CLINICAL PRACTICE GUIDELINE

Local Treatment of Chronic Wounds

in Patients With Peripheral Vascular Disease, Chronic Venous Insufficiency, and Diabetes

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SUMMARY

Background: A chronic wound is defined as an area where the skin is not intact that fails to heal within eight weeks. Such wounds usually develop on the lower limbs as a complication of diabetes, venous insufficiency, or inadequate arterial perfusion. Most of the roughly 45 000 limb amputations performed in Germany each year are necessitated by non-healing chronic wounds.

Methods: In the development of this S3 guideline, a systematic search was performed that yielded 4998 references including 38 randomized, controlled trials and 26 systematic reviews, which were used as the basis for the recommendations and statements made in the guideline. Twelve member societies of the umbrella Association of Scientific Medical Societies in Germany (Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften, AWMF), as well as the German Association of Nursing Science (Deutsche Gesellschaft für Pflegewissenschaft, and patient representatives participated in the consensus rounds in which the guideline’s recommendations and statements were agreed upon.

Results: This guideline contains seven evidence-based recommendations and 30 good clinical practice (GCP) recommendations. Evidence-based recommendations are given in favor of hydrogel, hyperbaric oxygenation, and integrated care, and against the use of medicinal honey and growth factors. Terms are defined precisely in order to ease communication and to specify what is meant by “wound debridement” (a procedure performed by a physician) as opposed to cleansing a wound. Under the premise of preventing pain, exudation, and maceration, local therapeutic agents can be chosen on the basis of the scientific evidence, the patient’s preference, the physician’s experience, and the wound situation. Costs should also be considered.

Conclusion: Scant evidence is available to answer many of the relevant questions about chronic wounds. There are valid data in support of hyperbaric oxygen and integrated care. More research is needed.

C hronic wounds are often treated unsystematically in routine practice, even though successful wound healing depends to a large extent on continuity in the re-evaluation of the state of the wound and reassessment of the treatment strategy.

Chronic wounds are associated with
- severe impairment of quality of life (1),
- long treatment times, and
- high costs (2).

In addition, they restrict patients’ everyday activities and mobility and cause emotional distress. As far as quality of life is concerned, systematic reviews have shown that pain is the most serious physical impairment of all (1, 3–6).

Inadequate venous return is the cause of about 1.2% of all days lost from work in Germany. About 1% of the total cost of inpatient medical care in Germany is spent on the treatment of venous leg ulcers (7). On average, one patient in three has a recurrence (8). It does seem, however, that the incidence and prevalence of venous leg ulcers are both lower than they were reported to be in the 1970s. Large-scale studies in the Rhineland region of Germany have revealed a current prevalence of about 0.08%, which would imply that about 50 000 to 80 000 persons in the country suffer from this condition.

Chronic wounds on the lower limbs can arise because of arterial hypoperfusion (arterial leg ulcers), often in combination with diabetes (diabetic foot ulcers). The prevalence of peripheral arterial hypoperfusion in the overall population is 3% to 10%, depending on the definition. 15% to 20% of persons over age 70 have peripheral arterial occlusive disease (PAOD) (9). No reliable figures are available for the prevalence or incidence of stage IV PAOD or of leg ulcers of mixed arterial and venous pathogenesis.

Studies of diabetic foot ulcers in various countries have yielded prevalence figures ranging from 2% to 10% of the diabetic population, with an annual incidence of 2% to 6% (10).

Foot ulcers can lead, in the worst case, to amputations of toes, the foot, or the entire lower limb. According to data from the German AOK health insurance company, amputations are carried out in about 29 000 diabetic patients in Germany every year (11).

Although no precise epidemiological data are available on the frequency of recurrence of chronic wounds, individual studies have shown that both diabetic foot ulcers and venous insufficiency ulcers tend to recur, particularly...
when peripheral arterial hypoperfusion is also present (12). Recurrent diabetic foot ulcers are the most likely of all to necessitate amputation (in up to 60% of cases) (13).

