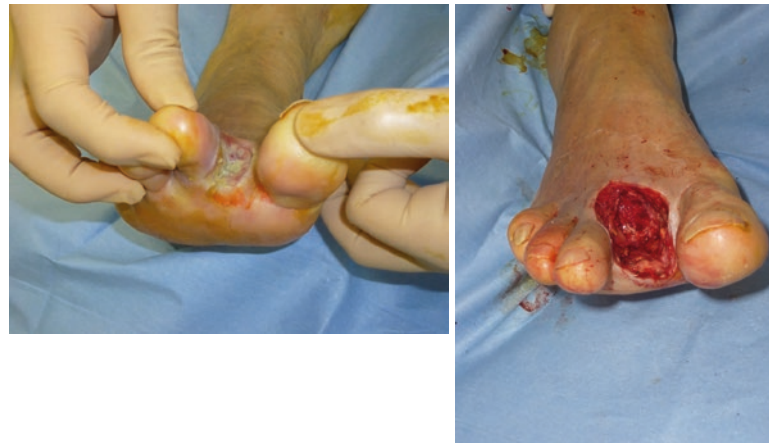

Fig. 42.4 A 72-year-old female, neuropathic diabetic foot ulcer in the first web (*left*), surgical debridement including removal of the 2nd toe (*right*)

with endothelial adhesion molecules is below 1 μm, the first step of leukocyte–endothelial interaction is the displacement of leukocytes by erythrocytes toward the endothelium. This process takes place preferentially in postcapillary venules. As circulating leukocytes encounter the endothelium, they may begin to form the so-called rolling–weak adhesive interactions mediated by L-selectin and P-selectin glycoprotein ligand-1 (PSGL-1) on leukocytes and P-selectin and E-selectin on endothelial cells. Hypertension in postcapillary venules has been demonstrated to enhance leukocyte rolling and adhesion. Rolling leukocytes can develop stationary adhesion. This firm adhesion is dependent on the formation of interactions between adhesion molecules CD11/CD18 on leukocytes and intercellular adhesion molecule-1 (ICAM-1) on endothelial cells. Once the leukocytes adhere firmly to the vascular wall, they can migrate into the extravascular space, become activated, and initiate inflammatory process in the skin and the surrounding tissues. VCAM-1 is another adhesion molecule that is involved in the process of leukocyte adhesion to the endothelium. The expression of VCAM-1 is enhanced in patients with CVI [9].

42.3 Choice of the Surgical Debridement

Wound bed preparation by sharp and mechanical debridement with surgical instruments is the most fundamental method for adequate wound healing management. It is able to reduce most selectively and effectively a bio-burden of a wound. The elimination necrotic tissue, which behaves as a substrate for proliferating bacteria that strives for the same nutrients and oxygen molecules essential for wound healing, is crucial for the promotion of the normal wound healing process of tissue. If the border of the normal healthy and devitalized skin is not determined clearly, tangential excision, starting at the center of the necrotic skin, should be considered until scattered bleeding is observed in the dermis. Bleeding is less indicative for subcutaneous tissue debridement because fat tissue is poorer in vascularity than skin is. Debridement until the shimmering yellowish fat tissue level should be performed. Hemostasis is usually achieved by clamping or compression. Scattered bleeding is well controlled with electrocautery. If bleeding from greater diameter vessels is observed, ligation should be attempted.

Non-vascularized fascia should be removed with a special caution to the neurovascular bundles in the superficial vicinity. The muscle, tendon, cartilage, and bone can be resected when apparent blood supply is not observed. In case of deep tissue injury in pressure ulcer, sharp penetration to the muscle and deeper tissue level is very helpful for determining the extension of the wounds.

Surgical equipment is composed of scalpel blades, pickups, electrocautery, scissors, curettes, rongeurs, elevators, chisels, osteotomes, saws, rasps, burrs, Harmonic scalpel, Cavitron

ultrasonic surgical aspirator (CUSA®), water-jet (hydro-jet) system (Versajet), radio-frequency energy system (Coblation® technology), and so on. Further details will be discussed in "Surgical Debrider" chapter.

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43 Stabilisation of Necrotic Tissue Using Cerium Nitrate Silver Sulfadiazine

Chloé Trial

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43.1 Introduction

The compound composed of the association of silver sulfadiazine and cerium nitrate is a topical cream classically used in third-degree burn management. Its antibacterial efficacy and its importance in necrotic skin stabilisation with the formation of a crust make it a serious option when surgical debridement cannot be realised.

A number of wounds, aside from burns, are candidates to debridement before healing by spontaneous intention or using a covering surgical technique. Their management needs a previous assessment of the wound and the patient capacity to heal after debridement. In some cases, these conditions are not met, and the surgical debridement is not possible. The notion of "surgical moment" is important when deciding the strategy [1, 2].

A major vascular insufficiency will contraindicate the surgical technique, the risk being the extension of the necrotic process, compared to a cancer wound where the risk of dissemination and contamination of the edges is present.

The use of this technique can be understood as an alternative to surgery or a waiting technique before a surgery.

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43.2 Classical Indication: Third-Degree Burns

This antibacterial cream, efficient on *Staphylococcus aureus* (85–93 %) and *Pseudomonas aeruginosa* (83–98 %) [3], is composed of silver sulfadiazine and cerium nitrate. It contributes to prevention of infection.

In third-degree burns [4], it acts by forming a protective crust is formed on the burn eschar. This crust has the capacity to reduce the risk of infection and to limit the penetration of germs in the separation fold; in fact there is no more separation fold as the bacteria cannot separate any more the living tissues from the dead ones.

The cream could reduce the fluid and caloric loss. By delaying the need for debridement, it allows to choose the surgical moment.

This drug is not considered as a medical device, but it has recognised indications mainly in the prevention and treatment of burn infection [5].

A comprehensive review of the literature realised in 2005 [6] could establish that the dressing could reduce the morbi-mortality in the treatment of severe burns by way of creating a crust over the burns and by drawing of the lipid-protein complex delivered by the burnt skin, responsible for a drastic local immunosuppression.

It has been demonstrated that Flammacerium® allowed to delay the surgical decision of excision and grafting without long-term consequences on the scar process [7].

A study published in 2007 on the mortality predictive markers concluded that the use of Flammacerium could be considered as a turning point in terms of morbi-mortality even if the large diversity of outcomes in severe burns did not allow to confirm the predominant role of this treatment in the improvement of the patients [8].

43.3 Contraindications and Undesired Effects

The only known contraindication is the use over more than 80 % of TBSA burns without checking the methaemoglobinaemia of the patient, some risks existing of oxygen transport impairment. Some allergies to sulfamides have been described in liver and renal insufficiencies [9] as well as in the pregnant female. The risk of maceration and mycosis when applied into the web spaces has also been described.

Some undesired effects have been reported in the studies: the sulfamide systemic passage may lead to leucopenia (rare) or methaemoglobinaemia [10–12] (in patients presenting large burn surfaces); these effects disappear immediately when the product application is stopped. Eczema has also been described (linked to an excipient like the cetylic alcohol or the propylene glycol) (less than 1 %) or granulomatous gangrene (only one case described in the literature [13]).

More than its antibacterial effects, the cerium will help to prevent septicaemia and limit the systemic inflammatory response by means of fixing the toxins. These effects have been noted a long time ago in patients presenting large surface burns [3, 14–18]; however, there are a few (or possibly none) literature concerning the use of this topic in other indications like necrotic wounds and cancer wounds.

43.4 Necrotic Skin Stabilisation: New Indications

43.4.1 The Arterial Leg Ulcer

When a necrotic skin is present over a wound, a debridement technique may be necessary to eliminate necrosed tissues, limit the risk of infection, improve the speed of healing and prevent complications [19, 20]. However it is not recommended to debride a severe arteriopathic limb, the risk being the extension of necrosis in case of arterial ulcers; the recommendations indicate that debridement is contraindicated when vascular compromise is probable [21–23] (Fig. 43.1).

Indeed the guidelines will specify that before any debridement of the distal limb segments, particularly below the knee, the patient should be evaluated on the arterial side, and an ABPI should be realised combined to an arterial echo Doppler [24].

