Wound Healing

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1 Introduction

1.1 Molecular and Cellular Mechanisms

The restoration of the barrier function of the skin after an injury is of elementary importance for every organism, and represents the primary goal of wound healing (Eming et al. 2017). The wound healing process activates molecular and cellular mechanisms, which, in principle, are also observed in other physiological (embryonic development) or pathological processes (fibrosis, tumor growth, metastasis). These processes have in common the stimulation of cell growth by a complex network of numerous cytokines and extracellular matrix molecules. However, tissue proliferation during development and wound healing differs from pathological processes, in that cell proliferation and differentiation are subject to stringent, temporally, and spatially coordinated control. Disturbances of the interactions between cells, structural proteins, and cytokines can lead to a disconcerting wound-healing response, causing a persistent inflammatory reaction, fibrosis, or tumor growth.

For simplification, the physiological wound healing process is divided into three temporally overlapping phases: **inflammation**, **tissue growth,** and **scar formation**. Post injury, the coagulation cascade is initially activated, and at the same time, an inflammatory reaction develops, which helps to eliminate defective tissue and invading pathogens. New dermal tissue (granulation tissue) is subsequently formed by vascular sprouting, the proliferation of fibroblasts and their differentiation into myofibroblasts, and the synthesis of extracellular matrix (tissue growth). Keratinocytes originating from the skin appendages migrate over the granulation tissue and lead to restoration of the epithelial barrier. Epidermal wound closure is followed by adaptation of the replaced dermal tissue to biomechanical requirements (scarring).

The efficiency and the quality of the healing response changes with age (Fig. 1). A distinction is made between two principally different outcomes: tissue regeneration and tissue repair.

Regeneration leads to restoration of the original injured tissue in function and morphology without scar formation. Tissue repair leads to defective healing, with loss of skin appendages and replacement of the injured tissue by a scar. While wound healing of the skin in the early fetal period is characterized by tissue regeneration, the post-natal healing process is characterized by loss of skin appendages and scarring. The underlying molecular mechanisms for the post-natal loss of the skin's ability to regenerate are currently not fully understood. In addition to wound depth (erosion, ulcer) and localization, intrinsic factors, wound contraction, and the inflammatory response play an important role in scar development.

1.2 Epidemiology

Although not yet uniformly defined, a wound is described as chronic if wound closure is not reached within 8 weeks. The prevalence of **chronic wounds** is estimated at 1–3% in Europe, and is strongly age dependent (Eming et al. 2014). In addition, wound healing disorders often occur as a symptom of age-associated underlying diseases, for example in the context of venous or arterial vascular diseases or diabetes mellitus. It is not known to what extent wound healing disorders in the elderly are caused by the consequences of an underlying systemic disease or specific mechanisms of the physiological aging process, including reduced DNA repair, disturbance of the regulation of oxidative stress, and cellular

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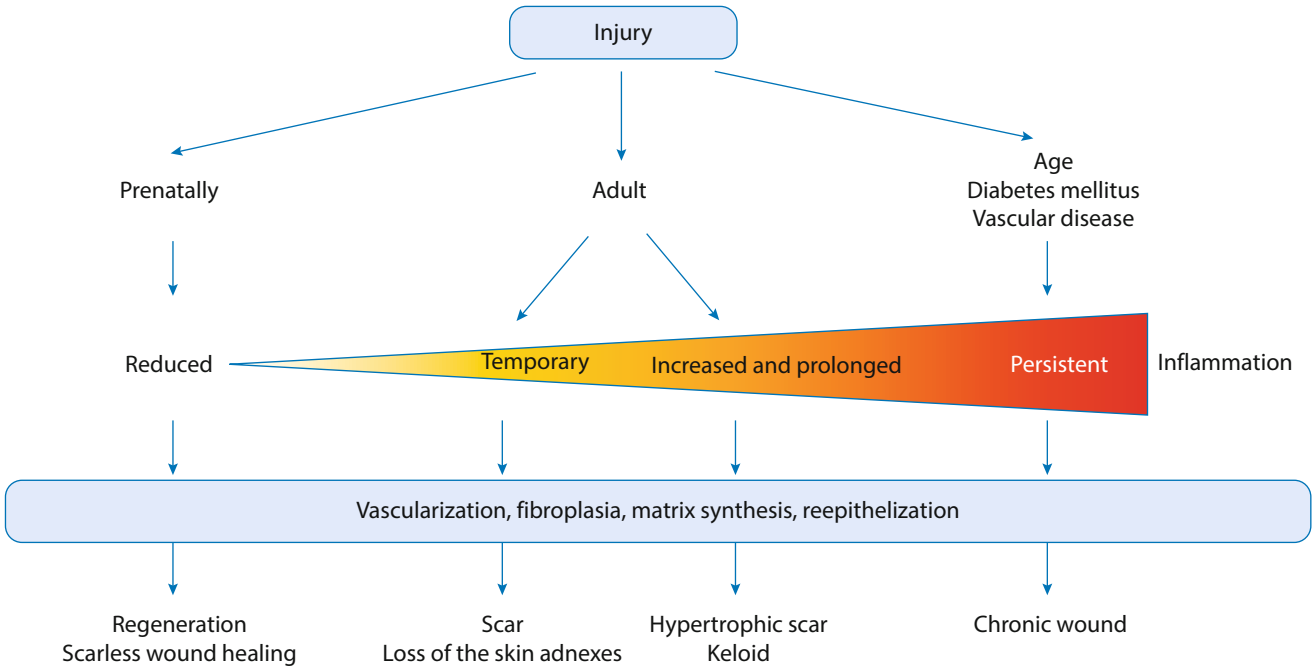

