

Kriterien zur Bestimmung der zweckmäßigen Vergleichstherapie

und

Recherche und Synopse der Evidenz zur Bestimmung der zweckmäßigen Vergleichstherapie nach § 35a SGB V

**Vorgang: 2014-06-01-D-115
Lebende Larven von *Lucilia sericata***

Stand: 01.09.2014

I. Zweckmäßige Vergleichstherapie: Kriterien gemäß 5. Kapitel § 6 VerfO G-BA

Lebende Larven von *Lucilia sericata* [Anwendungsgebiet abgekürzt]

Kriterien gemäß 5. Kapitel § 6 VerfO

Sofern als Vergleichstherapie eine Arzneimittelanwendung in Betracht kommt, muss das Arzneimittel grundsätzlich eine Zulassung für das Anwendungsgebiet haben.	Siehe Tabelle II. Zugelassene Arzneimittel im Anwendungsgebiet
Sofern als Vergleichstherapie eine nicht-medikamentöse Behandlung in Betracht kommt, muss diese im Rahmen der GKV erbringbar sein.	Chirurgisches Debridement, Mechanisches Debridement (inkl. Ultraschall-Debridement, Wasserstrahldruck), Autolytisches Debridement
Beschlüsse/Bewertungen/Empfehlungen des Gemeinsamen Bundesausschusses zu im Anwendungsgebiet zugelassenen Arzneimitteln/nicht-medikamentösen Behandlungen	Es liegen keine Beschlüsse vor
Die Vergleichstherapie soll nach dem allgemein anerkannten Stand der medizinischen Erkenntnisse zur zweckmäßigen Therapie im Anwendungsgebiet gehören.	<i>Siehe systematische Literaturrecherche</i>

I. Zugelassene Arzneimittel im Anwendungsgebiet

Wirkstoff ATC-Code Handelsname	Anwendungsgebiet (Text aus Fachinformation)
Zu bewertendes Arzneimittel:	
Goldfliegenlarven, lebend D03AX32 BioMonde BioBag, BioMonde Freie Larven	Anwendungsgebiet laut Zulassung (DIMDI-Datenbank): Debridement belegter chronischer oder schwer heilender Wunden, wenn eine instrumental-chirurgische Behandlung nicht erwünscht ist
Zweckmäßige Vergleichstherapie:	
Filtrat von <i>Clostridium histolyticum</i> D03BA Iruxol® N	Zur enzymatischen Reinigung kutaner Ulzera von nekrotischem Gewebe
Lysate aus <i>P. aeruginosa</i>, <i>S. aureus</i>, <i>E. coli</i>, <i>S. pyogenes</i>, <i>E. facialis</i> D03AX79 Pyolysin	Dieses Arzneimittel wird empirisch angewendet bei oberflächlichen Wunden, z.B. als Adjuvans bei Ulcus cruris.
Streptokinase, Streptodornase D03BA54 Varidase	Fibrinolyse bei infektiösen und traumatischen Entzündungen, Verflüssigung von Blutkoagula und Eiter bei: infizierten Wunden und Ulzerationen jeder Genese, Verbrennungen und Radionekrosen, entzündlich-eitrigen Prozessen in der Gynäkologie und Urologie.

Quellen: AMIS-Datenbank, Fachinformationen

Recherche und Synopse der Evidenz zur Bestimmung der zweckmäßigen Vergleichstherapie (zVT):

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Indikation für die Recherche bei Wirkstoff (evtl. Markenname):

BioMonde Biobag und BioMonde Freie Larven zum Debridement belegter chronischer oder schwer heilender Wunden.

Berücksichtigte Wirkstoffe/Therapien:

Für das Anwendungsgebiet zugelassenen Arzneimittel, s. Unterlage zur Beratung in AG: „Übersicht zVT, Tabelle II. Zugelassene Arzneimittel im Anwendungsgebiet“

Systematische Recherche:

Es wurde eine systematische Literaturrecherche nach systematischen Reviews, Meta-Analysen, HTA-Berichten und evidenzbasierten systematischen Leitlinien zur Indikation „chronische oder schwer heilende Wunden“ durchgeführt. Der Suchzeitraum wurde auf die letzten 5 Jahre eingeschränkt und die Recherche am 25.03.2014 abgeschlossen. Die Suche erfolgte in folgenden Datenbanken bzw. Internetseiten folgender Organisationen: The Cochrane Library (einschl. NHS CRD-Datenbanken), MEDLINE (PubMed), Leitlinien.de (ÄZQ), AWMF, DAHTA, G-BA, GIN, IQWiG, NGC, TRIP. Bei der

Recherche wurde keine Sprachrestriktion vorgenommen. Die detaillierte Darstellung der Suchstrategie ist am Ende der Synopse aufgeführt.

Die Recherche ergab 298 Quellen, die anschließend nach Themenrelevanz und methodischer Qualität gesichtet wurden. Zudem wurde eine Sprachrestriktion auf deutsche und englische Quellen vorgenommen. Davon wurden 97 Quellen eingeschlossen. Insgesamt ergab dies 10 Quellen, die in die synoptische Evidenz-Übersicht aufgenommen wurden

Abkürzungen

ÄZQ	Ärztliches Zentrum für Qualität in der Medizin
AWMF	Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften
DAHTA	Deutsche Agentur für Health Technology Assessment
G-BA	Gemeinsamer Bundesausschuss
GIN	Guidelines International Network
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
NGC	National Guideline Clearinghouse
NHS CRD	National Health Services Center for Reviews and Dissemination
NICE	National Institute for Health and Care Excellence
NIHR HSC	National Institute for Health Research Horizon Scanning Centre
TRIP	Turn Research into Practice Database
WHO	World Health Organization
ABI	ankle brachial pressure index
CCO	clostradial collagenase ointment
DFU	diabetic foot ulcers
MA	meta-analysis
MDT	maggot debridement therapy
NA	not available
NR	not reported
NRS	non-randomized study
PAD	peripheral artery disease
prep	Preparation
RCT	randomized controlled trial
SOC	standard of care
SMG	saline moistened gauze
vs	versus
k.A.	Keine Angabe

IQWiG Berichte/ G-BA Beschlüsse

Es liegen bisher keine IQWiG-Berichte oder G-BA Beschlüsse zur Fragestellung vor

Cochrane Reviews

Aus der Suche ist ein relevantes Cochrane Review hervorgegangen: Edwards J, Stapley S. Debridement of diabetic foot ulcers. Cochrane Database Syst Rev 2010; (1): CD003556. Da es sich ausschließlich mit der Versorgung diabetischer Fußulzera beschäftigt und die Inhalte in anderen Übersichtsarbeiten weiter unten in dieser Synopse zitiert wurden, ist es nicht gesondert extrahiert.