The guidelines also mention that the debridement is contraindicated in the presence of a dry

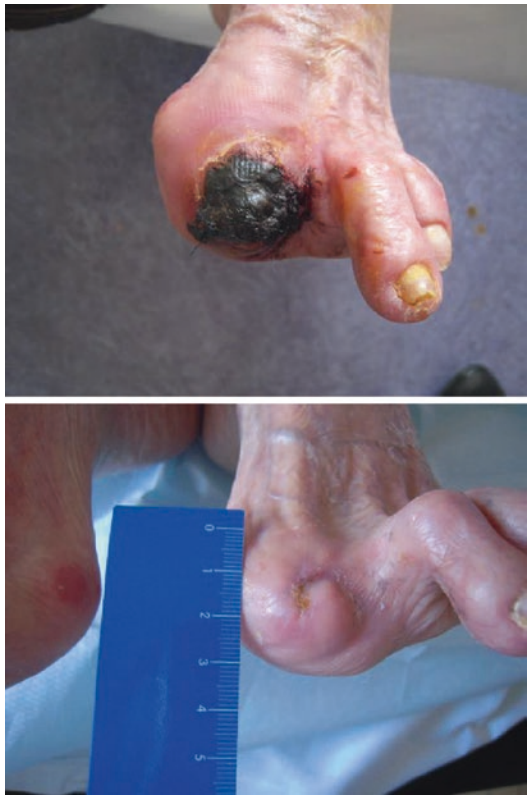

Fig. 43.1 Renecrosis after amputation on a compromised vascularisation. Result three month later after flammacerium

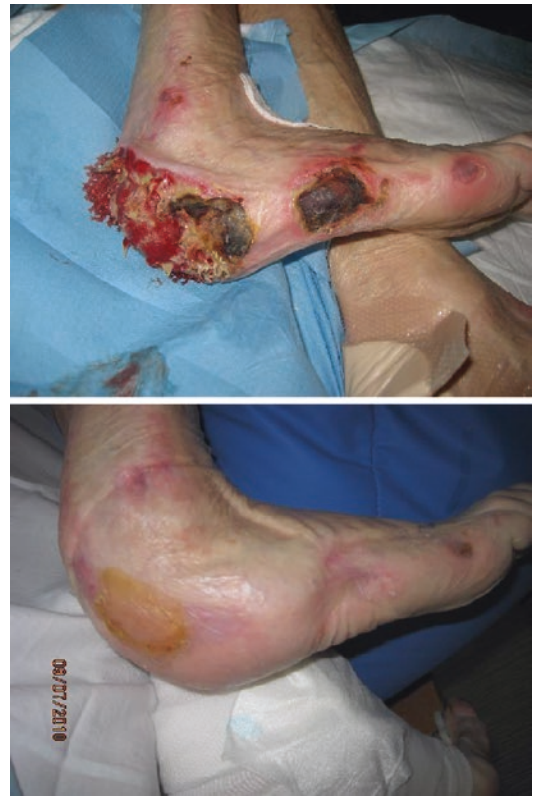

Fig. 43.2 Renecrosis of a pressure ulcer of the heel on a poorly nutrished arteriopathic patient. Results after 5 months of flammacerium

gangrene or an ischaemic dry wound until a complete vascular evaluation is realised [21] and when waiting for a revascularisation procedure, the necrosis should be maintained as dry as possible in order to prevent infection.

43.4.2 Heel Pressure Ulcer

Following recommendations, arteriopathy prevention should include the detection of the early signs of vascular insufficiency in patients presenting risks of pressure ulcers aged less than 65 years and systematically over 65 years [25] (Fig 43.2).

A cohort review driven by S.Meaume in 2007 established the links between arteriopathy and heel pressure ulcer [26]. Strategies for limiting the pressure over the heel are becoming insufficient to prevent PU due to the increase in rate of arteriopathy (most of the time unknown) in aged patients.

And reversely patients having heel PU may present associated risk factors like peripheral vascular disease leading to delayed wound healing [26, 27].

The vascular disease is a comorbidity associated with lower limb extremity PU [28], which should be recognised by analysis of the clinical evaluation, presence of pulses, time of capillary recolouration, oedema or mobility.

The realisation of an ABPI and its value >0.86 aim to eliminate an arterial disease in the PU pathogenesis [29].

Patients presenting an ABPI <0.8 should be considered as at risk of post heel PU debridement complication [30].

The procedure should be delayed if ABPI cannot be realised or if the values are low. A local strategy of stabilisation of the lesions should then

be proposed before a procedure of revascularisation has been realised, if possible. In a recent article on NPUAP recommendations, caution would be to maintain as long as the possible a dry eschar over the wound (mummification) to prevent infection and odour [31].

43.4.3 The Diabetic Foot

Diabetic foot ulcers are most of the time contemporary with severe arteriopathy, out of the possibility of revascularisation, with a high risk of necrosis and severe infection, rendering this situation at the highest risk of non-traumatic amputation [32–34]. The stabilisation of necrosis is needed to save the limb (Fig 43.3).

43.4.4 Cancer Wound

The debridement of a tumour wound is associated with a high risk of bleeding, pain and potentially a dissemination of cancerous cells. The wound bed is composed of necrotic and cancerous tissues due to the cancer, and it is impossible in most of the cases to remove all of them, healing being possible only if the carcinologic excision has been completed [35].

The necrosis is linked to the ischaemia of the tumour. It is so the local consequence and not the cause of a local disease (primitive cancer) or disseminated (skin metastasis) most of the time evolutive. The fact of leaving a wound covered with necrotic tissue is out of the normal recommended practice over a tumour wound, contrary to other types of chronic wounds. However the presence of prenecrotic tissue exposes the patient to infection, to the extension of the lesion and numerous inconveniences like heavy exudates, sévère odours linked to the présence of anaerobes [36] the management should then be aimed at complete healing but to clean the wound or to treat sequentially the symptoms like odours [37].

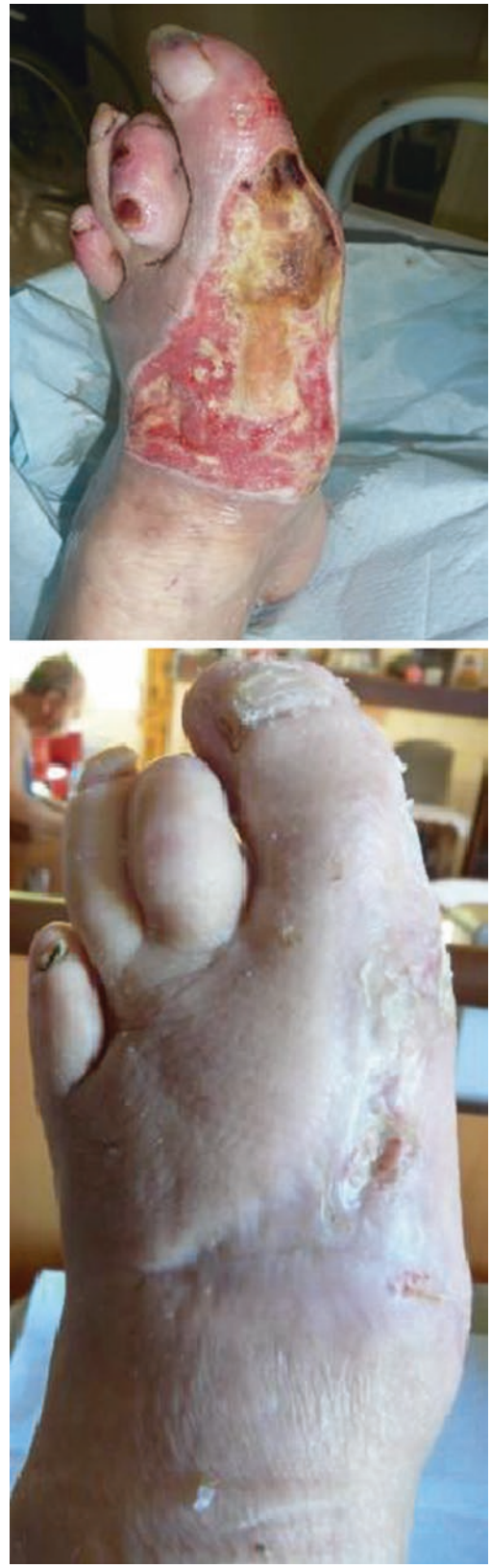

Fig. 43.3 Ischaemic diabetic foot ulcer

43.4.5 Osteoradionecrosis

One of the late complications of radiotherapy is skin radionecrosis. When standard care is not satisfactory (anti-inflammatory drugs, local care) [38] surgical excision and coverage surgical technique (skin grafting, flap) can be proposed. The complete excision is sometimes very difficult because of the anatomical structures involved and the poor quality of the covering skin. When the radionecrotic process involves bones in areas like the thorax or skull, it is sometimes impossible to extensively remove the bones and the underlying structures like the pleura or meningeal sheets. RMI or scanner is useful to check the bone involvement and the extent on the surrounding tissues. The decision to keep and stabilise the necrotic tissue using flmamacerium may be proposed when the skin is of poor quality.