Fig. 1 Relationship between quality of wound healing and age

senescence. The prevalence of chronic venous insufficiency in adults is 1–4% in Western countries. Of patients aged over 60 years with varicose veins, 1–2% develop a venous leg ulcer. Approximately 5–10% of type 2 diabetics over 60 have wound-healing disorders. It can be assumed that the incidence of chronic wounds will continue to rise in the future due to demographic developments (Gottrup et al. 2010).

2 Systemic Diseases and Other Causes of Impaired Wound Healing

2.1 Systemic Diseases as a Cause of Impaired Wound Healing

Numerous factors can lead to disturbances in the physiological course of the wound-healing process, which manifest themselves in clinically different ways (Eming et al. 2014). Excessive tissue formation leads to the development of a hypertrophic scar or keloid. A chronic wound is characterized by a pathological delay in the proliferation of granulation tissue and wound closure. In most cases, chronic wounds are the result of an underlying disease. These are often vascular or metabolic diseases (Zamboni et al. 2005). However, there are numerous diseases that must be considered diagnostically as a potential cause for a "poorly healing wound" (Table 1). Vasculitis, genetic diseases, pyoderma gangrenosum, calciphylaxis, medication, or hematological diseases must be taken into account. Local disruptive factors, such as increased mechanical stress, infection, or the consequences of a persistent inflammatory reaction can also create a hostile microenvironment, and impede the healing response.

2.2 Local Factors as Causes of Impaired Wound Healing

In addition to the systemic diseases mentioned above, metabolic changes in the local microenvironment of the wound can also contribute to the pathophysiology of impaired wound healing. Here, the consequences of a chronic persistent inflammation are essential, which can be caused both by the systemic disease and/or by the absence of an epithelial barrier, with accompanying pathological germ colonization. The persistence of inflammatory factors such as cell detritus and bacterial toxins in the wound leads to increased recruitment and activation of neutrophil granulocytes and macrophages into the wound tissue. This process is followed by the increased release and synthesis of inflammatory cytokines such as interleukin-1 (IL-1), tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), as well as various proteases and reactive oxygen species (ROS) (Eming et al. 2010).

The imbalance between increased activity of proteolytic enzymes and decreased activity of their inhibitors is considered to be one of the major local disruptive factors in chronic wounds. Compared to healing wounds, significantly increased activities of different proteases have been detected in the exudate of chronic wounds. These include matrix metalloproteases (MMP-2, MMP-9) and serine proteases (elastase, plasmin, cathepsins, plasmin activators released