Systematische Reviews

Nach der Volltextsichtung liegen 22 methodisch adäquate und relevante systematische Übersichtsarbeiten/HTA-Berichte vor. Hier extrahiert werden die Inhalte der acht Übersichtsarbeiten, die sich – entsprechend des Anwendungsgebietes – mit chronischen Wunden im Allgemeinen beschäftigen. Die Inhalte der verbleibenden Arbeiten beschäftigen sich mit der Versorgung von Dekubituswunden (n = 8) und diabetischem Fußsyndrom (n = 4). Zwei Arbeiten beschäftigen sich mit der Untersuchung der Effektivität von Larventherapie selbst.

Canadian Agency for Drugs and Technologies in Health (CADTH), 2013	1. Fragestellung
	1. What is the clinical evidence regarding the effectiveness of non-surgical debridement for the treatment and management of chronic, lower extremity wounds? 2. What are the evidence-based guidelines regarding the use of non-surgical debridement for the treatment and management of chronic, lower extremity wounds?
Non-Surgical Debridement for Chronic Lower Extremity Wounds: Clinical Effectiveness and Guidelines	2. Methodik
Rapid Response Report: Summary of	Population: people with chronic, lower extremity wounds Intervention: non-surgical debridement Komparator: k.A. Endpunkt: k.A. Suchzeitraum: January 1, 2009 and November 20, 2013 Datenbanken: PubMed, The Cochrane Library (2013, Issue 10), University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and major international health technology

<p>Abstracts</p>	<p>agencies, focused Internet search Einschlusskriterien: no filters applied to limit retrieval by study type, human population, English language documents Anzahl eingeschlossene Studien/Patienten (Gesamt): 16/k.A., 8 LL</p> <hr/> <p>3. Ergebnisdarstellung</p> <ul style="list-style-type: none"> • 5 SR, 3 RCTs, 8 non-randomized studies, 9 evidence-based guidelines included • no relevant HTA identified <p><u>Maggot debridement therapy (MDT)</u></p> <ul style="list-style-type: none"> • 3 SR (Tian et al. 2013, Game et al. 2012, Edwards et al. 2010), 2 RCTs (Opletalova et al. 2012, Dumville et al. 2009), 5 non-randomized trials (Igari et al. 2013, Gilead et al. 2012, Mumcuoglu et al. 2012, Wang et al. 2010, Paul et al. 2009) • simple and effective debridement technique to treat chronic lower extremity wounds • works quickly in the first week of treatment • reduces wound areas • reduces debridement time • not observed to significantly increase the rate of healing in one RCT • associated with pain throughout treatment cycles in one NRS <p><u>Enzymatic therapy</u></p> <ul style="list-style-type: none"> • 1 SR (Ramundo et al. 2009), 1 RCT (Tallis et al, 2013) • equivalent to saline moistened gauze in one RCT <p><u>Hydrogels</u></p> <ul style="list-style-type: none"> • 1 SR (Edwards et al. 2010), 1 RCT (Dumville et al. 2009), 1 non-randomized trial (Gethin et al. 2009) • increased healing rates in one RCT <p><u>Debrisoft</u> (1 NRS: Bahr et al. 2011)</p> <ul style="list-style-type: none"> • efficacious simple procedure in one NRS <p><u>DermaStream</u> (1 NRS: Neiderer et al. 2011)</p> <ul style="list-style-type: none"> • no conclusions reported <p><u>Manuka honey</u> (1 NRS: Gethin et al. 2009)</p> <ul style="list-style-type: none"> • increased healing incidence and desloughing and associated with lower incidence of wound infection when compared to hydrogel in one NRS <p>The nine evidence-based guidelines (Canada, USA, Australia, GB,</p>
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	<p>Mexico) identified produced the following recommendations on debridement techniques:</p> <p><u>Hydrocolloidal dressings</u></p> <ul style="list-style-type: none"> o reduced pain associated with its use o improves healing when compared to gauze <p><u>Hydrogels</u></p> <ul style="list-style-type: none"> o may use topical hydrogel dressings in non-ischemic, non-healing dry wounds with non-viable tissue <p><u>MDT</u></p> <ul style="list-style-type: none"> o bagged or loose MDT debrides faster, with similar healing properties of hydrogel, but can be more painful o medical grade maggots are required o qualified personnel are required o can also be used when conventional treatment is not working o can be used in wounds where surgical debridement cannot be performed <p><u>Mechanical/Sharp</u></p> <ul style="list-style-type: none"> o best at removing tissue or eschar¹⁹ in non-ischemic wounds o removes non-vital tissue and slough o less painful o faster progression with the use of eutectic mixture of local anesthetics (EMLA) cream
	<p>4. Anmerkungen/Fazit der Autoren</p> <p>siehe oben</p> <p>(5. Hinweise durch FB Med)</p> <ul style="list-style-type: none"> • Qualitätsbewertung der eingeschlossenen Arbeiten erfolgte anhand des Studiendesigns • no information about CoI and funding
<p>Madhok BM, et al. 2013</p> <p>New techniques for wound debridement</p>	<p>1. Fragestellung</p> <p>The purpose of this review was to critically evaluate the current evidence behind the use of newer techniques in clinical practice.</p> <hr/> <p>2. Methodik</p> <p>Population: k.A.</p> <p>Intervention: wound debridement (especially ultrasound, hydrosurgery, debrisoft, plasma-mediated bipolar radiofrequency ablation)</p>

Komparator: k.A.
Endpunkt: healing

Suchzeitraum: search conducted on 4 May, 2012
Datenbanken: PubMed, Google Scholar, references of all relevant papers examined for any related publications

Anzahl eingeschlossene Studien/Patienten (Gesamt): k.A.

