Treatment of chronic ulcers

A critical short analysis

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Summary
Chronic ulcers (CUs) are a major cause of morbidity and mortality with increasing prevalence, in part due to the ageing population, and an increase of risk factors such as diabetes and obesity. CUs are caused by numerous diseases including venous dysfunction, diabetes mellitus, infections, peripheral neuropathy, pressure, and atherosclerosis. The current standard therapy for CUs includes compression, surgical débridement, infection control, and adequate wound dressings. As a high percentage of CUs do not adequately heal or quickly relapse with standard treatments, additional therapeutic approaches are pursued, termed “advanced wound care therapies”. Here, an overview on commonly applied therapies lacking significant evidence for wound healing is reviewed, followed by therapies with significant evidence supporting the routine use in the treatment of CUs, and a short outlook in a possible future wound treatment landscape. To give a résumé, the presented literature reveals that most of the commonly applied topical and advanced ulcer treatments largely lack solid scientific evidence for the induction or acceleration of wound healing. Surprisingly only “classical” treatments such as wound cleansing, débridement and compression have significant evidence. Novel approaches such as bilayered skin reconstructs, cell suspensions or extracorporal shock waves seem promising. Considering the increasing number of ulcer patients, there is a strong need for further basic research to fully understand all factors involved in wound development and healing of the various ulcer pathophysologies, and the urgent need for prospective clinical trials comparing the various treatment options.

Schlüsselwörter
Ulkus, Wundbehandlung, Wundaufflage, Therapie

Zusammenfassung
Chronic ulcers (CUs) are a major cause of morbidity and mortality with increasing prevalence, in part due to the ageing population, and an increase of risk factors such as diabetes and obesity (27, 35). CUs can be defined as a disruption of skin tissue that takes more than six weeks to heal (37). CUs are caused by numerous diseases including venous dysfunction, diabetes mellitus, infections, peripheral neuropathy, immobility and pressure, rheumatologic diseases, and atherosclerosis. Non-healing CUs are often a result of a complex cascade of several pathogenetic factors.

For diabetic foot ulcers, epigenetic mechanisms such as DNA methylation from long standing hyperglycemia and non-coding RNAs seem to have a key role in the complex interplay between genes and the environment (24). Venous disease is the major reason for the development of chronic leg ulcers (CLU). Chronic venous hypertension will eventually damage the vessel walls, thus causing the development of edema and other pathological skin conditions such as purpura jaune docre, eczema, atrophy blanche, and eventually skin breakdown with ulceration (8).

Additional, cellular factors contributing to the development of venous ulcers are inflammatory processes resulting in disturbed microcirculation, leukocyte activation, dysregulated epidermal and dermal cells, and a variety of endocrine mechanisms (1, 7, 46). CLUs severely lower the quality of life and productivity of afflicted patients (22, 47, 48). In the U.S. between 500,000 and 2 million persons annually suffer from venous CLUs, thus accounting for >50% of lower leg ulcers (32, 44). The prevalence of CLU varies from country to country: 0.62/1000 in Australia, 1/1000 in China, 1.6/1000 in Sweden, 1.5 to 3/1000 in the United Kingdom (reviewed by [54]). In Germany, the overall estimated incidence rate of active venous CLU of all insured persons was 0.34% from 2010 to 2012. Adapted to the overall German population, n = 229,369 persons nationwide suffered from active venous CLU in 2010–2012 (23). The current standard therapy for venous CLUs includes compression therapy, surgical débridement, infection control, and local ulcer care using various wound dressings. Thus, approximately 50–60% of venous leg ulcers can be healed (6). The direct costs for care of CLUs including their complications amount to approximately 25 billion dollars per year in the U.S. (49), representing one of the largest cost factors for public health care. In Germany, the annual total costs of leg ulcer care are 9060 €/patient/year, amounting to more than 6 billion € in 2010–2012 (5).

A high percentage of chronic ulcers do not adequately heal or quickly relapse with standard treatments. Therefore, additional therapeutic approaches are pursued, that are termed “advanced wound care therapies”. Yet, clinical evidence of efficacy in terms of induction of healing and/or shortening the healing time of most of the commonly applied “classical” and “advanced” therapies is limited. To make a long story short, there is surprisingly little evidence that any given topical treatment or dressing induces or accelerates the healing of chronic (venous) ulcers (55). In the following, an overview on commonly applied therapies lacking evidence for healing of chronic ulcers is summarized, followed by therapies with significant evidence supporting the routine use in the treatment of chronic ulcers, and an outlook in a possible future wound treatment landscape. In particular, the respective Cochrane Database systematic reviews were analyzed.