Table 1 Causes of chronic wounds

Category	Illness
Vascular	Chronic venous insufficiency Peripheral arterial occlusive disease Diseases of the lymphatic system Hypertensive ulcer (Martorell)
Vasculitis	Granulomatosis with polyangiitis (Wegener's disease) Polyarteritis nodosa Cryoglobulinemic vasculitis Rheumatoid vasculitis Behçet's disease
Vasculopathy	Livedoid vasculopathy Thrombangiitis obliterans
Metabolic	Diabetes mellitus Calcinoses Calciphylaxis Oxalosis
Autoinflammatory	Pyoderma gangrenosum PAPA syndrome PASH syndrome
Autoimmunological	Lupus erythematosus Scleroderma Graft-versus-host disease Pemphigus vulgaris Bullous pemphigoid Epidermolysis bullosa acquisita
Genetic/hereditary	Epidermolysis bullosa hereditaria simplex/dystrophic Ehlers-Danlos-syndrome Werner syndrome Sickle cell disease Thalassemia Leukocyte adhesion deficiency-syndromes Factor V Leiden mutation, prothrombin mutation Protein C/-S deficiency Klinefelter syndrome
Exogenous	Pressure ulcer Wounds caused by heat, cold, radiation Dermatitis artefacta
Neoplastic	Squamous cell carcinoma Basal cell carcinoma Melanoma Metastasis Lymphoma
Drugs	Hydroxyurea Glucocorticoids Kinase Inhibitors Heparins Coumarins mTOR-inhibitors
Vaso-occlusive	Cholesterol embolism Cryoglobulinemia Cryo proteinuria
Infectious	Ecthyma gangrenosum Syphilis (lues maligna) Deep mycoses Leishmaniasis Buruli ulcer
Other	Necrobiosis lipoidica

from neutrophil granulocytes). However, proteolytic enzymes synthesized by bacteria may also be of pathogenetic relevance. It has been shown that the increased activity of different proteases leads to the uncontrolled degradation of growth factors and structural proteins, which are thus limited in their effectiveness and no longer available for the wound healing process.

2.3 Neoplasia

If the etiology of a chronic wound cannot be clearly assigned, or if there is no corresponding healing tendency after consistent treatment, a neoplastic event should be excluded promptly by tissue biopsy. Squamous cell carcinomas or basal cell carcinomas can develop secondarily in the area of a persistent leg ulcer, an older scar, burn, or radiation field, and are classified as a **Marjolin ulcer**. Basal cell carcinomas and many other skin tumor entities can also manifest themselves through ulceration, and thus appear as chronic wounds.

3 Diagnostics of Chronic Wounds

Chronic wounds do not represent a separate disease entity, but are usually symptoms of a basic disease or a local disturbance factor. Early diagnosis of the underlying causes is essential in order to achieve timely and sustained treatment success. The longer a chronic wound already exists, the less likely it is to heal. Causal treatment of the underlying disease, in combination with efficient local treatment, is important for wound closure (Jones et al. 2018). Often, a detailed medical history and careful clinical inspection (see overview: ABCDE rule) will identify the etiological factors (Dissemond 2017). Information on the localization, the wound size, margin, and base, as well as pain perception, leads to a clinical diagnosis (Tables 2 and 3). However, the clinical diagnosis should be confirmed by the appropriate radiologic, and, if necessary, laboratory chemical diagnostics (Table 4) (Moffatt et al. 2010).

If the treatment is unsuccessful, the diagnosis must be reconsidered and an extended diagnostic program must be implemented (see overview: Laboratory chemical tests). In non-specialized practice, it is often difficult to design such complex and sometimes cost-intensive procedures efficiently. In order not to jeopardize the quality of the diagnostics, and ultimately, the treatment, a step-by-step, standardized, interdisciplinary approach is required, together with angiologists, radiologists, vascular surgeons, orthopedists, and internal specialists (Singer et al. 2017).

ABCDE rule for the diagnosis of chronic wounds

A – Anamnesis:

The medical history should always be the first step in diagnostics. The patient is asked about current symptoms (pain, intermittent claudication), duration of persistence, underlying diseases, medication, diet, habits (nicotine, alcohol), and previous treatment.

B – Bacteria:

In most cases, bacterial superinfections with clinical manifestation, for example as cellulitis, represent a complication of chronic wounds. If an infection is clinically suspected, blood count, C-reactive protein, and blood sedimentation rate are determined, in addition to body temperature. However, bacterial diagnostics is also used for the exclusion of multidrug resistant (MDR) bacteria such as methicillin-resistant *Staphylococcus aureus* (MRSA), as special hygiene measures are necessary in this case. If osteomyelitis is suspected, an imaging procedure should be performed.

C – Clinical investigation:

In clinical examination, the description of the wound (localization, size/depth, wound margin, wound environment, necrosis, exudate), sensitivity test, edema, mobility in the ankle joint, and evaluation of malposition are important.

D – Blood circulation:

For vascular diagnostics, both the venous and arterial systems should be examined. Arterial diagnosis of the lower extremities begins with palpation of the foot pulses and determination of the ankle brachial pressure index (ABI). The basic diagnosis for suspected CVI includes Doppler sonography or, even better, a color-coded duplex sonography of leg veins.