Methods
This S3 guideline was created in accordance with generally recognized quality criteria (14) under the aegis of the German Association for Wound Healing and Wound Treatment (Deutsche Gesellschaft für Wundheilung und Wundbehandlung e.V.) in collaboration with 11 societies belonging to the Association of Scientific Medical Societies in Germany (AWMF, Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften), the German Association of Nursing Science, and patient representatives. The persons who developed the guideline thus came from multiple medical disciplines and other health occupations involved in the treatment of wounds; the participants were selected because of their expertise and because they had minimal personal conflicts of interest.

A comprehensive set of key questions about the current methods of cleaning and dressing wounds and about various physical treatments served as the basis for a literature search and assessment performed externally by Kleijnen Systematic Reviews Ltd. (UK).

Individual guideline authors carried out systematic literature searches on further subjects, such as patient preferences or organization. In total, 4998 publications on wound-treatment interventions were retrieved, including the reports of 38 randomized controlled trials that were used to develop the guideline. In addition, 103 randomized controlled trials from 26 systematic reviews were used. The effects on clinical endpoints such as wound healing, reduction of wound size, pain, and complications were systematically assessed according to the GRADE scheme (15), which also provides an overview of the quality of the evidence. On the basis of this evidence, the participating guideline authors issued graded recommendations that were developed in multiple consensus-building sessions (Table).

In areas where scientific evidence could not be obtained or was not considered essential, good clinical practice (GCP) recommendations were issued by consensus.

On the basis of the recommendations and statements for which a consensus could be obtained, an algorithm was created that encapsulates the basic principles of diagnostic assessment and wound treatment (Figures 1 and 2 and eFigure 1). The development of this guideline is described in a comprehensive guideline report (16).

Diagnostic assessment and documentation
The clinical approach to chronic wounds begins with history-taking and the diagnostic assessment of the underlying disease, which should be performed as recommended in the guidelines of the relevant medical specialty society. The general procedure is shown in the algorithm for history-taking and diagnostic assessment (Figure 1).

A recommendation of major importance is that, if no trend toward wound healing is evident after six weeks of treatment in conformity with the guidelines, there should be further differential-diagnostic assessment for other potential causes of impaired wound healing. In case of doubt, a second opinion should be obtained (GCP).

Moreover, microbiological testing is recommended only when antibiotic treatment of a bacterial infection emanating from the wound is being considered.

Adequate documentation is very important and serves as the basis of communication among treating personnel, as well as of quality management and billing. At a minimum, documentation must include the (established or suspected) cause of impaired wound healing, the size of the wound, the visual appearance of the wound surface and its edge and surroundings, the treatment(s) ordered and provided, and any changes made in the treatment.

The guideline also contains definitions and explanations of terms. For example, the proper use of the term “debridement” is explained. This word is often used inappropriately for lesser procedures; a clear distinction is drawn between debridement and simple wound cleansing.

Wound cleansing and surgical debridement
The literature search did not reveal any high-grade evidence (see Table) for either wound cleansing or wound debridement, yet there was a strong consensus among the experts that wound healing is impaired by the presence of dead tissue, foreign bodies, coatings, and detritus. The recommendation for initial treatment is, therefore, that dead tissue should be radically removed up to and including the top layers of intact anatomical structures (as far as possible without causing unnecessary discomfort). This is called debridement. The indications for surgical debridement include signs of local infection, systemic spread of infection from the wound, and large areas of necrosis or coating of the wound. Pain should be treated appropriately when necessary.