Methods
For this article a literature search was conducted in PubMed using the following key words (in various combinations): leg ulcer, wound, healing, therapy, wound dressing, venous disease, Cochrane Database. Additional papers were identified from reference lists in published papers.

Results
1. Therapies lacking evidence for the induction or acceleration of ulcer healing:
There is insufficient evidence to determine whether the choice of topical agent or dressing affects the healing of arterial leg ulcers (21). Likewise, there is currently no robust evidence for differences between wound dressings for any outcome in diabetic foot ulcers (53). In particular, hydrogel is not more effective than larval therapy or platelet-derived growth factors in healing diabetic foot ulcers (18) and alginate or foam wound dressings are not more effective in healing diabetic foot ulcers than other types of dressing (17, 14). In line, there is no evidence for effects of alginate or hydrogel dressings compared with alternative treatments for pressure ulcers (15, 19).

The same holds true for dressings in venous ulcers: foam dressings are not more effective than other wound dressings, and alginate dressings are not more or less effective than hydrocolloid or plain non-adherent dressings (42, 43). As far as „advanced wound care therapies“ are concerned, there is no evidence on the effectiveness of negative pressure wound therapy (NPWT) as a primary treatment for chronic leg ulcers (16). For hyperbaric oxygen therapy (HBOT), an increased rate of healing of diabetic foot ulcers was observed only at six weeks, but there was neither benefit at one year nor a difference in major amputation rate. For venous ulcers, HBOT showed only a short-term benefit at six weeks in terms of wound size reduction and complete healing, but not at 18 weeks (30). The evidence for honey as topical treatment for chronic wounds was not considered as convincing (25), and there is no evidence for the use of Aloe vera in the treatment of chronic wounds (12).

There is some evidence that supports the use of cadexomer iodine as topical antiseptic, but no evidence for the routine use of honey- or silver-based products as antiseptics on venous ulcers (40). There is insufficient evidence for a definite conclusion for the application of phototherapy (UV, laser) for the treatment of pressure ulcers (10). As far as systemically administered therapies are concerned, there was neither evidence that oral zinc sulphate improves the healing of arterial and venous leg ulcers (52), nor that the routine use of oral antibiotics promotes healing of venous leg ulcers (40). For the treatment of diabetic ulcers, the systemic administration of granulocyte-colony stimulating factor (G-CSF) does not increase the likelihood of resolution of infection or wound healing (11).
2. Therapies with significant evidence for the induction or acceleration of ulcer healing:

Compression increases venous leg ulcer healing rates compared with no compression; multi-component compression systems (short stretch bandage) are more effective than single-component systems, and more patients heal on high-compression stocking systems than with the short stretch bandage (41); the two-layer bandage is as effective as the four-layer bandage in the treatment of venous leg ulcers (3).

In this respect, a recent consensus paper on practical aspects of compression therapy in patients with venous leg ulcers provides detailed recommendations for routine implementation of compression therapy (13). Maggot therapy for débridement of chronic ulcers is significantly better for wound healing and more cost-effective than conventional wound therapy (51).

The latter observation was confirmed by a recent randomized clinical trial showing that larval therapy, in the form of a BioFOAM dressing, débrided venous ulcers and mixed arterial/venous ulcers considerably more quickly than a hydrogel (36). There is no evidence that using tap water to cleanse acute wounds in adults increases infection compared to normal saline, and some evidence that it reduces it. In Pacific Northwest Veterans with diabetic/neuropathic ulcers, the chance of healing increases 2.5-fold when débridement is performed at 80% of visits, and doubles when ischemia is assessed at the first visit (26). Adhering to treatment modalities with proven evidence (such as compression, débridement and regular cleansing of the wound) in a surrounding of structured wound management such as the Swedish Registry of Ulcer Treatment significantly shortens the healing times and thus reduces treatment costs (39). Sulodexide, a highly purified glycosaminoglycan with antithrombotic and profibrinolytic properties as well as anti-inflammatory effects, may increase the healing of venous ulcers, when used alongside local wound care (application route: intramuscular injection or orally). However, the evidence is of low quality only due to risk of bias and needs to be confirmed by future trials (54).

3. Novel treatment options:

Regarding the high number of therapies largely lacking evidence in the healing of chronic ulcers, the high financial burden to the public health systems, and the amount of suffering imposed on the millions of afflicted patients (4), there is a high need for novel therapeutic approaches for the treatment of chronic ulcers.