3. Ergebnisdarstellung

Ultrasound

- good evidence to suggest that high frequency ultrasound therapy does not improve ulcer healing rates: 1 RCT with low risk of bias (Watson et al. 2011), 1 SR of 6 poor quality RCTs (Cullum et al. 2010)
- some evidence in favour of low frequency ultrasound therapy especially in patients with venous ulcers and diabetic foot ulcers: 3 small RCTs (Peschen et al. 1997, Ennis et al. 2005, Kavros et al. 2007), 1 SR/MA of small RCTs (Voigt et al. 2011 – siehe unten in dieser Tabelle)
- limited evidence for the efficacy of therapeutic ultrasound for wound debridement: 1 SR (Ramundo and Gray 2008)
- ongoing study: single centre RCT comparing low frequency ultrasound to sharp debridement (NCT01237392)

Hydrosurgery

- role of this therapy in wound debridement unclear: 1 CS (Vanwijck et al. 2010), 1 NRS (Mosti et al. 2005), 1 well conducted but small RCT (Caputo et al. 2008)
- 1 SR (Sainsbury et al. 2009): attempt to review the costeffectiveness of hydrosurgery debridement, limited due to paucity of available data and poor quality of studies
- ongoing studies: single centre RCT comparing hydrosurgery debridement to conventional surgical debridement in leg ulcers (NCT00521027), another similar study is underway for treatment of acute and chronic surgical wound dehiscence (NCT01050673)

Monofilament polyester fibre pad

- studies to examine cost-effectiveness and assess complete wound healing warranted
- today 1 small prospective pilot study (Haemmerle et al. 2011), 1 NRS (Bahr et al. 2011), 1 case series (Gray et al. 2011) published

Plasma-mediated bipolar radiofrequency Ablation

	<ul style="list-style-type: none"> studies are warranted to assess the application of PBRA for wound debridement today in vitro/in vivo studies and a case series published <p>4. Anmerkungen/Fazit der Autoren</p> <p>There is some evidence to suggest that low frequency ultrasound therapy may improve healing rates in patients with venous ulcers and diabetic foot ulcers. Hydrosurgery debridement is quick and precise, but the current evidence is limited and further studies are underway. Debridement using a monofilament polyester fibre pad and plasma-mediated bipolar radiofrequency ablation are both very new techniques. The initial evidence is limited, and further studies are warranted to confirm their role in management of chronic wounds.</p> <p>(5. Hinweise durch FB Med)</p> <ul style="list-style-type: none"> authors do not declare any Col relevant to the manuscript no funding information
<p>Vandamme L, et al. 2013</p> <p>Honey in modern wound care: A systematic review</p>	<p>1. Fragestellung</p> <p>The objective of this systematic review is to evaluate the available evidence and the role of honey in contemporary wound care.</p> <p>2. Methodik</p> <p>Population: human burns, ulcers and other wounds (e.g. trauma, post-operative wounds, . . .) Intervention: honey Komparator: k.A. Endpunkt: wound healing</p> <p>Suchzeitraum: last search on July 15, 2012 Datenbanken: PubMed and ISI Web of Science Studiendesign: randomized controlled trials (RCTs), clinical controlled trials (CCTs), clinical trials (CTs), case reports (CRs) Einschlusskriterien: English, French, German, Dutch language Anzahl eingeschlossene Studien/Patienten (Gesamt): 55/k.A.</p> <p>3. Ergebnisdarstellung</p> <ul style="list-style-type: none"> 19 trials that examined the effects of honey in chronic ulcers included 4 RCTs, 1 CT, 4 CRs report on antibacterial effect of honey, 1 RCT found a positive effect in favour of honey, not statistically significant wound healing stimulating capacity of honey: 2 out of 4 RCTs report a statistically significant reduction in wound size, 2 CTs and 7 CRs support the positive effect

	<ul style="list-style-type: none"> • anti-inflammatory, deodorizing and debridement properties all supported by 1 RCT, 2 CTs and multiple CRs • wound pain: according to 1 RCT significantly reduced by honey • available evidence is weak <p>4. Anmerkungen/Fazit der Autoren</p> <p>Overall, it can be concluded that the evidence for the antibacterial, anti-inflammatory, deodorizing, debridement and wound pain reducing properties of honey in ulcers is less conclusive. Most evidence had been found for the wound size reducing effect of honey, which was statistically significant in favour of honey in 50% of the trials. However, it can be argued if this is enough evidence to make well-substantiated conclusions towards clinical practice.</p> <p>(5. Hinweise durch FB Med)</p> <ul style="list-style-type: none"> • authors do not have any interests that might be interpreted as influencing the review • review did not receive any support from industry or private corporations
<p>Brolmann FE, et al. 2012</p> <p>Evidence-based decisions for local and systemic wound care</p>	<p>1. Fragestellung</p> <p>The aim of this meta-review was to compile best available evidence from systematic reviews in order to formulate conclusions to support evidence-based decisions in clinical practice.</p> <p>2. Methodik</p> <p>Population: adults as well as in children with open wounds of any type and aetiology (examples of chronic wounds: pressure ulcers, arterial or venous leg ulcers, diabetic foot ulcers) Intervention: therapeutic and preventive, local and systemic Komparator: k.A. Endpunkt: k.A.</p> <p>Suchzeitraum: up to June 2011 Datenbank: Cochrane Database Studiendesign: Cochrane systematic reviews (CSRs), published by the Cochrane Wounds and Peripheral Vascular Diseases Groups Studienbewertung: combined system of GRADE and PRISMA developed (siehe Abbildung 2 im Anhang dieser Synopse) Anzahl eingeschlossene Studien/Patienten (Gesamt): 44 relevant reviews/k.A.</p> <p>3. Ergebnisdarstellung</p> <p><u>venous ulcers:</u></p>