### Table: Evidence levels and recommendation grades in the S3 guideline on the local treatment of chronic wounds

<table>
<thead>
<tr>
<th>Type of study</th>
<th>Quality level according to GRADE (34)</th>
<th>Recommendation grade and illustrative example</th>
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| Systematic reviews (meta-analysis) and randomized controlled therapeutic trials | High (It is highly unlikely that further research will alter confidence in the observed treatment effect.) | Recommendation grade A  
Example: “Treatment X clearly should / should not be used” |
| Randomized controlled trials with an intermediate risk of systematic error | Moderate (Further research is likely to have a major impact on our confidence in the observed treatment effect. The treatment effect may turn out to be different than observed in this trial.) | Recommendation grade B  
Example: “Treatment X should / should not be used” |
| Randomized, controlled trials with a high risk of systematic error | Low (Further research will very likely have a major impact on our confidence in the observed treatment effect. The treatment effect will probably be different than observed in this trial.) | Recommendation grade O  
Example: “Treatment X can be used” |
History, diagnostic evaluation, and treatment plan

**History-taking (R2)**
- Symptoms and signs, current illnesses, vascular disease and/or prior vascular surgery, family history, tetanus immunization, medications
- Treatment to date and response to it, wound-care products and medications, allergies
- Assessment of the patient’s competence for everyday activities and self-care

**Basic diagnostic evaluation of underlying disease according to guidelines (R1) and additional diagnostic evaluation as needed (R3, R4, R5), wound assessment (R7)**
- Evidence of chronic venous insufficiency (CVI)? E.g., skin changes, varices, status post DVT → Evaluation S3-GL, CVI no. 037-009
- Evidence of PAOD? E.g., muscle pain with exercise or at rest → Evaluation S3-GL, PAOD no. 065-003
- Evidence of diabetic foot syndrome (DFS)? E.g., neuropathy, abnormal foot posture, joint symptoms → Evaluation NCG DFS
- Structural abnormality? Histology
  - Six weeks of treatment according to guidelines without any healing trend? → Differential-diagnostic evaluation of other causes, second opinion if warranted
- Evidence of infection, consideration of antibiotic therapy? → Culture and sensitivities

**Assessment and grading of impairment of quality of life (R6)**

**Patient counseling (R12) about the cause of the disease and its treatment**
- Ways to mitigate factors impairing quality of life
- Counseling and support to maintain and promote everyday skills

**Patient care should involve integration of interdisciplinary care elements from multiple sectors in reasonable combination (R36)**
- E.g.: Promotion of everyday skills and self-management, orthopedic technical aids, podology, lymphological measures, support with / assumption of responsibility for wound care

**Generation of treatment plan**
- Treatment of underlying disease according to guidelines (R11)
- Decision on wound treatment on the basis of general therapeutic goals and the patient’s individual preference (R13)

**Wound documentation (R9)**
- Documentation of treatment measures (R8), pain (R10)

**History and diagnostic evaluation completed and documented; treatment plan created**

**Need for further expertise?**
- No

**Further diagnostic evaluation & second opinion, as needed**

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**Algorithm for wound-specific diagnostic evaluation and history-taking**

R, recommendation; DVT, deep vein thrombosis; DNQP, German Network for Quality Development in Nursing (Deutsches Netzwerk Qualitätsentwicklung in der Pflege); PAOD, peripheral arterial occlusive disease; NCG, national care guideline; S3-GL, S3 guideline

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Staff qualifications should be structured on the basis of the current guidelines of the medical specialty societies, which are published in registers, and on the basis of the current national nursing standards (DNQP) (R37)
Wound cleansing is defined as the removal of dead tissue, necrosis, wound coatings, and/or foreign bodies down to the anatomically intact structures, with preservation of granulation tissue. Like debridement, wound cleansing serves the purpose of complete removal of all elements impeding wound healing. It should be performed primarily mechanically and with accompanying analgesic medication when needed.