43.4.6 Other Types of Wounds

Other situations may present contraindication to debridement like necrosis secondary to antimitotic toxic drugs (Avastin, corticosteroids) or other pathologies like sclerodermia where the pathology is linked to microvascular lesions. In these cases stopping the treatment or treating the cause may lead to wound healing. In some situations the treatment itself may lead to proper complications like the corticosteroid treatment (Figs. 43.4 and 43.5).

A waiting option should be opted aiming to gain time for better wound healing conditions, like the decrease of inflammation and pain which is always observed when using the Flammacerium cream.

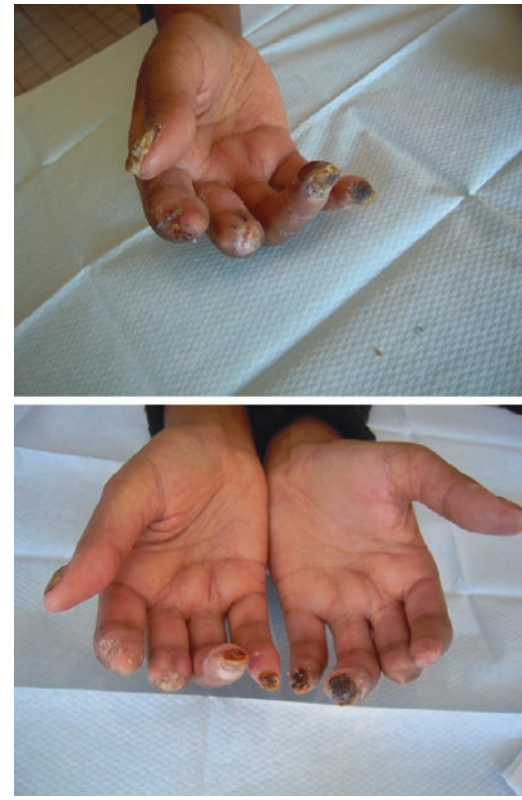

Fig. 43.4 Sclerodermia complications at the level of the distal end of the fingers: a perfect indication for flammacerium

43.5 Discussion and Perspectives

A retrospective study was realised and published in 2010 [39] to determine the efficacy of Flammacerium in stabilising the necrotic skin in chronic wounds. Ninety-nine patients were analysed, into which debridement was contraindicated (42 arterial leg ulcers, 30 PU, 5 cancer wounds, 10 trauma wounds and 12 others). This analysis showed a reduction in pain, exudates, odour and a positive effect on the quality of life, corresponding to an increase in patient comfort, social activity and psychological welfare. Moreover, when limiting the necrotic process, the use of the device extends the time of preparation of the surgical procedure.

The comfort offered by the Flammacerium, more than a protective crust, is due to the limitation of inflammation and pain, especially in arteriopathic patients, in osteoradionecrosis. The anticancer potential of the cerium compound still needs to be studied [4].

Conclusion

Flammacerium® has for a long time demonstrated its capacity in the prevention of severe infections in burns and its role in the inflammatory response. Its main advantages include its facility of application and use,

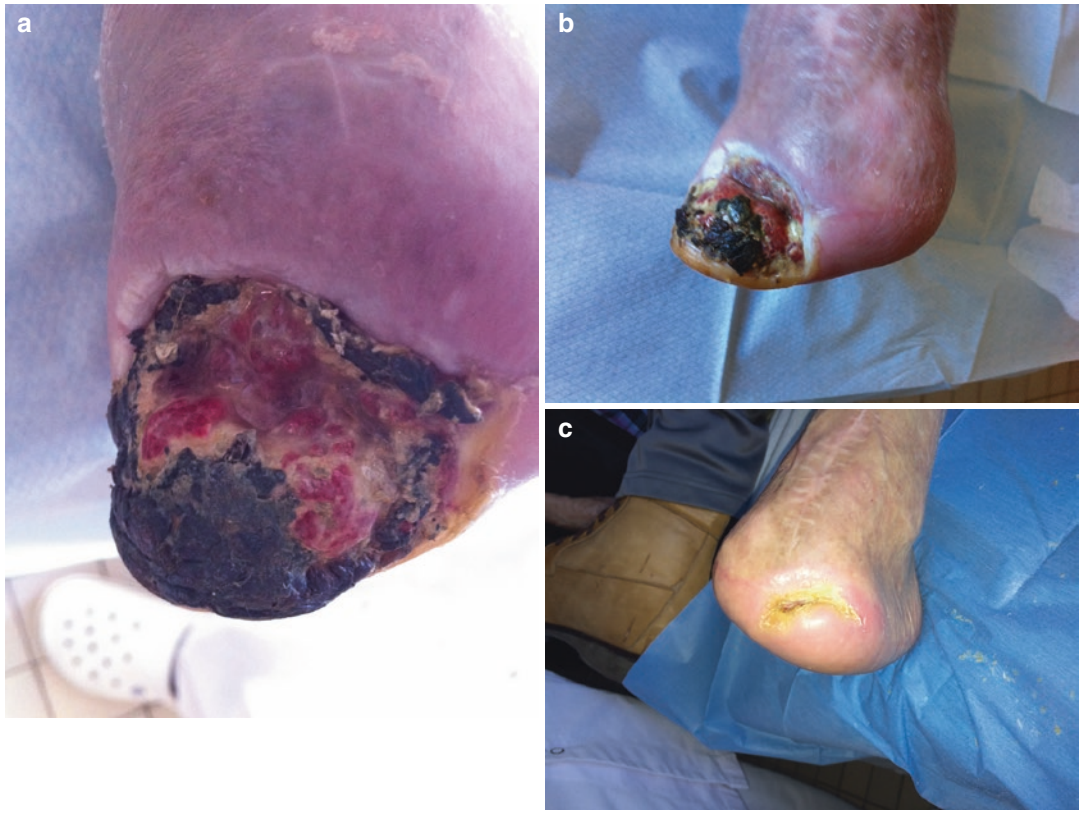

Fig. 43.5 Long term successful management of a necrotic foot using flmamacerium (one year of treatment)

allowing a mechanical barrier against infection. These properties may be extended to other pathologies like arteriopathies and all types of wounds where skin necrosis is present and debridement contraindicated.

Flammacerium has for a long period of time shown its efficacy in managing third degree burns. The main interest include an easy application, drastically abolishing pain at dressing change and pain induced by persistent inflammation. The obtention of a crust limit the possibility for germs to penetrate the wound, issuing to a better resistance to infection. The Flammacerium should certainly be proposed in other clinical indications, like chronic wounds when debridement is contraindicated. When a vascular impairment is in cause, the absence of elimination fold on the peripheral aspect of the wound covered with flammacerium is a benefit , limiting the surgical debridement, and allowing a revascularisation procedure in a non infected area. This product, even if debridement remains the first choice in most of the wounds, flammacerium may find a specific place in severely devascularised wounds.

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Honey Debridement

44

Vijay K. Shukla

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Honey has been used as nutrition and in different products for thousands of years. The earliest documented evidence of the medical use of honey for wounds is estimated to be from 2500 BC [1, 2]. A renewed interest has especially been developing the past 5–10 years where new products filled with honey have been introduced.

