Treatment of chronic ulcers

A critical short analysis

Ch. Busch[1,2]; I. Aschermann[1]; Ch.D. Mnich[2]

[1]Department of Dermatology, University of Tuebingen, Germany, [2]Dermateam, Bankstrasse 4, CH-8400 Winterthur, Switzerland

Keywords
Ulcer, wound healing, wound dressing, therapy

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 pathophysiologies, and the urgent need for prospective clinical trials comparing the various treatment options.

Schlüsselwörter
Ulkus, Wundbehandlung, Wundauflage, Therapie

Zusammenfassung
Das chronische Ulkus ist eine schwerwiegende Erkrankung mit steigender Inzidenz, was vor allem auf die alternde Gesellschaft und die Zunahme von Risikofaktoren wie Diabetes mellitus und Adipositas zurückzuführen ist. Chronische Ulzera haben vielerlei zugrundeliegende Pathologien wie beispielsweise venöse Dysfunktion, Diabetes mellitus, Infektionen, Neuropathie, Druck und Atherosklerose. Die gegenwärtige Standardbehandlung des chronischen Ulkus beinhaltet Kompression, Débridement, Infektionsprophylaxe sowie der Heilungsphase angepasste Wundauflagen. Da ein grosser Anteil chronischer Wunden unter der Standardbehandlung nicht vollständig abheilt oder rasch rezidiviert, werden häufig moderne Zusatzbehandlungen notwendig. Im vorliegenden Übersichtsartikel wurde mittels Literaturrecherche die aktuelle Datenlage bezüglich Wundbehandlungen untersucht. Insbesondere wurde gezielt danach gefragt, in wie fern sich die jeweiligen Behandlungsmethoden auf wissenschaftliche Evidenz stützen, bzw. für welche Behandlungsmethoden es keine belastbaren wissenschaftlichen Daten gibt. Darüber hinaus wurden neuartige Wundbehandlungen untersucht, welche in Zukunft eine wichtige Rolle in der Wundbehandlung spielen könnten.
Zusammenfassend lässt sich feststellen, dass die meisten der derzeitigen klassischen und modernen Wundbehandlungen auf nur wenig belastbaren wissenschaftlichen Daten beruhen und der Evidenzgrad in Bezug auf Induktion bzw. Beschleunigung der Wundheilung sehr niedrig ist. Erstaunlicherweise lassen sich aus den vorliegenden Studiendaten bisher nur klassische Behandlungen wie Wundreinigung, Débridement und Kompression als gesicherte Therapien mit solider Evidenzlage ableiten. Neue Therapieansätze wie zelluläre zweischichtige Hautrekonstrukte, Zellsuspensionen oder extrakorporale Stoßwellen scheinen wirksam zu sein. In Anbetracht der steigenden Inzidenz des chronischen Ulkus ist weitere Grundlagenforschung dringend notwendig, um die Mechanismen der Wundentstehung und -heilung der verschiedenen zugrundeliegenden Pathophysiologien im Detail zu verstehen. Darüber hinaus besteht eine große Notwendigkeit für klinische Studien, in denen die verschiedenen Behandlungsoptionen prospektiv miteinander verglichen werden.

Corresponding author
Dr. med. Christian Busch
Department of Dermatology, University of Tuebingen
Liebermeisterstr. 20, D-72076 Tuebingen, Germany
E-mail: Christian.Busch@med.uni-tuebingen.de

Die Behandlung chronischer Ulzera
Eine kritische Bestandsaufnahme
Phlebologie 2017; 46: 13–18
https://doi.org/10.12687/phleb2327-1-2017
Received: July 8, 2016
Accepted: December 22, 2016

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 (CLUs). Chronic venous hypertension will eventually damage the vessel walls, thus causing the development of edema and other pathological skin conditions such as purpura jaune d'ocre, 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 (WoundExpert, 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 cm^2 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 cm^2 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 cm^2 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 extracorporal 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/mm^2. 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/biweekly 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