	<ul style="list-style-type: none"> • strong evidence of effect: elastic compression improves wound healing more than inelastic compression, high compression improves wound healing more than low compression, Lidocaine–prilocaine cream decreases pain during ulcer debridement (not clear whether this affects healing), Bilayer artificial skin increases the proportion of ulcer healing more than standard care, Cadexomer iodine increases ulcer healing compared with standard care both with, and without compression therapy • strong evidence of no effect: type of wound dressing beneath compression does not influence healing (trials included hydrocolloids, foam dressings, alginates, low-adherent dressings and hydrogels), Ibuprofen slow-release foam dressing has no effect on pain relief, intermittent pneumatic compression (IPC) with compression does not contribute to ulcer healing compared with compression treatment alone <p><u>diabetic ulcers:</u></p> <ul style="list-style-type: none"> • strong evidence for effectiveness of hydrogel on healing rate of diabetic foot ulcers, fewer complications occur when using hydrogel <p><u>arterial ulcers:</u></p> <ul style="list-style-type: none"> • insufficient evidence for ulcer healing or area reduction for any dressing or topical agent for arterial leg ulcers <p><u>pressure ulcers:</u></p> <ul style="list-style-type: none"> • strong evidence for ineffectiveness of therapeutic ultrasound for ulcer healing <p><u>miscellaneous chronic wounds:</u></p> <ul style="list-style-type: none"> • Only low level evidence available for the use of topical agents as silver, honey or others <p>4. Anmerkungen/Fazit der Autoren</p> <p>For some wound care interventions, robust evidence exists upon which clinical decisions should be based. Obviously, the conclusions given here do not offer treatment solutions for every wound type, because strong evidence is not yet available for all situations.</p> <p>(5.Hinweise durch FB Med)</p> <ul style="list-style-type: none"> • authors declare no conflict of interest • no funding information
Doerler M, et al. 2012	1. Fragestellung

Impact on wound healing and efficacy of various leg ulcer debridement techniques	<p>To evaluate the evidence on the impact of different debridement techniques on healing and their efficacy in the treatment of leg ulcers.</p>
	<p>2. Methodik</p> <p>Population: leg ulcers Intervention: surgical, enzymatic, autolytic, osmotic, ultrasound-assisted, and biosurgical wound debridement Komparator: k.A. Endpunkt: healing and efficacy</p> <p>Suchzeitraum: up to 2011 Datenbank: PubMed Studiendesign: RCT Ausschlusskriterien: reviews, case reports, studies on high-frequency ultrasound therapy without reference to its debridement effects Anzahl eingeschlossene Studien/Patienten (Gesamt): 20/k.A.</p>
	<p>3. Ergebnisdarstellung</p> <ul style="list-style-type: none"> • type of debridement: surgical-hydrosurgical (n = 5), autolytic, enzymatic, or osmotic (n = 6), low-frequency ultrasound therapy (n = 4), biosurgical (n = 5) • surgical and hydrosurgical methods proved to be effective • conventional surgical debridement: significantly greater reduction of wound surface area and higher healing rate reported • studies on autolytic, osmotic, and enzymatic wound debridement showed effective debridement for krill enzymes, dextranomer and manuka honey • manuka honey: significantly greater reduction of wound surface area compared to standard treatment • 1 study comparing fibrinolysin/DNase with placebo and 1 comparing autolytic with enzymatic debridement showed no significant differences between the respective techniques • ultrasound-assisted wound debridement: positive impact on healing, significant wound surface area reduction • Maggot therapy led to effective debridement, largest trial showed no significantly improved healing
	<p>4. Anmerkungen/Fazit der Autoren</p> <p>Debridement of leg and foot ulcers is a part of everyday routine clinical care. In our opinion, there is currently a discrepancy between the scientific evidence for improved healing as a result on the one hand and clinical practice and experience on the other. Based on currently available studies, a positive influence on healing</p>

	<p>of chronic leg ulcers is probably best achieved with surgical wound debridement.</p> <p>Considering that chronic wounds are an enormous healthcare expense, there is an urgent need for efficient and evidence-based treatment schemes. For patients with chronic wounds, not only healing but also quality of life is a critical factor. Future studies should thus include as primary endpoints complete wound healing, percentage reduction in wound size, and quality of life.</p> <p>(5. Hinweise durch FB Med)</p> <ul style="list-style-type: none"> • Conflict of interest: None • No funding information • study quality not assessed or discussed
<p>Hoppe IC, Granick MS. 2012</p> <p>Debridement of chronic wounds: a qualitative systematic review of randomized controlled trials</p>	<p>1. Fragestellung k.A.</p> <hr/> <p>2. Methodik</p> <p>Population: wounds located externally or cutaneously, described as chronic in nature Intervention: debridement Komparator: k.A. Endpunkt: k.A.</p> <p>Suchzeitraum: 1946 until July 2011 Datenbanken: Cochrane library, Medline Studiendesign: RCT Einschlusskriterien: clinical human study</p> <p>Anzahl eingeschlossene Studien/Patienten (Gesamt): 19/k.A.</p> <hr/> <p>3. Ergebnisdarstellung</p> <p><u>Surgical Debridement</u></p> <ul style="list-style-type: none"> • 2 studies included (Steed 1996, Caputo 2008), provide evidence that surgical debridement is effective in managing venous leg ulcers and diabetic foot ulcers <p><u>Biologic Debridement</u></p> <ul style="list-style-type: none"> • 1 study included (Dumville 2009), no difference in time to healing, larval therapy significantly decreased the time to debridement, Health-related quality of life not different <p><u>Mechanical Debridement (Wet-to-dry dressing changes, Wound Irrigation, Hydrotherapy, Negative pressure wound therapy - NPWT)</u></p> <ul style="list-style-type: none"> • <u>comparison of wet-to-dry dressing changes and NPWT</u>: 7 studies included (only 2 reported significant differences)