44.1 Mechanisms of Action

Honey is a complex natural substance that may contain 600 components [3]. As a highly concentrated sugar product with low moisture content and low acidity, it is likely to prevent growth of vegetative microbial cells. The antimicrobial activity may also be in certain honeys based on an enzyme (glucose oxidase), which converts glucose to hydrogen peroxide and gluconic acid [4, 5]. The antimicrobial effects also include MRSA from both infected and colonised wounds [1, 6]. The generation of peroxide subdivided the honey in peroxide or non-peroxide honey types.

While the broad spectrum of antimicrobial activity is well known, the mechanism of the debriding action of honey is almost unknown. Honey has not directly been reported to have a proteolytic activity [7], and it can therefore be assumed that honey removes attached slough, necrotic tissue and eschar by facilitating autolytic debridement. This can be achieved through the high sugar content of honey resulting in an osmotic withdrawal of fluid (lymph) from the

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wound bed, which is replaced from the underlining circulation. Honey has, however, demonstrated a faster rate of debridement than using hydrogels. This suggests that honey may have a stimulatory action on proteases in the wound bed [7]. The osmotic-induced outflow of lymph may also lead to extra oxygenation and an improved supply of nutrients to the growing cells, resulting in an improved healing of the wounds. Differences in the degree of activation of proteolysis between different types of honey may account for the differences in speed of debridement reported.

Another mechanism of action could relate to the effect honey has on biofilm production in the wound. Honey has been shown to prevent biofilm formation in vitro at concentrations below MIC [2] and interfere with the ability of biofilm-producing bacteria such as *P. aeruginosa* and *Salmonella enteritidis* to adhere to cell surfaces.

Honey has shown different clinical relevant effects like: clearance of infection, reduction of malodour, improved wound healing (granulation and epithelialisation), decreasing oedema and others. Many of these positive effects are based on a debriding effect of honey in wound bed.

44.2 Indications and Contraindications

In principle, all wounds with slough, necrotic tissue and eschar are indications for honey debridement. However, each case has to be evaluated for the most appropriate debridement type. In most cases where autolytic debridement is indicated, honey will be a faster type of debridement, especially if the wound is critically colonised or infected.

Honey is well accepted by most patients, and few contraindications have been identified [8]. Some patients can experience initial pain and stinging sensations and only a few patients severe pain. Mild analgesics may overcome this problem.

Allergy to honey is rare and anaphylaxis has until now not been seen [1].

Raw honeys should not be used because it contains yeasts and bacteria, especially spore-forming types [9]. In arterial leg ulcers and scleroderma, honey has shown less effect or even deteriorated the condition.

44.3 Honey in Clinical Practice

The evidence for the effect of honey debridement is weak. In an RCT on leg ulcers, the effect of manuka manual honey was compared to a hydrogel [10].

Honey's debriding effect has been shown in different types of acute wounds like postoperative and infected surgical wounds and Fournier gangrene but also in case of chronic ulcers like leg ulcers, pressure ulcers and diabetic foot ulcers. A range of products like dressing tubes containing honey e.g. Therahoney gel dressings, Medihoney dressings and Medihoney paste etc. are presently available. The amount of honey typically applied depends on the size of the wound and the amount of exudate produced by the wound. Differences in speed of debridement may also relate to differences in how well honey is kept in contact with the wound bed and to what degree it is diluted by exudates. In practice it means that the frequency of dressing changes that is needed depends on the amount of exudates produced by the wound. For these reasons it is important to follow the manufacturer's instructions carefully.

Conclusions

In spite of the relative weak evidence and insufficient RCTs, honey treatment has increasingly been popular in recent years. Different types of activities make honey a usable alternative for debridement of wounds. The major advances of honey are that it is a natural existing and readily available product, which has shown no development of resistance, is well accepted by the patients and is inexpensive.

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Recent Technologies in Necrosis Surgical Debridement

45

Luc Téot, Christian Herlin, and S. Fluieraru

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45.1 Introduction

This chapter describes the updated methods and respective indications of recent surgical debridement technologies applied for the management of necrotic tissues.

Their respective indications vary depending essentially on criteria like the hardness of the black cover and the extent of necrosis in depth and the extent of necrotic tissue over the skin.

Techniques using mechanical removal of a necrotic tissue have largely been diffused for many years; new techniques based on electrochemical removal of tissues using plasma technologies are now available and promising. Most of these technologies are not evidence based but are strongly defended by surgeons who aggressively clean the wound before getting a prepared wound bed prior to realising a skin graft or a flap. A rapid and complete removal of undesired tissues from the wound, containing germs and biofilms, is the aim of any method of debridement [1, 2] (Fig. 45.1). Successive technologies were proposed, from basic techniques using a scalpel to electrocautery, ultrasounds, lasers, high-power jets and more recently plasma-based debriders.

In pressure ulcers the necrotic block offers simpler debridement strategies than when necrosis is spread all over the wound surface in an uneven manner.

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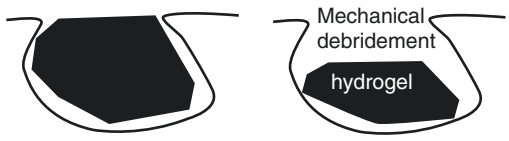

Fig. 45.1 Leg and abdominal involvement with ulceration and livedoid aspect

45.2 Description of Recently Developed Debridement Technologies

Blades and scissors were used by generations of surgeons, debridement being quickly and safely obtained within a short period of time. This technique used in trauma wounds is well defined, and, apart from necrosis, sloughy and fibrinous tissues should be removed, in order to minimise devascularisation of the surrounding tissues.

1. JAC™ (Medaxis) [3]
   - The system of wound rinsing uses a waterjet with a pressure reaching 20 bars adjustable with a control valve.
   - The system is filled with a 500 ml saline put under pressure, thanks to a gas cartouche. A protective film is placed around the wound and a single-use handpiece is connected to the system. Its use is recommended over the acute and chronic wounds. The JAC technique allows to reduce the bacterial burden and local infection, to reduce odour of malodorous wounds and to access difficult-to-reach areas and to stimulate the wound bed.
2. Debritom™ (Medaxis) (Fig. 45.2)
   - Microjet high-pressure technology (from 0 to 1,000 bars) for cleansing and debriding wounds.
   - Stationary and mobile use composed of a liquid pump aspirating the sterile water (NaCl 0.9 %) and drives it through a metallic high-pressure tube to a handpiece (foot pedal command).
   - The liquid is expulsed by the hose from the handpiece (single use). Protective tents are needed in order to protect the practitioner and the surrounding from any projections coming from the wound. The jet allows to clean, cut and debride with an adaptable pressure and stimulates the wound by microbleeding mechanical stimulation.

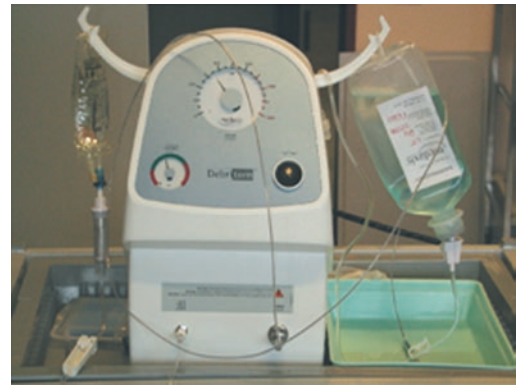

Fig. 45.2 Debritom™: the compressor is connected to a hand piece projecting high speed water jet over the wound

The Debritom offers a high-power jet but needs protection to prevent projections.

3. Versajet™ (Smith & Nephew)
   - High-pressure hydrosurgery system of lavage by impulsions incrementing the debriding effect combined to an aspiration system linked to the Venturi effect, may reach 850 bars [4].
   - Stationary and mobile use, the system includes an electrical power pad (pedal commanded) with a connection for saline perfusion and a single-use hose for saline perfusion connected to a trash collector to aspirate the debrided tissues [5, 6].
   - Allows to undermine, cut and excise, thanks to the high-speed liquid flow at the window level, with three different sizes (15°, 14 mm; 45°, 14 mm; 45°, 8 mm) (Fig. 45.3a, b, c).