E – Extras:

If the genesis of a wound cannot be unambiguously clarified with basic diagnostics, advanced diagnostic methods can be introduced in a gradual manner. Here biopsy has a very high priority. Serological examinations are carried out if diabetes mellitus, blister-forming autoimmune dermatoses, vasculitis, infectious diseases, coagulation disorder, or calciphylaxis are suspected. Further optional examinations are epicutaneous testing (allergic contact eczema), pathergy testing (pyoderma gangrenosum, Behçet's disease), capillary microscopy (collagenosis), and genetic analyses.

Table 2 Clinical symptoms of common forms of chronic wounds

Trait	Venous leg ulcer	Arterial ulcer	Diabetic foot ulcer
Localization	Distal lower leg, above or behind malleoli, frequently medial	Extremities, toes	Plantar, halux, metatarsal bone I/II/V, heel
Wound surrounding	Corona phlebectatica paraplantaris, atrophy blanche, purpura jaune d'ocre, dermatoliposclerosis, stasis dermatitis, edema	Atrophic skin and skin appendages	Callus, bullous lesion
Wound bed/edge	Fibrin, exudate	Pale wound bed, necrosis, punched out wound edge	Deep ulcer, without granulation tissue
Sensation of pain	Low/moderate pain	Painful	Low, missing
Other	Varicosis	Gangrene, missing/ weak pulse, cyanosis	Neuropathy, infection, malposition of the toes, xerosis cutis, disturbed foot mobility

Table 3 Diabetic foot syndrome: classification according to Wagner and Armstrong

Wagner grade	Armstrong stage			
	A	B	C	D
0 No ulcer, but high-risk foot	Without infection or ischemia	With infection	With ischemia	With ischemia and infection
1 Superficial full-thickness ulcer	Without infection or ischemia	With infection	With ischemia	With ischemia and infection
2 Deeper ulcer, penetrating tendons, no bone involvement	Without infection or ischemia	With infection	With ischemia	With ischemia and infection
3 Deeper ulcer, with bone involvement	Without infection or ischemia	With infection	With ischemia	With ischemia and infection
4 Partial gangrene (toes, forefoot)	Without infection or ischemia	With infection	With ischemia	With ischemia and infection
5 Gangrene of the whole foot	Without infection or ischemia	With infection	With ischemia	With ischemia and infection

Table 4 Types of apparatus used in different examination methods for frequent forms of chronic wounds

Venous leg ulcer	Arterial ulcer	Diabetic foot ulcer
Duplex sonography (color-coded) Photoplethysmography	Ankle brachial pressure index (ABI) Duplex sonography (color-coded) Angiography	Testing neuropathy with monofilament and tuning fork

Laboratory chemical analysis of a chronic wound with suspected vasculitis

- Blood sedimentation rate
- Differential blood count
- Liver and kidney function test
- Antinuclear antibodies (ANAs)
- Rheumatoid factor
- Complement factors (C3, C4)
- Cryoglobulins, cryofibrinogen
- Antineutrophil cytoplasmic antibodies (pANCA, cANCA)
- Anti-cardiolipin antibodies
- Urine status (proteinuria, erythrocyturia)
- Hepatitis serology

4 Treatment of Chronic Wounds

4.1 Treatment of Systemic Diseases Associated with Chronic Wounds

After the diagnosis has been made, the systemic disease is treated, and any local disruptive factors are eliminated (see overview: Treatment). In the case of chronic venous insufficiency (CVI), these are consistent compression treatment and/or the interventional/operative elimination of insufficient venous sections (see chapter ▶ "Diseases of the Veins") (Dissemond et al. 2016). The treatment also includes pharmacological and/or surgical measures for revascularization in peripheral arterial occlusive disease, optimization of the metabolic situation in diabetic foot ulcers, and pressure relief in pressure ulcers. Diseases such as vasculitis and pyoderma

gangrenosum require immunosuppressive treatment (see chapter ▶ "Vasculitis and Vasculopathies") (Löhrer et al. 2011). As a rule, a successful treatment concept is based on an interdisciplinary approach. After the chronic wound has healed, appropriate relapse prophylaxis should also be carried out.