- NPWT decreased the wound volume and depth compared with saline-moistened gauze in surgically debrided diabetic foot wounds (Eginton 2003)
- NPWT reduced wound surface area by more than conventional moist-gauze therapy on surgically debrided wounds, decrease in non-fermentative gram-negative bacilli and a significant increase in Staphylococcus aureus in the NPWT group (Moues 2004)
- variation on NPWT: 1 study included (Perez 2010)
- homemade NPWT system significantly reduced healing time compared with traditional saline soaked dressings, intervention group received more often surgical debridement before therapy than control group
- comparison of NPWT and advanced moist wound therapy: 1 study (Blume 2008) - no significant differences reported
- hydrotherapy (whirlpool use): 1 study included (Burke 1998) - no significant differences compared with traditional dressing reported

Enzymatic Debridement

- comparison of fibrinolysin-desoxyribonuclease solution with saline solution for the debridement of chronic leg ulcers (Westerhof 1987) - enzymatic preparation significantly more effective in percent of ulcer covered with debris and percent of wound covered with granulation tissue
- comparison of krill enzyme with saline in the debridement of venous leg ulcers (Westerhof 1990) - enzymatic preparation significantly more effective in computer imaging of the wound examining areas of black and yellow necrosis
- comparison of enzyme with autolytic dressing in the treatment of chronic leg ulcers (Konig 2005) – no significant difference reported
- efficacy of streptokinase/streptodornase in hydrogel vs hydrogel alone in stage IV pressure ulcers (Martin 1996) – no significant difference reported

Autolytic Debridement

- 4 studies included – none reported significant differences
- 1 Cochrane Library systematic review found no significant differences among dressings for treatment of venous leg ulcers (Palfryman 2006, CD001103)
- Cochrane Library systematic review regarding debridement of diabetic foot ulcers concluded that hydrogel use may result in faster healing than simple gauze dressings (Edwards 2010, CD003556)

	<p>4. Anmerkungen/Fazit der Autoren</p> <p>Of the methods discussed, surgical debridement provides the fastest route to an appropriate wound bed and, barring any comorbidities, should be considered the standard of care in wound debridement. Other methods have more specific indications and should be used accordingly.</p> <p>(5. Hinweise durch FB Med)</p> <ul style="list-style-type: none"> • no information on funding and CoI • study quality not assessed or discussed
<p>Canadian Agency for Drugs and Technologies in Health (CADTH), 2013</p> <p>Negative Pressure Wound Therapy for Patients with Diabetic Foot Ulcers and Pressure Ulcers: A Review of the Clinical Effectiveness</p> <p>Rapid Response Report: Summary with Critical Appraisal</p>	<p>1. Fragestellung</p> <p>1. What is the comparative clinical effectiveness of negative pressure wound therapy at -75 mmHg, -80 mmHg, and -125 mmHg for patients with diabetic foot ulcers and pressure ulcers?</p> <p>2. What is the comparative clinical effectiveness of continuous versus intermittent negative pressure wound therapy at -75 mmHg, -80 mmHg, or -125 mmHg for patients with diabetic foot ulcers and pressure ulcers?</p> <p>2. Methodik</p> <p>Population: Patients with diabetic foot ulcers or pressure ulcers Intervention: Negative Pressure Wound Therapy Komparator:</p> <p>Q1: Different pressures of NPWT (e.g., -75 mmHg, -80 mmHg, -125 mmHg) Q2: Continuous versus Intermittent NPWT Endpunkt: wound healing</p> <p>Suchzeitraum: between January 1, 2007 and May 24, 2012 Datenbanken: PubMed, The Cochrane Library (2012, Issue 5), University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and abbreviated lists of major international health technology agencies, focused Internet search Studiendesign: Health technology assessments, systematic reviews and meta-analysis, randomized controlled trials (RCTs) and non-randomized studies Einschlusskriterien: human population, English language</p> <p>Anzahl eingeschlossene Studien/Patienten (Gesamt): 0</p>

	<p>3. Ergebnisdarstellung</p> <p>APPENDIX 1: Selection of Included Studies</p> <pre> graph TD A[221 citations identified from electronic literature search and screened] --> B[13 potentially relevant articles retrieved for scrutiny (full text, if available)] A --> C[208 citations excluded] D[9 potentially relevant reports retrieved from other sources (grey literature, hand search)] --> B B --> E[22 potentially relevant reports] E --> F[0 reports included in review] E --> G["22 reports excluded: -Study design not of interest (3) -Population not of interest (3) -Intervention not of interest (1) -Comparator not of interest (15)"] </pre> <p>4. Anmerkungen/Fazit der Autoren</p> <p>Due to lack of evidence, the comparative clinical effectiveness of negative pressure wound therapy at different pressures or comparative clinical effectiveness of continuous versus intermittent negative pressure wound therapy for patients with diabetic foot ulcers and pressure ulcers remains to be established.</p> <p>(5. Hinweise durch FB Med)</p> <ul style="list-style-type: none"> • no information about Col and funding
<p>Voigt J, et al. 2011</p> <p>Low-Frequency Ultrasound (20-40 kHz) as an Adjunctive Therapy for Chronic Wound Healing: A Systematic Review of the Literature and Meta-Analysis of Eight Randomized Controlled Trials</p>	<p>1. Fragestellung</p> <p>The objective of this review was to determine whether low-frequency ultrasound used as an adjunctive therapy improves the outcomes of complete healing and reduction of size of chronic lower limb wounds.</p> <p>2. Methodik</p> <p>Population: chronic lower limb wounds (Venous insufficiency, Diabetes (type 1 or 2), Pressure/immobile patient, Arterial occlusive disease, Neuropathic insufficiency) Intervention: low-frequency ultrasound (low-frequency high-intensity contact ultrasound or LFHICU, low-frequency low-intensity noncontact ultrasound or LFLINCU) Komparator: k.A. Endpunkt: complete healing, percent wound area reduction</p>

Suchzeitraum: until March 2011

Datenbanken: PubMed, Cochrane/CENTRAL, technical assessment, relevant wound-related journals, and clinical guidelines were searched along with contacting manufacturers and authors of relevant randomized controlled trials

Studiendesign: RCT

Studienbewertung: assessment of risk of bias form used

Anzahl eingeschlossene Studien/Patienten (Gesamt): 8/k.A.