The literature does not provide evidence of any advantage for one kind of rinsing solution over another. A consensus statement was issued that rinsing with unsterile solutions or with non-sterilely filtered tap water carries the risk of introducing microbial pathogens. There is no evidence that Ringer’s lactate is any more efficacious as a rinsing solution than normal saline. Neutral solutions without active ingredients are to be preferred for periodic wound cleansing. The experts, therefore, agreed to seek recommendations for or against most of the product groups used as wound care products, whether or not they contain an active ingredient.

In distinction to surgical debridement, wound cleansing is defined as the removal of dead tissue, necrosis, wound coatings, and/or foreign bodies down to the anatomically intact structures, with preservation of granulation tissue. Like debridement, wound cleansing serves the purpose of complete removal of all elements impeding wound healing. It should be performed primarily mechanically and with accompanying analgesic medication when needed.

Wound cleansing with fly larvae (maggots) is faster than with hydrogel, but also significantly more painful. There is no significant difference between these two techniques with respect to the percentage of healed wounds at six to twelve months (RR 1.14; 95% CI 0.86–1.53) (21)

Dry areas of necrosis should not be rehydrated because of the risk of wet gangrene (GCP).

The guideline contains an explicit recommendation against the use of honey, because there is good evidence (19, 20) that honey does not accelerate wound healing (RR 1.15; 95% CI 0.96–1.38), while significantly more patients being treated with it complain of pain (RR 2.53; 95% CI 1.53–4.18) (19).

Wound cleansing with fly larvae (maggots) is faster than with hydrogel, but also significantly more painful. There is no significant difference between these two techniques with respect to the percentage of healed wounds at six to twelve months (RR 1.14; 95% CI 0.86–1.53) (21) (Figure 2; see eFigure 1 for long version).

The spectrum of available wound care products includes, for example, hydrocolloids, film overlays, foams, microfiber dressings, alginates, and polyacrylates, which are sold in various combinations of materials.

Wound fillers (e.g., alginates) are substances with which deep wounds can be filled; in contrast, hydrocolloids and films are laid over wounds. Some materials, such as foams, can be used in either manner, while others are offered in combination form, together with an active agent.

There was inadequate evidence to support any recommendation for or against most of the product groups used as wound care products, whether or not they contain an active ingredient. The experts, therefore, agreed to seek consensus on certain criteria for the selection of wound care products, to be issued as good clinical practice recommendations. These criteria include, for example,

- avoidance of pain,
- practicality for the patient,
- strength of adhesion,
- absorption and retention of exudate,
- avoidance of maceration.

The choice of wound care products depends, among other things, on the requirements of the wound situation, the patient’s goals, and cost considerations.
A physiologically moist environment in the wound should be created or maintained.

Wound care products containing silver do not promote wound healing to any significantly better extent than those that do not contain silver. This was the conclusion of four systematic reviews and nine randomized, controlled trials that fulfilled the criteria of the systematic literature search.

In vitro studies have shown that silver is both bactericidal and cytotoxic. There has not yet been any detailed comparative test of the various forms of silver-containing products that are currently sold (elementary-metallic, silver salts, ion exchangers).

Nor does the available evidence, some of which is of high quality (Table) (22), support any benefit on wound healing, or the prevention of infection, from cadexomer-iodine, PVP-iodine ointment, PVP-iodine gel, or PVP-iodine gauze. Less scientifically robust studies do, however, provide evidence of these substances’ toxicity, allergenicity, and iodine loading. Thus, in view of their questionable benefits and possible complications, these products are not recommended for use in the treatment of non-infected wounds.

In general, the local treatment of wounds must be based on knowledge of the materials used and their proper application, including their indications and contraindications and their allergenic and toxic potential (Figure 3; eFigure 2).

**Accompanying physical measures**

Various physical techniques, including vacuum therapy, stimulating current, shock-wave therapy, and magnetic-field therapy, are said to accelerate wound healing.

In recent years, vacuum sealing has come into very widespread use. The evaluation of the evidence for this technique is based on several systematic reviews (23–26).