Basic Principles of Complex Treatment of Chronic Wounds

Treatment of underlying disease

- Vascular surgical intervention
- Phlebological intervention
- Compression treatment
- Normalization of metabolic disorders
- Medical treatment

Local wound treatment

- Conservative treatment
  - cleansing
  - debridement
  - dressings
  - negative-pressure wound treatment (NPWT)
- Surgical treatment
  - ulcer surgery including shave excision
  - (split) skin transplantation
  - skin replacement methods

Adjuvant treatment

- Pressure relief
- Pain treatment
- Nutrition consultation

4.2 Local Treatment of Chronic Wounds

The local treatment of the wound is carried out at the same time as the treatment of the underlying disease. The treatment goal is to transfer the microenvironment of the chronic wound, which is characterized by persistent inflammation, into a microenvironment that promotes healing (Eming et al. 2010; Isoherranen et al. 2019). Within the framework of a phase-adapted treatment scheme, wound cleansing and debridement are performed first, followed by stimulation of granulation tissue growth and promotion of epithelialization (Fig. 2) (Dissemond et al. 2014).

Almost independently of the underlying disease, the application of the treatments currently available for local wound treatment depends on the clinical aspects, taking into account the wound bed, wound environment, infection status, and amount of exudate. The **M.O.I.S.T.** concept (M: moisture balance; O: oxygen balance; I: infection control; S: support of healing process; T: tissue management) was developed as a guide for the use of various local wound treatments, and represents a further development of the well-established T.I.M.E. (T: tissue; I: infection; M: moisture; E: edge) concept (Dissemond 2017).

4.2.1 Wound Cleansing

The first step in wound treatment should be wound cleansing and/or debridement. Avital tissue interferes with the regeneration of tissue. It provides a breeding ground for the multiplication of pathogens, and is thus a possible starting point for infections. In addition, diffusion processes within the avital tissue slow down, making it difficult to achieve appropriate concentrations of local and systemic treatments. Sterile solutions, such as Ringer's or physiological saline solution, as well as sterile cotton compresses for the atraumatic removal of loosely adhering avital tissue (fibrin, crusts), are used for wound cleansing. In many countries the use of non-sterile tap water is officially only permitted if it is filtered with filters that have a maximum pore size of 0.2 µm.

4.2.2 Debridement

Different treatment approaches are available for debridement. The removal of firmly adhering debris such as necrotic tissue can be facilitated by using autolytic hydrogels. The avital tissue is usually removed with a mechanical or surgical debridement, using a curette and/or scalpel. If possible, debridement should be carried out as radically as possible until a tissue rich in capillaries becomes visible in the entire wound bed.

In the maximum variant of surgical debridement, known as "shave excision," the ulcerations with surrounding sclerosis, fibrosis, and scars are completely removed, in a tangential way. Other methods of mechanical debridement use ultrasound, laser, or water jet lavage. One problem with all physical treatment options is the (often) pronounced pain. If mechanical debridement is not tolerated, **biosurgery** is one alternative as an effective treatment, with few side effects. In this approach, sterile maggots of the *Lucilia sericata* species are applied to the wound. The maggots secrete various enzymes in their saliva, which selectively lyse necroses and kill numerous bacteria, including MRSA. This extracorporeally formed nutrient broth is then absorbed by the maggots. The maggots are applied, either free-ranging or contained, in a nylon net (biobag).

The principle of **osmotic debridement** has been known for a long time. Currently, a large number of osmotically effective wound products are available, the application of which is particularly suitable for wounds with severe exudation. These are usually three-dimensional structures, such as