Weitere methodische Hinweise: heterogeneity checks performed, publication bias check performed

3. Ergebnisdarstellung

Complete Healing

LFHICU:

- over 3 months statistical difference demonstrated on this outcome between this and sharp debridement (RR = 0.64; 95% CI = 0.46-0.89; P = .009; I2 = 0%; Mantel-Haenszel fixed effects model)–favoring LFHICU, patients included diabetic foot ulcers with osteomyelitis and venous stasis ulcers
- at 5 months, this statistical difference persisted (RR = 0.52; 95% CI = 0.32-0.85; P = .008; I2 = 0%)–favoring LFHICU
- at 6 months statistical difference did not persist (RR = 0.66; 95% CI = 0.36-1.21; P = .18; I2 = 15%)

LFLINCU

- over a 3 month period statistical difference demonstrated on this outcome between LFLINCU and sham (RR = 0.74; 95% CI = 0.58-0.95; P = .02; I2 = 0%), patients included those with diabetic foot ulcers and chronic venous ulcers

Wound Size Reduction

LFHICU:

- over 3 months statistically significant difference on this outcome between LFHICU and sharps debridement–favoring LFHICU (mean difference = 25.93%; 95% CI = 14.2% to 37.66%; P < .0001; I2 = 0%; Inverse variance fixed effects model for continuous data), patients included those with diabetic foot ulcers and lower extremity ulcers of various etiologies (venous insufficiency, diabetes, pressure, and arterial insufficiency).
- several of the trials could not be combined for metaanalyses (duration of outcome evaluation, lack of specific outcome data) - reported separately:

- Li, 2009 examined the effect of LFHICU debridement vs. washing with isotonic normal saline in burn patients, percent of the wound that had healed over a 2 week period was significantly higher with LFHICU versus a saline wash (P = .006)
- Singh, 2006 examined effect of LFHICU debridement vs. sharp debridement in patients with diabetic foot ulcers, percentage of the wound that had healed over a 2-week period was significantly higher with LFHICU versus a sharp debridement (P = .001; Mann-Whitney U test)

LFLINCU

- over 2 months statistically significant difference on this outcome between LFLINCU and sham—favoring LFLINCU (mean difference = 25.97%; 95% CI = 11.09% to 40.86%; P = .0006; I² = 0%; inverse variance random effects model for continuous data), patients with chronic venous ulcers
- Kavros, 2007 (mainly diabetes patients with ulcers resulting from chronic critical limb ischemia) demonstrated a statistically significant difference in this end point, favoring LFLINCU (63% of the LFLINCU patients exhibited a reduction of >50% in wound size vs sham at 29%; P < .001 (Mann-Whitney U test)
- Park, 2011 had as an endpoint, wound percentage area reduction evaluated over a 5-week period in patients presenting with nonhealing diabetic foot ulcers, patients treated with LFLINCU (3 times per week; n = 4) plus standard of care (which included debridement) had a significant reduction in percentage area reduction versus those patients who had LFLINCU (1 time per week; n = 4) plus standard of care and those who had standard of care only (n = 4; P < .05)

4. Anmerkungen/Fazit der Autoren

Results demonstrated that early healing (at ≤5 months) in patients with venous stasis and diabetic foot ulcers was favorably influenced by both high- and low-intensity ultrasound delivered at a low frequency—either via contact or noncontact techniques.

However, the quality of the data may be suspect, especially for low-frequency low-intensity noncontact ultrasound because of significant biases. In patients presenting with either venous stasis or diabetic foot ulcers (Wagner classification 1-3), early healing appears to be facilitated by either low-frequency lowintensity noncontact ultrasound or low-frequency high-intensity contact ultrasound.

(5. Hinweise durch FB Med)

- author(s) declared no potential conflicts of interest with

	<p>respect to the research, authorship, and/or publication of this article. Jeffrey Voigt is a reimbursement consultant for a company involved in LFHICU.</p> <ul style="list-style-type: none">• author(s) received no financial support for the research, authorship, and/or publication of this article
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Leitlinien

Nach der Volltextsichtung liegen elf methodisch adäquate und relevante Leitlinien vor. Hier extrahiert werden die Empfehlungen der Leitlinie, die sich – entsprechend des Anwendungsgebietes – mit chronischen Wunden im Allgemeinen beschäftigt. Die Empfehlungen der verbleibenden Leitlinien beschäftigen sich mit der Versorgung von Dekubituswunden (n = 3), diabetischem Fußsyndrom (n = 3), pyoderma gangrenosum (n = 1) und ulcus cruris venosum (n = 3).