The available data are insufficient to provide a basis for any clear recommendation in favor of vacuum sealing. The benefit of the technique has been demonstrated to date only with respect to surrogate variables such as reduction of wound size (standardized mean difference [SMD] 0.45; 95% CI 0.87–0.04) (26). Vacuum sealing can therefore be considered as an aid to wound dressing with the goal of a reduction of its depth or volume (grade 0 recommendation).

Magnetic-field therapy can be considered for the accompanying treatment of venous ulcers; here, however, the recommendation (grade 0) is based only on low-grade evidence (cf. Table) (RR 2.025; 95% CI 1.055 to 2.768) (27). The optimal duration and frequency of application and the optimal field intensity have yet to be determined.

There is good evidence for the efficacy of whole-body pressure-chamber therapy (hyperbaric oxygen therapy, HBO) in the treatment of diabetic foot ulcers for which other forms of treatment have not brought about complete healing (RR 2.14; 95% CI 1.18–3.88) (28). Moderately good evidence (Table) supports therapeutic benefit with respect to the endpoint that is perhaps most important to patients, i.e., reduction of the rate of major amputations (RR 0.31; 95% CI I 0.13–0.71) (29). On the basis of these data, the guideline contains a grade B recommendation that hyperbaric oxygen therapy should be used as an additional treatment option for patients with diabetic foot syndrome in whom all possible revascularization measures have been tried without success and the danger remains that the limb may have to be amputated.

No RCTs of adequate quality are available to support any evidence-based judgment of the putative clinical utility of ultrasound therapy, water-filtered infrared A light, low-energy lasers, or shock-wave therapy.
Care of patients with chronic wounds by caregivers from multiple sectors and professions

The literature review that was performed for the guideline revealed moderately good evidence (30) that patients with chronic ulcers who receive combined and integrated treatment by caregivers from multiple sectors and professions experience a therapeutic benefit from such treatment, with improvement in endpoints that patients consider important, including quality of life, everyday activities, and pain. Although the results of randomized and controlled trials cannot necessarily be extrapolated to the German healthcare system as a whole, there is similar evidence within the German healthcare system that structured care has, indeed, improved outcomes for diabetic patients (31, 32).

There was, therefore, a strong consensus among the experts for the following recommendation: “Patients should receive integrated treatment from caregivers from multiple sectors and professions, with the individual elements combined in a reasonable manner (grade B recommendation).” Examples of such elements include coordination by a single center, quality assurance, and cooperation across sectors and professions.

Strengths and limitations of this guideline

In the preparation of this guideline, the various methods of local treatment of chronic wounds were assessed for the first time ever with strict methods of evaluation and with the participation of all professions involved in wound care. The analysis of the evidence showed that it is entirely possible to carry out high-quality RCTs in this field (e.g., [21, 22, 28]; Figure 4).

Nonetheless, the guideline group found only very few RCTs whose methods were sound enough to make their conclusions robust, perhaps because the certification procedures for medicinal products in this field do not yet require any proof of therapeutic benefit (33). Graded recommendations (A, B, or O) are given in this guideline only where supported by adequate evidence from randomized, controlled studies or meta-analyses. Wherever this is not the case, the guideline makes statements and good clinical practice recommendations rather than graded recommendations.

High-quality evidence allowing a clear, positive recommendation (i.e., at least grade B) was found to exist only for HBO therapy and for integrated care strategies. In all cases where insufficient evidence was available from randomized controlled trials, the guideline group took care to formulate its recommendations cautiously and responsibly. Whenever an expert consensus could be obtained, criteria are given in the form of good clinical practice recommendations and statements, which are intended to serve as a practical aid to clinicians in combination with the highly detailed discussion of the evidence found in the guideline. The guideline should help make the treatment of wounds an area of well-founded medical expertise, in which clinical practice is based on scientific evidence and interdisciplinary collaboration rather than on supposed knowledge derived principally from advertising.