(a) Electrical burns: the extent in depth cannot be determined precisely.
(b) Using Versajet, hypodense necrotic structures will be destroyed and removed.
(c) Debridement completed: all remaining structures are living and ready to be covered using skin grafting.

4. WoundWand™ (ArthroCare)
   - Electrochemically induced plasma creating an instant necrosis of tissues around the

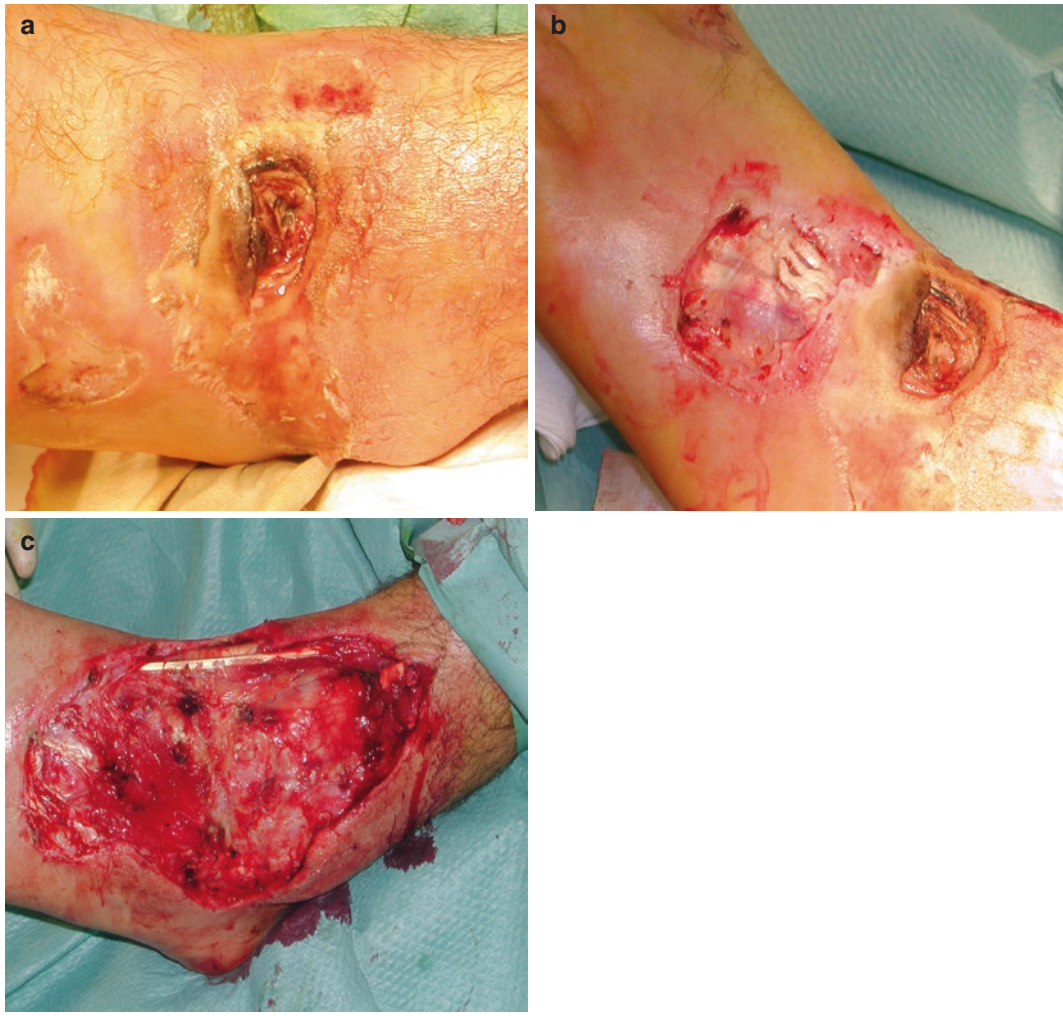

Fig. 45.3 (**a**) Electrical burns of the dorsal aspect of the foot. Extension of post burns necrotic tissue is hard to underline. (**b**) Starting debridement using Versajet™ exposes necrotic tendons. (**c**) Versajet™ has debrided step by step all devascularised structures, leaving the wound prepared for a skin graft

electrodes, with reduced thermal damages (45° max).

- Stationary use, the system includes a CCD machine to create electrochemical signals, with a connection to saline perfusion and a single-use hose for saline perfusion connected to a trash collector to aspirate the debrided tissues.
- Allows to eliminate locally undesired tissues with a minimum damage, to prevent excessive mechanical tissue disruption. A coagulation mode allows to insure local haemostasis when needed.

A plasma is created at the tip of the electrode, destroying tissues without thermal effect and inducing an antibacterial remanent effect [7].

Each passage removes a defined adaptable depth of tissue (Figs. 45.4 and 45.5).

45.3 Clinical Indications

The necrotic tissue density and the extent over the wound (uniform, sprayed, patches) and in the depth should be determined before using new expansive debridement techniques.

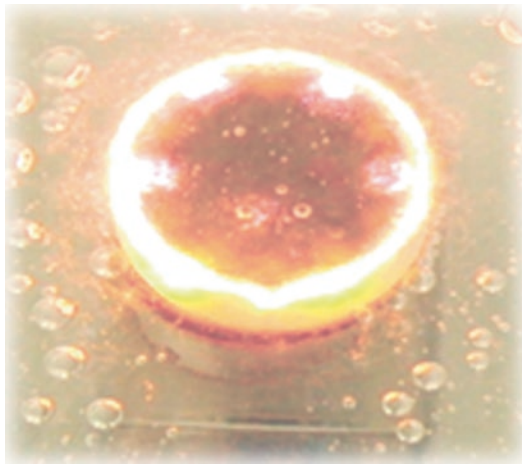

Fig. 45.4 Electrico-chemical light observed at the tip of the Woundwand™ handpiece

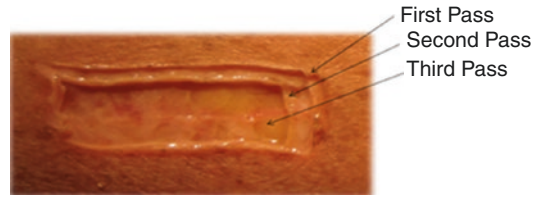

Fig. 45.5 Diagram showing the successive passages of the Woundwand™ over a pig skin

A necrotic tissue may also present different hardness, imposing different strategies in terms of management. In excessive bleeding observed in wound infection or in a patient under anticoagulation, haemorrhagic techniques should be limited. The need for saving blood during debridement is another important factor, having progressively restricted the use of sharp blade debridement to small wounds, preferring the use of Versajet™ or Coblation™ when extensive debridement is needed over bleeding anatomical structures.

The interest of Versajet™ has been described in cavities and uneven wounds and the potential bacteriological long-term removal of germs when using the plasma technique. Debridement should minimise the wound edge devascularisation and reduce the potential of renecrosis to minimum, using a good preoperative vascular check-up. Limits and contraindications of debridement are the poorly vascularised tissues where smooth nonaggressive technologies should be preferred.

45.3.1 Extent of Necrosis over the Wound Surface

The extent of a necrotic tissue may be presented under different aspects:

- Necrotic block: may form deep amount of necrotic tissues, extending in depth, with two separate parts, the superficial one, which looks hard and attached to the edges of the wound, and the deep one, which looks less dense, formed by sloughy tissue. Encountered mainly in pressure ulcer but also after extensive hematomas of the leg
- Superficial uneven necrotic area: necrotic angiodermatitis may be covered with this type of necrotic tissue, unevenly spread over the ulcer surface, burns

45.3.2 Necrotic Tissues Vary Depending on the Aetiopathogeny of the Wound

- Burns

Standard mechanical debridement using knives and/or scalpel is mostly used in this indication. However, local haemorrhage is the limiting factor, especially in extensive second-degree burns when tangential excision issues to excessive bleeding.