<p>Deutsche Gesellschaft für Wundheilung und Wundbehandlung (DGfW). 2012</p> <p>Lokaltherapie chronischer Wunden bei Patienten mit den Risiken periphere arterielle Verschlusskrankheit, Diabetes mellitus, chronisch venöse Insuffizienz</p>	<p>Fragestellung/Zielsetzung</p> <p>Welchen Effekt hat die passive periodische Wundreinigung mit Fliegenlarven/Enzymen auf die Wundheilung von Patienten mit chronischen Wunden im Vergleich zu keiner passiven periodischen Wundreinigung mit Fliegenlarven/Enzymen bzw. zu anderen relevanten Verfahren? Was sind die Effekte in verschiedenen Stadien (Granulation, Exsudation)?</p> <p>Welchen Effekt hat/heben Honig/Hydrogelen auf die Wundheilung von Patienten mit chronischen Wunden im Vergleich zu keinem/n Honig/Hydrogelen bzw. zu anderen relevanten Verfahren? Was sind die Effekte in verschiedenen Stadien (Granulation, Exsudation)?</p> <p>Die vorliegende Leitlinie bezieht sich auf die Lokaltherapie von</p> <ul style="list-style-type: none"> • Ulcus cruris arteriosum • Ulcus cruris venosum • Ulcus cruris mixtum • Ulcera im Rahmen des „diabetischen Fußes“ <p>Die Leitlinie bezieht sich nicht auf die Lokaltherapie akuter Wunden. ... Die Lokaltherapie von Ulcera anderer Genese wie z. B. ... von Dekubitalulcera sind nicht Gegenstand dieser Leitlinie.</p> <p>Im Rahmen dieser Leitlinie unterscheiden wir zwischen Lokaltherapie der Wunde und anderen wundheilungsfördernden Maßnahmen.</p> <hr/> <p>Methodik: S3-Leitlinie</p> <p>Grundlage der Leitlinie: systematische Recherche und Auswahl der Literatur, Bewertung mit GRADE, formaler Konsensusprozess zur Formulierung und Verabschiedung der Empfehlungen</p> <p>Suchzeitraum: bis September 2011</p> <p>LoE (Qualitätsstufen nach GRADE):</p> <p>Hohe Qualität = Es ist sehr unwahrscheinlich, dass weitere Forschung das Vertrauen in den beobachteten Behandlungseffekt verändert.</p>
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	<p>Mittlere Qualität = Weitere Forschung wird sich vermutlich erheblich auf unser Vertrauen in den beobachteten Behandlungseffekt auswirken. Möglicherweise ändert sich der Behandlungseffekt.</p> <p>Geringe Qualität = Weitere Forschung wird sich sehr wahrscheinlich auf unser Vertrauen in den beobachteten Behandlungseffekt auswirken. Wahrscheinlich ändert sich der Behandlungseffekt.</p> <p>Sehr geringe Qualität = Der beobachtete Behandlungseffekt ist mit sehr großer Unsicherheit behaftet.</p> <p>GoR: siehe Anhang dieser Synopse</p>
	<p>Freitext/Empfehlungen/Hinweise</p> <p>6.9. Empfehlungen zur passiven periodischen Wundheilung</p> <p><u>Statement S9:</u> Bezüglich der Wundheilung sind Fliegenlarven Hydrogel nicht überlegen. Es treten jedoch vermehrt Schmerzen auf. Im Vergleich zu Hydrogel erfolgt die Wundreinigung durch Fliegenlarven schneller. - LoE „hoch“ (Dumville JC, et al. VenUS II: a randomised controlled trial of larval therapy in the management of leg ulcers. Health Technology Assessment. 2009;13(55):1-206.)</p> <p><u>Statement S10:</u> Anhand der vorliegenden Studien können keine belastbaren Aussagen zum Nutzen oder Schaden der enzymatischen Wundreinigung getroffen werden. - LoE „gering“ (König M, et al. Enzymatic versus autolytic debridement of chronic leg ulcers: a prospective randomised trial. Journal of Wound Care. 2005;14(7):320-3)</p> <p><u>Empfehlung E21:</u> Beim diabetischen Fußulcus kann Hydrogel eingesetzt werden, wenn Rehydrierung erforderlich ist. - GoR 0, LoE „mittel“ (Jensen JL, et al. Diabetic foot ulcerations. A controlled, randomized comparison of two moist wound healing protocols: Carrasyn Hydrogel Wound dressing and wet-to-moist saline gauze. AdvWound Care. 1998;11 (7 Suppl):1-4, d'Hemecourt PA, et al. Sodium carboxymethylcellulose aqueous-based gel vs. becaplermin gel in patients with nonhealing lower extremity diabetic ulcers. Wounds: A Compendium of Clinical Research & Practice. 1998;10(3):69-75)</p> <p><u>Empfehlung E22:</u> Anhand der vorliegenden Studien können keine belastbaren Aussagen zum Nutzen oder Schaden von Hydrogel bei UCV/UCA getroffen werden. Hydrogel kann bei UCV/UCA eingesetzt werden, wenn Rehydrierung erforderlich ist. – Expertenkonsens</p> <p><u>Empfehlung E23:</u> Nekrosen sollen nicht rehydriert werden. – Expertenkonsens</p> <p><u>Empfehlung E24:</u> Anhand der vorliegenden Studien zeigt sich für medizinischen Honig keine Überlegenheit gegenüber Hydrogel. Es</p>

zeigen sich aber Hinweise auf mehr Schmerzen, deshalb sollte medizinischer Honig zur Behandlung von chronischen Wunden nicht eingesetzt werden. - GoR B negativ, LoE „hoch“ (Jull A, et al. Randomized clinical trial of honeyimpregnated dressings for venous leg ulcers. BrJ Surg. 2008;95(2):175-82, Gethin G, Cowman S. Bacteriological changes in sloughy venous leg ulcers treated with manuka honey or hydrogel: an RCT. J WoundCare. 2008;17(6):241-7)

Statement S11: Anhand der vorliegenden Studien können keine belastbaren Aussagen zum Nutzen oder Schaden der Wundreinigung mit Polyacrylat-Dauerbefeuchtung zur Wundheilung getroffen werden. – Expertenkonsens, LoE „gering“ (Konig M, et al. Enzymatic versus autolytic debridement of chronic leg ulcers: a prospective randomised trial. Journal of Wound Care. 2005;14(7):320-3)