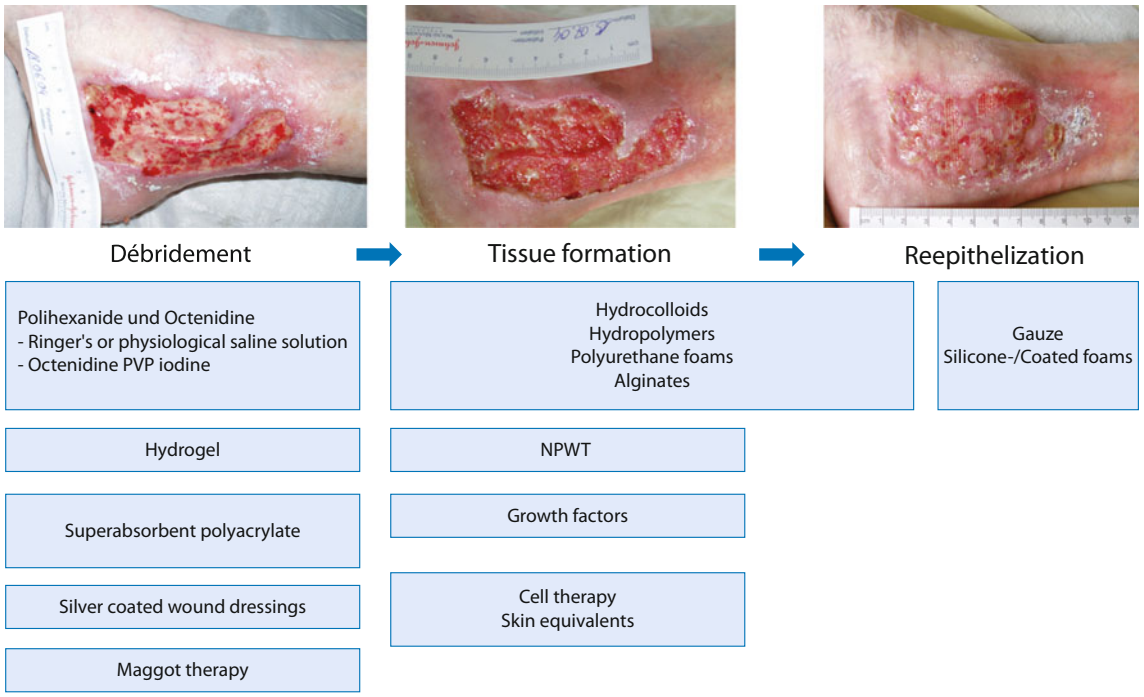

Fig. 2 Phase-adapted local wound treatment

superabsorbent polyacrylate, which absorb wound fluid and the macromolecules contained therein.

4.2.3 Antimicrobial Treatment

The detection of bacteria in wounds without clinical signs of infection does not require any specific treatment (Schwarzkopf and Dissemond 2015). For the diagnosis of superficial wounds, a bacteriological swab in the form of the Essen Rotary (Fig. 3) is usually enough (see overview: Bacteriological Diagnosis). The short-term use of antiseptics for pathogen reduction is recommended in the case of clinical signs of strong pathogen colonization, detection of multiresistant pathogens, or local infections (Kramer et al. 2018). Polihexanide is less cytotoxic, and therefore the first choice for many chronic wounds. Other alternatives for wound treatment are octenidine, hypochlorous acid, and povidone-iodine. Antimicrobial treatment can also be supplemented by the use of wound dressings containing silver, honey, or dialkyl carbamoyl chloride (DACC). Products that contain activated carbon are offered as effective odor binders. Due to their contact-sensitizing potential and the possible development of resistance, locally applied antibiotics should be avoided in wound treatment. In cases where there are signs of systemic infections such as erysipelas, antibiotics should be administered systemically. However, further studies are necessary to enable a final evaluation of the clinical efficacy of antimicrobial treatments with regard to an accelerated healing rate of chronic wounds.

Bacteriological diagnostics in patients with chronic wounds

Bacteriological swab **without** prior wound cleansing:

- Detection/exclusion of multi-resistant pathogens (screening)

Bacteriological swab **with** previous wound cleansing∗:

- Detection of causal pathogens in wound infection
- Colonization/infection with yeast fungus.

Biopsy/excision:

- Wound infection in patients with deeper ulcerations such as diabetic foot ulcers
- Fistula tissue, if no fistula content can be obtained
- Suspected pathogens: mycobacteria, Leishmania, actinomycetes, nocardia, mold fungus
- Wound infection without pathogen detection in swabs.

∗ To reduce possible contamination, prior wound cleansing is performed with sterile cotton compresses and sterile Ringer's or physiological saline solution.

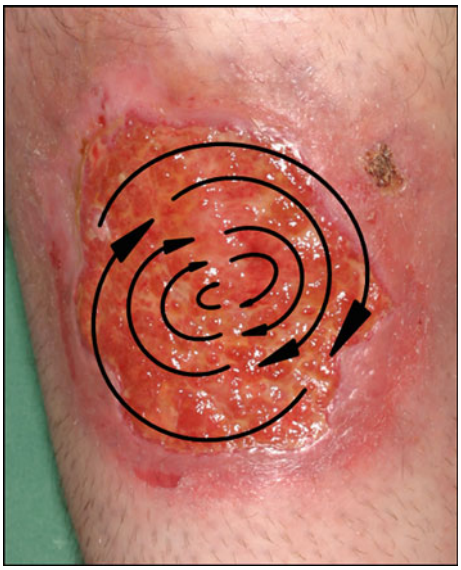

Fig. 3 When the swab is taken using the Essen Rotary technique, it is guided under light pressure, from the outside to the inside, in a spiral motion, over the entire wound surface, to the center