The extent of the necrotic or sloughy tissues and the need to debride large areas should be analysed before surgery, limiting the choice of the debriding operative technique. Time for surgical procedure and precise analysis of blood loss should help to choose the adapted technology. Most of the authors would agree not to exceed 10–15 % of the body surface excision, plus harvesting the skin surface for skin grafts when necessary.

In electrical burns, the extent of necrosis remains tricky to determine in the early stage as the complete necrosis will take two weeks before being obvious over the different impacted areas.

- Pressure ulcer cavity wounds

Cavity wounds are difficult to debride, essentially at the cover level of undermined areas. This part had to be surgically removed to increase the granulation tissue formation coming from the lateral aspects and the deep part of the wound.

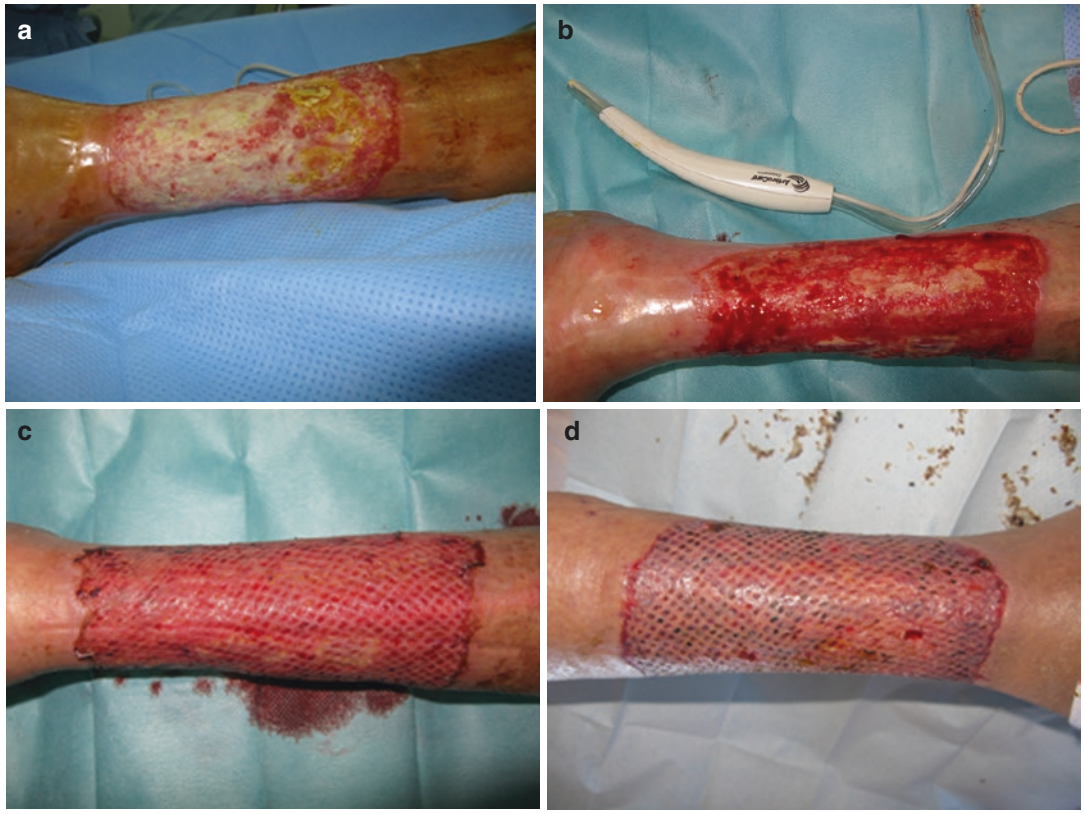

Fig. 45.6 (**a**) Chronic venous leg ulcer with extensive biofilm. (**b**) Wound bed preparation using Woundwand™. (**c** and **d**) Skin grafting evolution one week after surgery

Using new hydrojets, it is possible to get access to the whole cavity, opening the cover enough to allow to insert a tool inside the cavity and properly treat the edges.

- Necrotising fasciitis

The necrotic tissue is spread on an uneven manner, due to the heterogeneity of toxin repartition along the different tissues. The intensity of necrotic capacity is depending on the virulence of the germ.

45.4 Respective Indications of New Technologies

The JAC offers an adjunct to cleansing at home. This ambulatory technique has been proposed as capable of debriding small amount of tissues without the need for anaesthesia. The induced pain can easily be managed in the community or at home with simple measures.

Versajet offers the capacity of debriding localised hard necrotic tissue with a good precision, even if the window remains limited, creating a difficulty to uniformise the wound bed.

Coblation offers a debridement without lesion induced by thermal injury (functions at a t° of 45 °C), leading to a germ-free wound bed well prepared for skin grafting. The action of plasma on germs has been demonstrated by Davis et al. Practicability of the device is easy to learn, and no water projection is observed (Fig. 45.6).

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Regulations for Conservative Sharp Debridement for Nurses in the USA

46

Nancy Tomaselli

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46.1 Introduction

Sharp debridement can be performed either by conservative sharp wound debridement (CSWD) or by surgical sharp debridement. Conservative sharp wound debridement (CSWD) is defined as the removal of loosely adherent devitalized tissue with a scalpel or scissors, above the level of viable tissue, and is not likely to result in blood loss. It is different from sharp debridement performed by physicians and is performed by other health-care professionals. CSWD is not as aggressive as debridement performed by physicians who remove devitalized tissue down to a viable, bleeding wound bed. Any method of surgical debridement requires specially trained, competent, qualified health-care professionals [1, 2].

46.2 Regulations in the USA for Conservative Sharp Wound Debridement

In the USA, regulations for sharp debridement vary from state to state, and each state's Nurse Practice Act or Board of Nursing dictates specific regulations for this procedure.

The following information is a state-by-state summary and can be used as a guide.

Note: Regulations may change, so the nurse who may want to practice sharp wound debridement is responsible for contacting the individual state practice act prior to performing this procedure.

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A list of contact information for each state board can be found at the following link: www.allnursingschools.com/faqs/boards.php [3]

Alaska

The Nursing board determined that it is an acceptable practice only for the CETN/CWOCN to perform sharp debridement. They must have a physician's order and a clear policy and procedure at their place of employment.

RNs that do not meet above criteria and LPNs may not perform this procedure.

Alabama, Arizona, Arkansas, California, Colorado, Connecticut, Delaware, Florida, Iowa, Maine, Maryland, Mississippi, Montana, Nevada, New Hampshire, New York, North Dakota, Oregon, South Carolina, Vermont, Wisconsin, and Wyoming

RNs can perform sharp debridement as long as they have taken a course and had supervised clinical practice. The facility policy and procedures must reflect the RN's capacity to perform this skill.

LPNs may not perform this procedure.

District of Columbia

RN and LPNs may not perform CSWD. APRNs may perform this procedure.

Georgia, Illinois, and Massachusetts

RNs can perform CSWD as long as they have taken a course and had supervised clinical practice. The facility policy and procedures must reflect the RN's capacity to perform this skill.

Hawaii

Per the state board, there is no definitive statement allowing or prohibiting RNs and LVNs from performing CSWD. There is no established decision-making tree to follow.

Idaho

Per the state board, RNs must use the decision-making tree for CSWD. LPNs may perform this procedure if delegated by an RN, and the RN deems they are competent. The board has not made a definitive decision on this matter.

LPNs may not perform this procedure.

Indiana

The practice act does not address CSWD, and the board has not ruled on this procedure. The RN/LPN must check with facility/institution's policy and procedure and/or an attorney regarding this matter.

Kansas, Rhode Island, Tennessee

RNs and LPNs may not perform CSWD.

Kentucky, North Carolina, South Dakota, Texas, Virginia

RNs and LPNs can perform CSWD as long as they have taken a course and had supervised clinical practice. The facility policy and procedures must reflect the RN's and LPN's capacity to perform this skill.

Louisiana

RNs can perform CSWD as long as they have taken a course and had supervised clinical practice. They must also have validation of technical skills on an annual basis. The facility policy and procedures must reflect the RN's capacity to perform this skill.

LPNs may not perform this procedure.