The guideline itself has been published on the website of the AWMF (in German). A short version is now in preparation.

Conflict of interest statement

Dr. Rütermann and Dr. Maier-Hasselmann state that they have no conflict of interest.

M. Burkhardt has received honoraria for lecturing at continuing education presentations of the Transfernetzwerk Bildung and the PFAD-Akademie (two private associations providing continuing education for health professionals).

B. Nink-Grebe has received funding from the Medi company for performing presentations of the Transfernetzwerk Bildung and the PFAD-Akademie (two private associations providing continuing education for health professionals).

REFERENCES


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eFigures:
www.aerzteblatt-international.de/13m0025
Is surgical debridement indicated by conditions such as the following: local evidence of infection, systemic infection originating from the wound, large areas of necrosis or necrotic wound areas and coatings?

**Wound cleansing**

Wound healing is impeded by the presence of dead tissue, foreign bodies, coatings, and detritus. Therefore, dead tissue should be removed down to anatomically intact structures, as far as possible without causing unnecessary discomfort (R16).

If wound cleansing is performed, it should be primarily mechanical (R17).

The available evidence does not permit any robust conclusion about the putative benefit of wound-cleansing solutions containing octenidine, polyhexanide, PVP-iodine, hydrogen peroxide, chlorhexidine, and dyes including ethacridine lactate.

Some substances may be toxic or allergenic or give rise to an iodine load, depending on their pharmacy compounding, concentration, and time to effect. Therefore, neutral solutions free of active substances are preferable for periodic wound cleansing (R19).

**Exception:**

If wound infection is suspected, cleansing with an approved antiseptic solution containing polyhexanide, octenidine, or PVP-iodine can be considered (R20).

Wound cleansing should be accompanied by adequate analgesia when necessary (R18).

**Initial surgical debridement**

Wound healing is impeded by the presence of dead tissue, foreign bodies, coatings, and detritus. Therefore, the first step of care consists of the radical removal of dead tissue up to and including the top layers of anatomically intact structures, as far as possible without causing unnecessary discomfort (R25).

Surgical debridement should be accompanied by adequate analgesia when necessary (R26).

**Dead tissue, necrosis, coatings, and/or foreign bodies completely removed**

Repeat if necessary
Wound treatment should create and maintain a physiologically moist environment in the wound. An exception may be made to this rule when the creation or maintenance of dry necrosis is advantageous, e.g., in distal end-stage diabetic gangrene (R28).

The choice of materials should depend on the patient’s goals, the requirements of the wound situation, and cost considerations. The criteria to be borne in mind are: avoidance of pain, practicality for the patient, state of the wound edge and surroundings, adhesiveness, ability to absorb and retain exudate, allergies, and side effects (R29).

Accompanying physical measures:
- Limb at risk for amputation → HBO (R35)
- Other physical measures such as topical negative pressure therapy (R33), magnetic field treatment (R34).

The wound should be regularly re-evaluated over the course of treatment, particularly when any change of therapy is made or contemplated (R7).

Is dry necrosis present?
- Yes: Necroses should not be rehydrated (R23). Goal: keep necrosis dry
- No

Marked exudate?
- Yes: Use of highly absorbent materials (wound fillers and/or coverings) with high absorption and retention of exudates;
  - if necessary, additional measures for skin care and protection to maintain skin barrier function (R32)
- No

Moderate exudate?
- Yes: Use of materials (wound fillers and/or coverings) with adequate, moderate absorption and retention of exudates combined with maintenance of a physiologically moist environment in the wound
- No

Mild exudate?
- Yes: Use of materials (wound fillers and/or coverings) that create or maintain a physiologically moist environment in the wound
- No

Further goals:
- Avoidance of fluid leak from under dressing (R14)
- Prevention of maceration and drying of the wound edge and surroundings (R32)
- Protection of the wound edge and surroundings (R32)
- Maintenance of skin barrier function (R32)

Healed wound