4.2.4 Granulation Tissue Proliferation

Dressings

After cleaning the wound bed and removing the avital tissue, the next goal is to fill the defect with a capillary-rich granulation tissue. A wide range of wound dressings is available, and these have played an important role in the standard of care for chronic wounds over the last decades (Langer and Rogowski 2009). These include, for example, hydrocolloids, alginates, hydrofiber, hydropolymer, and polyurethane foam dressings. Some of these products have an external adhesive edge that prevents wound exudate from escaping and fixes the wound dressings in place. In contrast to simple gauze dressings, modern wound products should not stick to the wound tissue, thus reducing pain when the dressings are changed.

Despite their diversity, similar effective principles of action are propagated for the respective wound dressings. Good absorption of wound exudate leads to the elimination of factors harmful to wound healing (bacteria, toxins, proteases), prevents maceration of the wound environment, and helps to maintain a moist wound environment. It is plausible that these materials promote tissue formation, and thus also the healing process. In addition, numerous other products are offered, in which heterogeneous mechanisms of action are postulated by the manufacturers (Dissemond et al. 2020). The primary goal is to actively influence factors that impede wound healing in the wound environment. Examples are MMPs, pH value, oxygen supply, reactive oxygen species (ROS), as well as growth or coagulation factors. For this purpose, products with collagen, chitosan, hyaluronic acids, hemoglobin, or growth factors are offered.

Wound dressings have facilitated the practical treatment of patients with chronic wounds, and contribute decisively to an improved quality of life for patients.

Growth Factors

From a pharmacological point of view, modulating the activity of growth factors is a promising approach for controlling tissue growth and stimulating it in chronic wounds. Growth factors such as keratinocyte growth factor (KGF), platelet-derived growth factor (PDGF), and transforming growth factor-β (TGF-β) are released from inflammatory cells and various other skin cells during wound healing. The complex processes of dermal and epidermal tissue growth are thus regulated in many ways. Chronic wounds are characterized by an increased proteolytic degradation and a corresponding loss of activity of these factors. The production of recombinant growth factors, and their topical application into the wound, have opened up the possibility of active pharmacological intervention in the wound-healing process. However, the great euphoria regarding this approach at the beginning of the 1990s was followed by disappointment, as many clinical studies on the efficacy of different recombinant growth factors in chronic wounds showed no significant effects on the healing rate. Recent studies indicate that a deeper understanding of molecular pathophysiology is required for the development of recombinant protein activity in the microenvironment of chronic wounds. The successful application of growth factors in chronic wounds requires combination with various other methods, such as surgical debridement. In summary, the benefit of a treatment with growth factors is a promising option today, but for each patient, it must be individually weighed against the background of the usually very high costs.

Negative-Pressure Wound Treatment

Negative-pressure wound treatment (NPWT) is an effective method, especially for stimulating the formation of granulation tissue. In recent years, NPWT has become an interdisciplinary standard procedure in the treatment of large-area, deep acute, and chronic wounds. In this treatment, a sponge or gauze is inserted into the wound defect. After the application of an airtight foil, a subatmospheric pressure of 75–125 mmHg is generated; this has a positive effect on the stimulation of different wound-healing processes. The exact principle of this method is unclear. A continuous removal of excess exudate and bacteria, mechanical stimulation of cell growth, edema reduction, and improved perfusion have been shown in various studies. A potential side effect is the pain that patients can experience. This can either occur permanently during treatment due to the suction, or exclusively during dressing changes. Therefore, adequate analgesia should always be considered. Moreover, the application of the dressings can lead to maceration and secondary skin

damage in the wound environment. Adequate skin protection of the surrounding skin should thus always be provided. There is also an increasing benefit of NPWT in numerous other indications, such as the fixation of split skin grafts.

4.2.5 Cell Treatment and Skin Equivalents

For wound closure, surgical procedures with subsequent split skin transplantation (mesh graft, Reverdin's plastic) as well as the application of artificial skin equivalents are available. A decisive new development in the field of biological skin replacement has been the introduction of keratinocyte cell cultures. New cell culture methods have made it possible to cultivate a multi-layered, transplantable epithelium in a short time. This technique of tissue replacement has been taken up by many working groups worldwide, is offered commercially, and is available for defect coverage of chronic wounds of different causes. The mechanism of action of keratinocyte transplants has not been clarified. The clinical success of allogeneic transplants also makes it clear that the cells do not have to grow in order to achieve their effect. Several products of dermal tissue replacement have been approved and are available for the treatment of dermal tissue defects (Kosaric et al. 2019). A distinction is made between dermal equivalents (requiring an additional split skin transplant) and full skin equivalents (already containing an epidermal and dermal component during transplantation). These products have been tested in clinical trials for the treatment of chronic wounds. It must be considered that the application of these treatment modalities and their successful control are complex and cost-intensive, and that their use is currently reserved only for special facilities that focus on wound care.