A more recent development as advanced wound treatment modality is a biologically engineered living skin reconstruct, also termed bilayered living cellular construct (BLCC). The effectiveness of a BLCC (Apligraf®) and an acellular porcine small intestine submucosa collagen dressing (SIS) for the treatment of venous leg ulcer was compared by using data from a national wound-specific electronic medical record (Wound-Expert, Net Health, Pittsburgh, PA) (33).

In the latter study data from 1,489 patients with 1,801 refractory venous leg ulcers (as defined by failure to have >40% reduction in size in the 4 weeks prior to treatment) with surface areas between 1 and 150 cm² in size were analyzed. In this retrospective analysis, Kaplan-Meier-derived estimates of wound closure for BLCC (1,451 wounds) was significantly greater by weeks 12 (31 vs. 26%), 24 (50 vs. 41%), and 36 (61 vs. 46%), respectively, compared with SIS (350 wounds). BLCC treatment reduced the median time to wound closure by 44%, achieving healing 19 weeks sooner (24 vs. 43 weeks).

However, the arbitrary definition of a therapy refractory ulcer this this study (failure to have >40% reduction in size in the 4 weeks prior to treatment) and ulcer sizes from 1 to 150 cm² make a general interpretation of the results almost impossible. Furthermore, the authors did not verify the effectiveness of either BLCC or SIS treatments in comparison to the continuation of standard ulcer treatment for more than 4 weeks, which is an unusually short duration for a standard therapy in ulcer care. In a follow-up study by the same team of authors the effectiveness of BLCC (Apligraf®) was compared to a dehydrated human amnion/chorion membrane allograft (dHACM) for the treatment of diabetic foot ulcers (DFUs) in 218 patients with 226 DFUs at 99 wound care centers using the same medical database (29).

The latter retrospective analysis included DFUs ≥1 and <25 cm² with duration ≤1 year and area reduction ≤20% in 14 days prior to treatment (N=163, BLCC; N=63, dHACM). The median time to closure for BLCC was 13.3 weeks compared to 26 weeks for dHACM, and the proportion of wounds healed were significantly higher for BLCC by 12 weeks (48 vs. 28%) and 24 weeks (72 vs. 47%). However, the fact the 218 patients were treated in 99 different wound care centres, the inclusion criteria of patients, and the conflicts of interest of all the authors of the latter two studies considerably lower the significance of the results presented.

Prospective studies comparing standard ulcer care with Apligraf® are still missing for venous ulcers. Nevertheless, such biologically engineered human skin reconstructs represent an interesting novel therapeutic approach for non-healing ulcers. A comprehensive overview of the different types of currently available commercial skin substitutes for use in chronic wounds, including a critical analysis of cost-effectiveness, was recently published (38).

A comparable approach using human tissue to promote wound healing is the application of cryopreserved umbilical cord. A recent study suggested that cryopreserved umbilical cord used as an adjunctive tissue therapy in conjunction with surgical débridement, resection of infected bone, open cortex, and antibiotic treatment may be an effective overall treatment strategy to promote wound healing of complex foot ulcers associated with osteomyelitis (9). In the latter retrospective study 79% of treated wounds achieved complete wound closure.

Since the “active” compounds of such skin reconstructs driving wound healing are cytokines secreted by fibroblasts and keratinocytes (such as vascular endothelial growth factor, basic fibroblast growth factor, keratinocyte growth factor, transforming growth factor α), it can be speculated that topical application of a cocktail of such isolated cytokines or the isolated cells themselves should have a similar impact on wound healing.

In line with this assumption, a prospective clinical trial assessed the efficacy of a spray-applied cell therapy containing growth-arrested allogeneic neonatal keratinocytes and fibroblasts when applied to chronic venous leg ulcers (28). In the latter
study, primary outcome analysis demonstrated greater mean reduction in wound area associated with active treatment compared with vehicle, with the dose of 0.5 × 10^5 cells/mL every 14 days showing the largest improvement compared with vehicle (15.98%). This study suggested that allogeneic cell therapy for venous leg ulcers is somehow effective; however, an additional size reduction of only 15.98% compared to the vehicle group questions whether such a therapy, which is likely to be very expensive, will become a standard therapy.