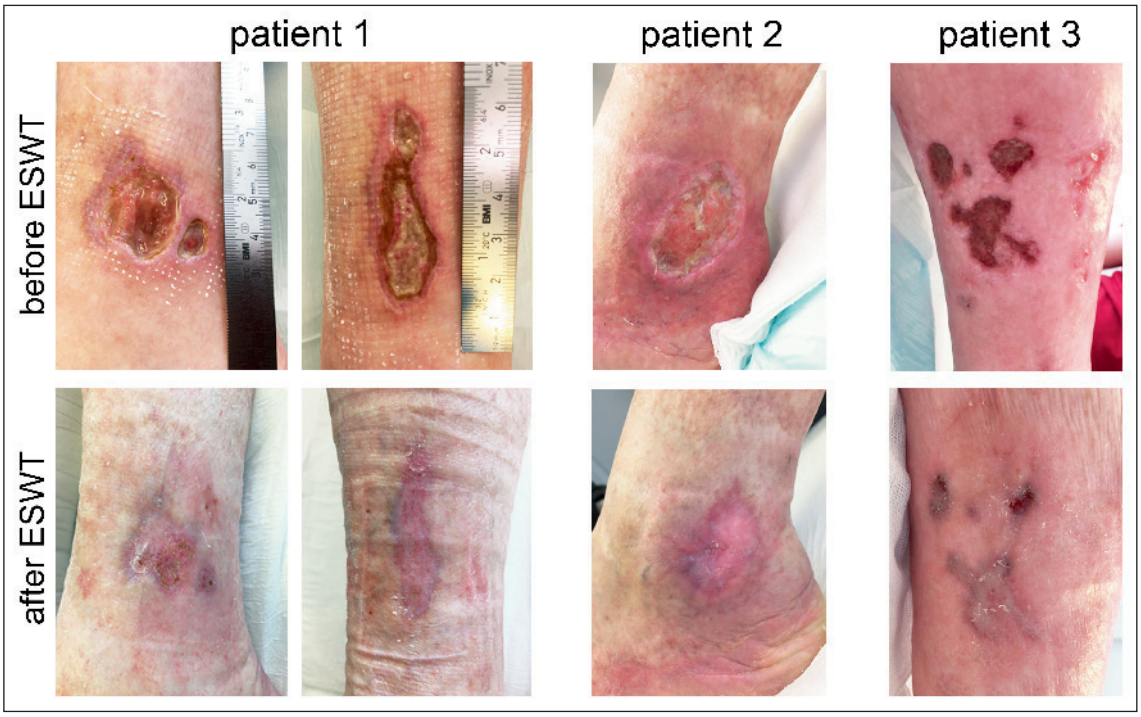

Fig. 1 Extracorporal shock wave therapy induces healing of chronic venous leg ulcers. Images before and after extracorporal shock wave therapy (CellSonic®) as compassionate use on three patients.

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 cm^2 + 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, débridement 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 biotechnically engineered skin grafts, cell grafts or extracorporal 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.

Sources of Funding

The own works cited were enabled by research grants to CB by the Deutsche Gesellschaft für Phlebologie (DGP).

Conflict of interest

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

Ethical guidelines

The manuscript was prepared in accordance with national ethical guidelines and the current Declaration of Helsinki.