Michigan

RNs and LPNs can perform CSWD as long as they have had education and training and work under the supervision of a physician. The facility policy and procedures must reflect the RN's and LPN's capacity to perform this skill.

Minnesota

RNs can perform CSWD as long as they have taken a course and had supervised clinical practice. The facility policy and procedures must reflect the RN's capacity to perform this skill.

LPNs may perform CSWD if competent (additional education and clinical practice), and the RN delegates the task to the LPN. Facility policy and procedures should reflect the LPN's capacity to perform this skill.

Missouri

RNs can perform CSWD as long as they have taken a course and had supervised clinical practice.

The facility policy and procedures must reflect the RN's capacity to perform this skill.

The board has not made a practice decision for LPNs and advises use of a decision-making tree.

Nebraska

RNs and LPNs can perform CSWD as long as they have taken a course and had supervised clinical practice. The facility policy and procedures must reflect the RN's and LPN's capacity to perform this skill. LPNs must work under the direct supervision of the RN.

New Jersey

The state board has made no specific ruling regarding CSWD. RNs and LPNs must use the decision-making model algorithm.

New Mexico

RNs and LPNs can perform CSWD as long as they have taken a course and had supervised clinical practice. The facility policy and procedures must reflect the RN's and LPN's capacity to perform this skill.

Ohio

RNs can perform CSWD as long as they have taken a course and had supervised clinical practice. The facility policy and procedures must reflect the RN's capacity to perform this skill.

LPNs can also perform this procedure, if they meet the same criteria as RNs.

Oklahoma

RNs can perform CSWD as long as they have taken a course and had supervised clinical practice. The facility policy and procedures must reflect the RN's capacity to perform this skill.

LPNs may perform this procedure under the direct supervision of an RN or physician as well as meeting the RN criteria.

Pennsylvania

RNs can perform CSWD as long as they have taken a course and had supervised clinical practice. The facility policy and procedures must reflect the RN's capacity to perform this skill.

The LPN practice act has no definitive statement, and no ruling has been made by the board.

If the LPN chooses to engage in this skill, they should at least meet the criteria of an RN.

Utah

RNs and LPNs may only perform CSWD under the direct and visual supervision of a physician who is delegating the task.

Washington

RNs can perform CSWD as long as they have taken a course and had supervised clinical practice. The facility policy and procedures must reflect the RN's capacity to perform this skill.

The LPN practice act does not address this skill. If the LPN chooses to perform this procedure, they should meet the same criteria as an RN and work under supervision of an RN or MD.

West Virginia

The board has not made a definitive statement regarding RNs or LPNs performing CSWD. They recommend using the decision-making model.

The above state-by-state information was compiled in 2006 by Bill Richlen, PT, WCC, CWS, from Infinitus, LLC. Used with permission from Bill Richlen [4].

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Necrotic Burns

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Necrosis in Burns: Pathophysiology, Etiology, and Prevention

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47.1 Pathophysiology of Burns with Respect to Necrosis

Burn wound progression refers to the phenomenon of continued tissue necrosis in the zone of stasis after termination of the initial thermal or toxic exposition. It includes partial or full-thickness dermal burns.

The basis of necrosis in burns has been introduced in 1953, when Jackson described the three concentric zones of a burn wound as the basis of research on burn wound necrosis and progression: the central zone of coagulation, the intermediate zone of stasis, and the outer zone of hyperemia [1]. The zone of coagulation received the greatest damage due to direct thermal or toxic exposition and has been characterized by irreversible necrosis with complete destruction of the subdermal capillary network. In 1969, the zone of stasis was observed to have the ability to recover with bleeding from a small number of arterioles [2]. Subsequently, investigations focused on the questions what factors may contribute to or even ameliorate the progression of tissue destruction in the zone of stasis [3]. The answer to this question was expected to lead to interventional measures with high clinical significance. It was expected that improved perfusion in the zone of stasis may influence the depth and total body surface area determining both mortality and morbidity, rates of delayed wound healing, hypertrophic scarring, dyspigmentation, contractures, infection, and shock [3–5].

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A cascade of various endogenous factors triggers the local pathophysiologic process of burn wound progression [3]. The continuous release of cytotoxic mediators and free radicals maintains inflammation. In addition, an increase in secretion of neutrophils has been demonstrated which leads to clotting of obliterated dermal venules. The decrease of venous drainage leads to increased vascular permeability and interstitial hydrostatic pressure. Capillary leakage contributes to augmented interstitial fluid retention and hydrostatic pressure and thus leads to edema with potential ischemia. In accordance, hypercoagulability and venous thrombosis impair blood flow, and hypoxia induced mediators lead to endothelial cell damage with compromised arteriole and capillary circulation. Singh et al. reviewed all peer-reviewed, original, and review articles published in English-language literature relevant to the topic of burn wound conversion and furthermore described infection, tissue desiccation, circumferential eschar, metabolic derangements, advanced age, and poor general health as further factors with influence on necrosis [6].

Various authors have approached the mechanisms of burn wound progression and necrosis in order to investigate strategies and agents which aim to reduce inflammation, capillary leakage, edema, hypercoagulability, and venous thrombosis in acute burns [7–10].

Nevertheless, the clinical benefit and applicability of the results still raise controversial discussions. Further research is necessary to improve the understanding of all interrelated mechanisms and the convergence of burn wound progression in order to limit cell apoptosis as the basis of burn necrosis (Fig. 47.1) [3].

47.2 Apoptosis and Oncosis in Burn Wounds

Apoptotic dermal cells are found in normal, unburned skin, in superficial partial-thickness and in full-thickness burns. Nevertheless, a higher rate is found in deep partial-thickness burns than in normal skin, superficial partial-thickness burns, and full-thickness burns [9, 11]. These results suggest that apoptosis has an impact on burn wound progression of deep partial-thickness wounds. Apoptosis has been shown to continue for at least 23 days after the initial burn injury which represents the window for pharmacologic intervention [12]. Apoptotic rates are mainly influenced by the local conditions in the zone of stasis.

Further investigation by Singer et al. showed that both apoptosis and oncosis to cell death in the zone of stasis play a role in burn wound necrosis and progression [13]. In order to approach apoptosis in the zone of stasis, Giles et al. developed a pharmaceutical agent to block the mechanism of apoptosis before irreversible loss of cell viability [14]. Giles et al. investigated inhibition of c-Jun, a transcription factor involved in multiple cell processes, including inflammation, proliferation, and apoptosis in an animal model. They found that direct application of the c-Jun inhibitor to full-thickness burn wounds in mice resulted in improved reepithelialization and a reduction in apoptotic cells at 24 h after burn injury [14].

47.3 Inflammation as a Key Step in Burns

Inflammation has an important key role in promoting local wound healing. Nevertheless, depending on the extent, it may constrain the healing process. Positive effects of local inflammation include local clearance of cellular fragments and local immunoactivity against microbial agents [15]. In contrast, prolonged inflammation mediated by neutrophils and macrophages release may increase secretion of proinflammatory cytokines. This secretory imbalance may trigger collagen degradation and keratinocyte cell apoptosis, adherence of neutrophils to the venular endothelium, production of oxygen-derived free radicals with disruption of plasma membranes, DNA cross-links and strand breaks, and peptide fragmentation [3, 16]. Further regulatory steps which keep up an imbalanced inflammation are delayed neutrophil apoptosis, local neutrophil aggregation, venule