Similar to the spray-applied cell therapy described above, the application of autologous platelet-rich plasma (PRP) containing fibrin and high concentrations of growth factors is suggested as treatment for chronic ulcers. Indeed, PRP improves the healing of foot ulcers associated with diabetes, but this conclusion is based on low quality evidence from two small randomized controlled trials. It remains unclear whether PRP influences the healing of other chronic wounds. Thus, the overall quality of evidence of autologous PRP for treating chronic wounds is still low (34).

During the past years, the application of extracorporeal shock wave (ESW) therapy (ESWT) has been extended to a variety of pathological conditions. ESWs are defined as a sequence of acoustic pulses characterized by ultrafast pressure rise within several nanoseconds, a high peak pressure (100 MPa), and short duration of several microseconds. The greater the difference in impedance the more energy is released in form of mechanical energy. ESWs are conveyed to a specific target area by an appropriate generator with an energy density in the range of 0–3 mJ/mm². ESWT employs medical high-energy focused shockwaves such as generated by the electro-hydraulic CellSonic® medical machine.

Increasing evidence suggests that ESWT supports healing of therapy-refractory ulcers (31, 45, 50). In a current study, we analysed the effects of shock waves (CellSonic®) on human fibroblasts, keratinocytes, and microvascular endothelial cells (2). Our in vitro analyses demonstrated an induction of a comprehensive wound healing program on the molecular and the morphological levels by shock waves in all three cell types analysed. We therefore treated 60 consecutive patients with 75 therapy-refractory chronic ulcers with various underlying diseases with ESWT during ambulant routine visits at the Department of Dermatology, Tuebingen, Germany. Our retrospective analysis showed that 41% of ESWT-treated chronic ulcers showed complete healing, 16% significant improvement (>75% size reduction), 35% improvement (20–75% wound size reduction), while only 8% of the ulcers did not improve under ESWT (<20% wound size reduction). The induction of healing by ESWT was independent of patient age, duration of the ulcer, size of the ulcer, and the underlying pathophysiology (2).

Encouraged by these clinical results, the authors have implemented ESWT as routine ulcer treatment in addition to “classical” ulcer care. Our standard weekly/bi-weekly routine ulcer treatment algorithm (e.g. for venous leg ulcers or diabetic foot ulcers) is as follows: 1. cleansing/disinfection of the wound with Octenisept® for 3 min, 2. application of ESWT (CellSonic®) onto the entire wound surface and edges, 3. surgical débridement using a ring curette (which is much easier to perform after ESWT), 4. measurement and photo-documentation of the wound, 5. application of a wound dressing (e.g. Mepilex®, Allevyn®, Aquacel®, Sorbact Gel®), 6. compression, if indicated, using the Rosidal® TCS System or two-layered ulcer compression stockings. If necessary, additional advanced therapies are applied (e.g. Apligraf®, PICO®).

Figure 1 depicts three exemplary ulcers treated with ESWT, which was performed as supportive therapy in addition...
to standard care that had failed to heal the ulcers at external dermatological practices. All three patients were carefully instructed about the compassionate use of ESWT (lacking data of prospective clinical trials for the specific application on chronic venous leg ulcers), and gave written informed consent. ESWT was well tolerated and performed every 7–14 days. The number of pressure impulses applied per treatment was calculated according to the size of the ulcer: 100 impulses per cm² + 200 impulses. The pressure impulses were homogeneously applied to the entire surface of the ulcer plus the edges of the wound. Patient No. 1 (three ulcers on both legs) received a total of 17 ESWT, patient No. 2 (one ulcer) 11 ESWT, and patient No. 3 (four ulcers on one leg) 10 ESWT. All ulcers healed after ESWT (ulcer images are published with written informed consent of the patients); a clinical effectiveness could be observed already after the first application of ESWT in all three patients.

To give a résumé, the above presented literature shows that the current ulcer treatment landscape largely lacks scientifically proven treatment options both topically and systemically. As limiting factor, we obviously discussed only a fraction of all available options for wound therapies and might additionally have missed efficacious treatment approaches during our literature search. Yet, it seems odd that only classical treatments such as disinfection/cleansing of the wounds, debridement and compression have convincing evidence, while the variety of wound dressings or advanced therapies do not seem to positively influence wound healing so far. Novel approaches such as biotechnologically engineered skin grafts, cell grafts or extracorporeal shock waves seem promising.

Taken together, there is a strong need for further basic research to fully understand all factors involved in wound development and healing, and the urgent need for clinical trials comparing the various treatment options.

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### Conflict of interest
The authors declare that there is no financial conflict of interest.

### Ethical guidelines
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### References