References

1. Adams J, Schott S, Bern A, et al. A novel role for relaxin-2 in the pathogenesis of primary varicosis. PLoS One 2012; 7: e39021.
2. Aschermann A, Noor S, Venturelli S, et al. Extracorporal shock waves activate migration, proliferation and inflammatory pathways in fibroblasts and keratinocytes, and improve wound healing in an open-label, single-arm study in patients with therapy-refractory chronic leg ulcers. Cell Physiol Biochem 2017; in press.
3. Ashby RL, Gabe R, Ali S, et al. Clinical and cost-effectiveness of compression hosiery versus compression bandages in treatment of venous leg ulcers (Venous leg Ulcer Study IV, VenUS IV): a randomised controlled trial. Lancet 2014; 383: 871–879.
4. Augustin M. Cumulative life course impairment in chronic wounds. Curr Probl Dermatol 2013; 44: 125–129.
5. Augustin M, Brocatti LK, Rustenbach SJ, Schäfer I, Herberger K. Cost-of-illness of leg ulcers in the community. Int Wound J 2014; 11: 283–292.
6. Bergan JJ, Schmid-Schonbein GW, Smith PD, et al. Chronic venous disease. N Engl J Med 2006; 355: 488–498.
7. Busch C, Schnabl S, Strölin A. Endocrine mechanisms in the pathogenesis of primary varicosis. Phlebologie 2013; 42: 13–18.
8. Busch C, Schnabl S. Characteristic skin changes in CVI. Phlebologie 2014; 43: 108–111.
9. Caputo WJ, Vaquero C, Monterosa A, et al. A retrospective study of cryopreserved umbilical cord as an adjunctive therapy to promote the healing of chronic, complex foot ulcers with underlying osteomyelitis. Wound Repair Regen 2016; 24: 885–893.
10. Chen C, Hou WH, Chan ES, Yeh ML, Lo HL. Phototherapy for treating pressure ulcers. Cochrane Database Syst Rev 2014; 7: CD009224.
11. Cruciani M, Lipsky BA, Mengoli C, de Lalla F. Granulocyte-colony stimulating factors as adjunctive therapy for diabetic foot infections. Cochrane Database Syst Rev 2013; 8: CD006810.
12. Dat AD, Poon F, Pham KB, Doust J. Aloe vera for treating acute and chronic wounds. Cochrane Database Syst Rev 2012; 2: CD008762.
13. Dissemond J, Assenheimer B, Bültemann A, et al. Compression therapy in patients with venous leg ulcers. J Dtsch Dermatol Ges 2016; 14: 1072–1087.
14. Dumville JC, Deshpande S, O'Meara S, Speak K. Foam dressings for healing diabetic foot ulcers. Cochrane Database Syst Rev. 2013; 6: CD009111.
15. Dumville JC, Keogh SJ, Liu Z, Stubbs N, Walker RM, Fortnam M. Alginate dressings for treating pressure ulcers. Cochrane Database Syst Rev 2015; 5: CD011277.
16. Dumville JC, Land L, Evans D, Peinemann F. Negative pressure wound therapy for treating leg ulcers. Cochrane Database Syst Rev 2015; 7: CD011354.
17. Dumville JC, O'Meara S, Deshpande S, Speak K. Alginate dressings for healing diabetic foot ulcers. Cochrane Database Syst Rev 2013; 6: CD009110.
18. Dumville JC, O'Meara S, Deshpande S, Speak K. Hydrogel dressings for healing diabetic foot ulcers. Cochrane Database Syst Rev 2013; 7: CD009101.
19. Dumville JC, Stubbs N, Keogh SJ, Walker RM, Liu Z. Hydrogel dressings for treating pressure ulcers. Cochrane Database Syst Rev 2015; 2: CD011226.
20. Fernandez R, Griffiths R. Water for wound cleansing. Cochrane Database Syst Rev 2012; 2: CD003861.
21. Forster R, Pagnamenta F. Dressings and topical agents for arterial leg ulcers. Cochrane Database Syst Rev 2015; 6: CD001836.
22. Green J, Jester R, McKinley R, Pooler A. The impact of chronic venous leg ulcers: a systematic review. J Wound Care 2014; 23: 601–612.
23. Heyer K, Protz K, Glaeske G, Augustin M. Epidemiology and use of compression treatment in venous leg ulcers: nationwide claims data analysis in Germany. Int Wound J 2016 May 19. doi: 10.1111/iwj.12605. [Epub ahead of print].
24. Jhamb S, Vangaveti VN, Malabu UH. Genetic and molecular basis of diabetic foot ulcers: Clinical review. J Tissue Viability 2016; 25: 229–236.
25. Jull AB, Cullum N, Dumville JC, Westby MJ, Deshpande S, Walker N. Honey as a topical treatment for wounds. Cochrane Database Syst Rev 2015; 3: CD005083.
26. Karavan M, Olerud J, Bouldin E, Taylor L, Reiber GE. Evidence-based chronic ulcer care and lower limb outcomes among Pacific Northwest Veterans. Wound Repair Regen 2015; 23: 745–752.
27. Kelly T, Yang W, Chen CS, Reynolds K, He J. Global burden of obesity in 2005 and projections to 2030. Int J Obes 2008; 32: 1431–1437.
28. Kirsner RS, Marston WA, Snyder RJ, et al. Spray-applied cell therapy with human allogeneic fibroblasts and keratinocytes for the treatment of chronic venous leg ulcers: a phase 2, multicentre, double-blind, randomised, placebo-controlled trial. Lancet 2012; 380: 977–985.
29. Kirsner RS, Sabolinski ML, Parsons NB, Skornicki M, Marston WA. Comparative effectiveness of a bioengineered living cellular construct vs. a dehydrated human amniotic membrane allograft for the treatment of diabetic foot ulcers in a real world setting. Wound Repair Regen 2015; 23: 737–744.
30. Kranke P, Bennett MH, Martyn-St James M, et al. Hyperbaric oxygen therapy for chronic wounds. Cochrane Database Syst Rev 2015; 6: CD004123.
31. Larking AM, Duport S, Clinton M, Hardy M, Andrews K. Randomized control of extracorporeal shock wave therapy versus placebo for chronic decubitus ulceration. Clin Rehabil 2010; 24: 222–229.
32. Margolis DJ, Bilker W, Santanna J, Baumgarten M. Venous leg ulcer: incidence and prevalence in the elderly. J Am Acad Dermatol 2002; 46: 381–386.
33. Marston WA, Sabolinski ML, Parsons NB, Kirsner RS. Comparative effectiveness of a bilayered living cellular construct and a porcine collagen wound