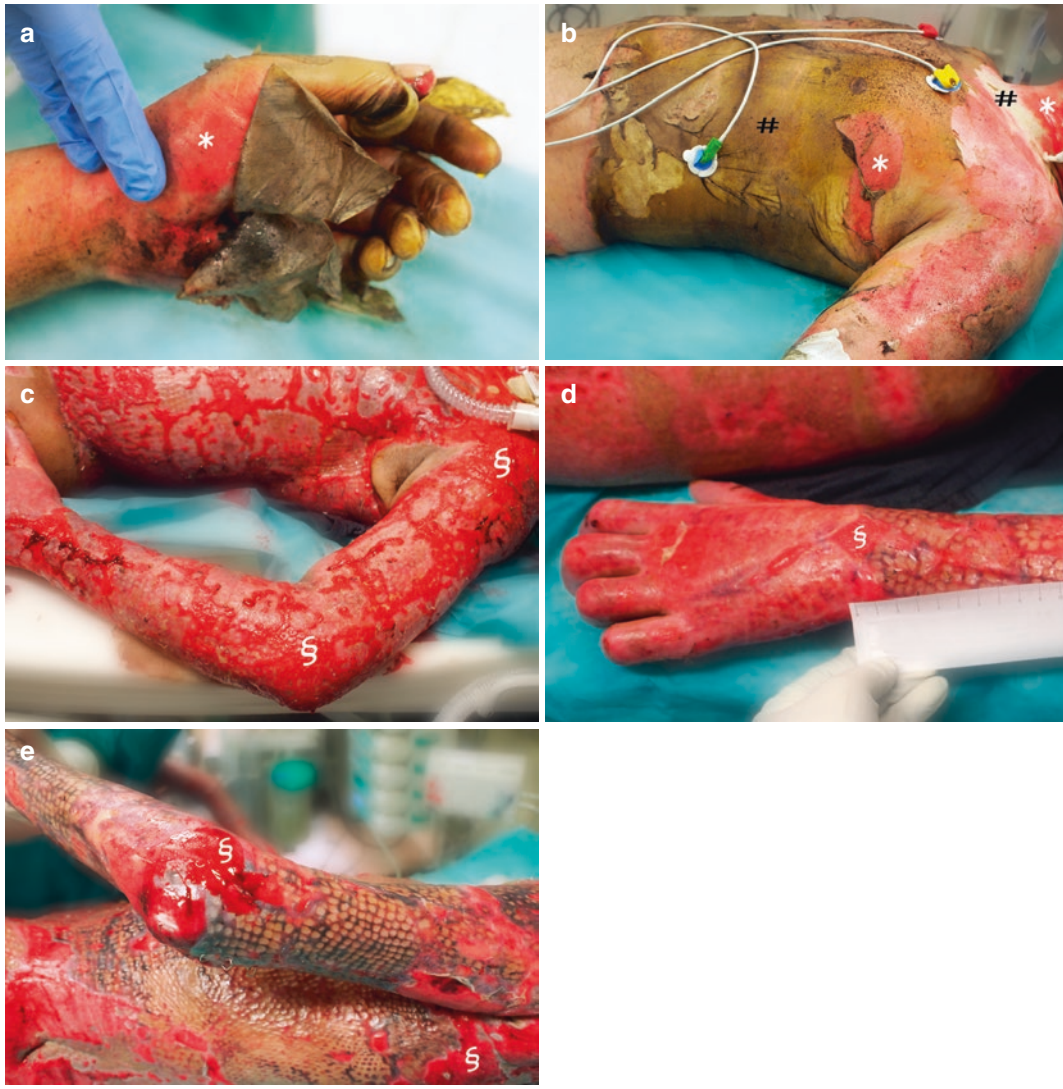

Fig. 47.1 Origination of burn necrosis. The acute trauma induced by heat or chemical toxins exposition leads to partial (*) dermal primary necrosis with necrotic epidermis layer (**a**). In case of partial necrosis (*), reduction of inflammation can limit full thickness necrosis (#) (**b**). If inflammation continues, secondary necrosis with necessity of split or full-thickness skin transplantation occurs. In case of tertiary necrosis of burns, transplant loss may lead to secondary healing (§) or requires retransplantation (**c**–**e**)

occlusion, and cytokine production. Wound infection has a major impact on inflammation due to endotoxin production and proteases release that destroy tissue but also perpetuate the prolonged inflammatory response [3, 16, 17].

Deep partial thickness burns are subject to these pathophysiological changes surrounding the primary zone of thermally induced coagulation, with potential expansion within 48 h postburn. From the clinical point of view, intervention by pharmacological interaction aims at reducing the need for surgical debridement and the area requiring skin grafting by keeping a balanced inflammation level, but potential systemic reactions have to be taken into consideration with limitation of application.

47.4 How to Prevent Necrotic Burns

In this chapter, primary necrosis is defined as resulting initially after the thermal or chemical exposition and is irreversible, while secondary necrosis results from conversion of the zone of stasis due to insufficient perfusion. Tertiary necrosis is defined as necrosis after transplantation with need for revision or secondary healing.

47.4.1 Primary Necrosis

The emergency preclinical and clinical therapy may have an early influence on burn wound progression and necrosis. With reference to the national and international guidelines, the early steps include stopping the burn, cooling the wound with care, appropriate dressings, and goal directed, individual burn wound care [18].

At the site of the accident, the burning process has to be stopped or rather extinguished. All burnt clothing and any jewelry should be removed unless it is merged with the patient (e.g., polyvinyl chloride, polyester). There are controversial discussions about cooling of burns, especially regarding the correct time, temperature, timeframe, and medium. Many patients are mistakenly cooled down and arrive with mild to severe hypothermia. Cooling has a high analgesic potency and can reduce area of the zone of stasis where capillary perfusion is reduced when applied correctly. If the burnt body surface area is small (<10 %), cooling of the burn should be performed [19]. Medium tempered running tap water (approximately 15–20 °C) with a maximum cooling time of 15 min is recommended, while specially manufactured burn dressings (Water–Gel®, Burn–Pack®) have raised concerns regarding hypothermia following application due to handling errors. Dressings are important for pain management and to prevent the burnt area from contamination as a potential source of infection and inflammation. Dressings also play a role for thermal balance. Customary metal films (e.g., Metalline®) can reduce the risk of undercooling as a further external measure with impact on burn progression [20, 21].

Goal directed, individual burn wound care includes specialist treatments, regular antiseptic dressing with appropriate wound climate, balanced fluid supply to prevent unnecessary edema, and analgesia in order to reduce pain-associated vasoactive mediator release.

47.4.2 Secondary Necrosis

Although research is going on, current milestones of treatment include adequate fluid resuscitation, nutritional support, and local wound care, with focus on topical antimicrobial agents and dressings. With potential therapeutic application, Resolvins, a class of endogenous mediators derived from omega-3 polyunsaturated fatty acids, has been shown to regulate the resolution of inflammation in an animal model. By preserving the microvascular network, the agent was shown to enhance neutrophil access to the dermis, but prevented neutrophil-mediated damage [8].

Ipaktchi et al. hypothesized that topical attenuation of burn wound inflammatory signaling will control the dermal inflammatory source, attenuate SIRS, and reduce acute lung injury. They applied a topical p38 mitogen-activated protein kinases (MAPK) inhibitor to wounds. Topical p38 MAPK inhibition resulted in significantly less pulmonary inflammatory response by reducing pulmonary neutrophil sequestration, pulmonary cytokine expression, and a significant reduction in pulmonary microvascular injury and edema formation. They concluded that there is a strong interaction between dermal inflammation and systemic inflammatory response; thus attenuating local inflammatory signaling appears effective in reducing SIRS and subsequent systemic complications after burn injury [22].

47.4.3 Tertiary Necrosis

In order to prevent tertiary necrosis, adequate necrectomy remains the key factor in preparation of high rate transplant take. In addition, a balanced specialist and multidisciplinary therapy includes adequate fluid supply, nutritional support, and local wound care. Vasoactive mediators

Key Messages for Necrosis in Burns

Primary necrosis:
Inflammation, capillary leakage, edema, hypercoagulability, venous thrombosis, and arteriole and capillary stasis lead to burn progression and involve a number of factors which are linked.

Establish early diagnosis of primary necrosis and debridement and adequate initial care.

Secondary necrosis:
Try to prevent or limit inflammation.

Conversion zones may lead to secondary necrosis.

Tertiary necrosis:
Sufficient necrectomy enables high rate of transplant take.

Loss of transplant may lead to tertiary necrosis.

Tertiary necrosis necessitates secondary healing or retransplantation.

may lead to capillary occlusion impairing transplant take. If epithelial islands are surrounded by tertiary necrosis, secondary wound healing vs. retransplantation have to be evaluated on the basis of affected burned area, localization, and expected healing period. Hypertrophic scarring, dyspigmentation, and potential contractures can result from tertiary necrosis.

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