4.2.6 Stimulation of Epithelization

At the same time as the formation of dermal tissue progresses, epithelization of the wound margins and skin appendages begins. While granulation tissue can form without epithelial influence, keratinocytes require growth signals from the dermis for epithelization. A well-vascularized and functional granulation tissue is a prerequisite for rapid restoration of the epidermal barrier. Similar to the growth of dermal tissue, a moist wound environment is also advantageous for the regeneration of the epidermis. Various wound dressings, in particular coated foams and hydrocolloids, can be used. Non-adhesive wound gauze or foil dressings are also suitable for supporting the epithelization of superficial wounds in which the formation of dermal tissue is already completed. At this stage, no specific treatment agent is available for the stimulation of epidermal wound healing. Dressings should not be changed too frequently during this wound phase, as wound healing might be disturbed.

4.3 Pain Treatment

Pain is very stressful for patients, leads to a reduced quality of life, and can contribute to slower wound healing. For patients with chronic wounds, the pain symptoms should therefore always be checked and objectified. The visual analogue scale (VAS) or numerical rating scale (NRS) are suitable for this purpose. When recording pain, care must be taken to ensure that it is differentiated from rest pain, through intervention and dressing changes. Therefore, the same question should always be asked on each occasion; for example, what was the most severe pain in the last 24 h? The best pain treatment is to treat the cause of the pain adequately, such as with glucocorticoids in the inflammation of vasculitis.

Other exogenous factors should also be identified and avoided. For example, the use of non-adhesive wound dressings coated with silicone or wound edge protection preparations can be helpful.

Before painful interventions such as surgical debridement, local anesthetics such as a mixture of lidocaine and prilocaine can be applied as a cream. The exposure time of this local anesthetic on the wounds should be 1 h or longer. If it is insufficiently effective, the procedure should be performed under partial or general anesthesia. Wound treatments to which analgesics have been added can also be integrated into the treatment concepts (see overview: Morphine Wound Gel) (Huptas et al. 2011). If a systemic pain treatment appears necessary, it should be carried out individually, in accordance with the principles of the WHO pain ladder. Co-medication with laxatives, antiemetics, or antidepressants can be useful.

Morphine wound-gel for the topical treatment of painful wounds

The preparation can be left on painful wounds for 24 h:

- Morphine HCl trihydrate 0.1 g
- Sodium edetate 0.1 g
- Hydroxyethyl cellulose 250 G 4.5 g
- Polyhexanide concentrate 20% 0.2 g
- Aqua dest. ad 100 g

4.4 Compression Treatment

Compression treatment with (at rest) pressure values of around 40 mmHg is an effective treatment for most patients with chronic wounds and edema of the lower extremities. After exclusion of the relevant contraindications (cave – critical ischemia in peripheral occlusive arterial disease), this applies not only to patients with venous leg ulcers (see

chapter ▶ "Diseases of Veins"), but also to almost all types of chronic wounds with edema, such as mixed leg ulcers, vasculitis, vasculopathy, or necrobiosis lipoidica. However, due to the pronounced pain of patients with chronic wounds, treatment often needs to be initiated with less pressure, of around 20 mmHg. In the initial phase of decongestion, for example, multi-component systems can be used; these are usually also available as "lite" variants with reduced pressure values, or so-called velcro bandages. With some of these velcro systems, the pressure values can be adjusted between 20 and 50 mmHg by the patients themselves. Ulcer compression stockings should only be adjusted in the maintenance phase, after the decongestion has been completed, and should be worn until complete healing. Medical compression stockings are essential in secondary prophylaxis.

5 Perspectives

When developing innovative approaches to wound treatment, it must be clarified whether the combinations of several treatment modalities, with different principles of action, such as growth factors, cell treatment, or skin equivalents, goes beyond the effect of a single approach, and opens up new treatment strategies (Yamanaka and Blau 2010). In addition, it will become increasingly important to prove the postulated effects in high-quality clinical trials.

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