dressing in the treatment of venous leg ulcers. Wound Repair Regen 2014; 22: 334–340.
34. Martinez-Zapata MJ, Martí-Carvajal AJ, Solà I, et al. Autologous platelet-rich plasma for treating chronic wounds. Cochrane Database Syst Rev 2016; 5: CD006899.
35. Mensah GA, Brown DW. An overview of cardiovascular disease burden in the United States. Health Aff 2007; 26: 38–48.
36. Mudge E, Price P, Walkley N, Harding KG. A randomized controlled trial of larval therapy for the debridement of leg ulcers: results of a multicentre, randomized, controlled, open, observer blind, parallel group study. Wound Repair Regen 2014; 22: 43–51.
37. Nelson EA, Adderley U. Venous leg ulcers. BMJ Clin Evid 2016; pii: 1902.
38. Nicholas MN, Yeung J. Current Status and Future of Skin Substitutes for Chronic Wound Healing. J Cutan Med Surg 2016 Aug 16. pii: 1203475416664037. [Epub ahead of print].
39. Öien RF, Forssell H, Ragnarson Tennvall G. Cost consequences due to reduced ulcer healing times – analyses based on the Swedish Registry of Ulcer Treatment. Int Wound J 2016; 13: 957–962.
40. O'Meara S, Al-Kurdi D, Ologun Y, et al. Antibiotics and antiseptics for venous leg ulcers. Cochrane Database Syst Rev 2014; 1: CD003557.
41. O'Meara S, Cullum N, Nelson EA, Dumville JC. Compression for venous leg ulcers. Cochrane Database Syst Rev 2012; 11: CD000265.
42. O'Meara S, Martyn-St James M. Alginate dressings for venous leg ulcers. Cochrane Database Syst Rev 2013; 4: CD010182.
43. O'Meara S, Martyn-St James M. Foam dressings for venous leg ulcers. Cochrane Database Syst Rev 2013; 5: CD009907.
44. Raju S, Neglen P. Clinical practice. Chronic venous insufficiency and varicose veins. N Engl J Med 2009; 360: 2319–2327.
45. Saggini R, Figus A, Troccola A, et al. Extracorporeal shock wave therapy for management of chronic ulcers in the lower extremities. Ultrasound Med Biol 2008; 34: 1261–1271.
46. Schott S, Adams J, Bern A, Garbe C, Busch C. Expression of oxytocin and its receptor in healthy and varicose great saphenous veins. Pathology 2012; 44: 670–673.
47. Schryvers OI, Stranc MF, Nance PW. Surgical treatment of pressure ulcers: 20-year experience. Arch Phys Med Rehabil 2000; 81: 1556–1562.
48. Scottish Intercollegiate Guidelines Network (SIGN), Management of chronic venous leg ulcers; A national clinical guideline (2010).
49. Sen CK, Gordillo GM, Roy S, et al. Human skin wounds: a major and snowballing threat to public health and the economy: perspective article. Wound Repair Regen 2009; 17: 763–771.
50. Stieger M, Schmid JP, Bajrami S, Hunziker T. Extracorporeal shock wave therapy as a treatment of a non-healing chronic leg ulcer. Hautarzt 2013; 64: 443–446.
51. Wilasrusmee C, Marjareonrungrung M, Eamkong S, et al. Maggot therapy for chronic ulcer: a retrospective cohort and a meta-analysis. Asian J Surg 2014; 37: 138–147.
52. Wilkinson EA. Oral zinc for arterial and venous leg ulcers. Cochrane Database Syst Rev 2014; 9: CD001273.
53. Wu L, Norman G, Dumville JC, et al. Dressings for treating foot ulcers in people with diabetes: an overview of systematic reviews. Cochrane Database Syst Rev 2015; 7: CD010471.
54. Wu B, Lu J, Yang M, Xu T. Sulodexide for treating venous leg ulcers. Cochrane Database Syst Rev 2016; 6: CD010694.
55. Zenilman J, Valle MF, Malas MB, et al. Chronic Venous Ulcers: A Comparative Effectiveness Review of Treatment Modalities [Internet]. Rockville (MD): Agency for Healthcare Research and Quality (US); 2013 Dec. Report No.: 13(14)-EHC121-EF.