Ergänzende Dokumente anderer Organisationen zu möglichen Komparatoren

<p>National Institute for Health and Care Excellence (NICE), 2011 The MIST Therapy system for the promotion of wound healing</p>	<p>Recommendations</p> <p>1.1 The MIST Therapy system shows potential to enhance the healing of chronic, 'hard-to-heal', complex wounds, compared with standard methods of wound management. If this potential is substantiated then MIST could offer advantages to both patients and the NHS.</p> <p>1.2 The amount and quality of published evidence on the relative effectiveness of the MIST Therapy system is not sufficient, at the time of writing, to support the case for routine adoption of the MIST Therapy system in the NHS.</p> <p>1.3 Comparative research is recommended in the UK to reduce uncertainty about the outcomes of patients with chronic, 'hard-to-heal', complex wounds treated by the MIST Therapy system compared with those treated by standard methods of wound care. This research should define the types and chronicity of wounds being treated and the details of other treatments being used. It should report healing rates, durations of treatment (including debridement) needed to achieve healing, and quality of life measures (including quality of life if wounds heal only partially). It is recommended that centres using the MIST Therapy system take part in research that delivers these outcomes. Current users of the MIST Therapy system who are unable to join research studies should use NICE's audit criteria to collect further information on healing rates, duration of treatment and quality of life and publish their results.</p> <p>1.4 NICE will review this guidance when new and substantive evidence becomes available.</p> <p>Description of the technology</p> <p>2.1 The MIST Therapy system (Celleration) aims to promote wound healing in chronic, 'hard-to-heal' wounds and acute wounds by delivering low-energy, low-intensity ultrasound to the wound bed through a continuous saline mist. The mist is claimed to transmit the ultrasonic energy to the wound bed, to activate healing by the removal of slough, exudate and bacteria, and to <i>stimulate tissue regeneration</i>.</p>
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Primärstudien

Da ausreichend Information aus aggregierter Evidenz vorliegt, wurde keine Suche nach Primärliteratur durchgeführt.

Detaillierte Darstellung der Recherchestrategie:

Cochrane Library am 25.03.2014

Suchschritt	Suchfrage
#1	MeSH descriptor: [Wound Healing] explode all trees
#2	MeSH descriptor: [Leg Ulcer] explode all trees
#3	MeSH descriptor: [Pressure Ulcer] explode all trees
#4	chronic wound* or nonhealing wound* or non healing wound* or hard to heal wound*:ti (Word variations have been searched)
#5	care or management or treatment or therapy or therapies or therapeutic or healing.ti
#6	wound*.ti
#7	#6 and #5
#8	pressure ulcer* or decubitus or bed sore* or bedsore* or pressure sore* or varicose ulcer* or stasis ulcer* or venous ulcer* or arterial ulcer* or ulcus cruris or leg ulcer* or foot ulcer* or diabetic foot or diabetic feet.ti
#9	chronic wound* or nonhealing wound* or non healing wound* or hard to heal wound*:ab (Word variations have been searched)
#10	care or management or treatment or therapy or therapies or therapeutic or healing.ab
#11	wound*.ab
#12	pressure ulcer* or decubitus or bed sore* or bedsore* or pressure sore* or varicose ulcer* or stasis ulcer* or venous ulcer* or arterial ulcer* or ulcus cruris or leg ulcer* or foot ulcer* or diabetic foot or diabetic feet.ab
#13	#10 and #11
#14	#1 or #2 or #3 or #4 or #7 or #8 or #9 or #11 or #12
#15	MeSH descriptor: [Debridement] explode all trees
#16	debridement*:ti (Word variations have been searched)
#17	debridement*:ab (Word variations have been searched)
#18	#15 or #16 or #17
#19	wound*:ab (Word variations have been searched)
#20	#10 and #19
#21	#14 or #20
#22	#21 and #18
#23	#22 Publication Date from 2009 to 2014

MEDLINE (PubMed) am 25.03.2014

Suchschritt	Suchfrage
#1	wound healing[MeSH Terms]
#2	leg ulcer[MeSH Terms]
#3	pressure ulcer[MeSH Terms]

#4	((chronic wound*[Title/Abstract]) OR nonhealing wound*[Title/Abstract]) OR non healing wound*[Title/Abstract] OR hard to heal wound*[Title/Abstract]
#5	(wound*[Title/Abstract]) AND (((((((care[Title/Abstract]) OR management[Title/Abstract]) OR treatment[Title/Abstract]) OR therapy[Title/Abstract]) OR therapies[Title/Abstract]) OR therapeutic[Title/Abstract]) OR healing[Title/Abstract])
#6	((pressure ulcer*[Title/Abstract]) OR decubitus[Title/Abstract]) OR bed sore*[Title/Abstract] OR bedsore*[Title/Abstract] OR pressure sore*[Title/Abstract]
#7	((varicose ulcer*[Title/Abstract]) OR stasis ulcer*[Title/Abstract]) OR venous ulcer*[Title/Abstract] OR arterial ulcer*[Title/Abstract] OR ulcus cruris[Title/Abstract]
#8	((leg ulcer*[Title/Abstract]) OR foot ulcer*[Title/Abstract]) OR diabetic foot[Title/Abstract] OR diabetic feet[Title/Abstract]
#9	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8
#10	Search debridement[MeSH Terms]
#11	Search debridement*[Title/Abstract]
#12	Search (#18 OR #19)
#13	Search (#13 AND #20)
#14	Search (((((((trials[Title/Abstract] OR studies[Title/Abstract] OR database*[Title/Abstract] OR literature[Title/Abstract] OR publication*[Title/Abstract] OR Medline[Title/Abstract] OR Embase[Title/Abstract] OR Cochrane[Title/Abstract] OR Pubmed[Title/Abstract])) AND systematic*[Title/Abstract] AND (search*[Title/Abstract] OR research*[Title/Abstract]))) OR (((((((HTA[Title/Abstract]) OR technology assessment*[Title/Abstract]) OR technology report*[Title/Abstract]) OR (systematic*[Title/Abstract] AND review*[Title/Abstract])) OR (systematic*[Title/Abstract] AND overview*[Title/Abstract])) OR meta-analy*[Title/Abstract]) OR (meta[Title/Abstract] AND analyz*[Title/Abstract])) OR (meta[Title/Abstract] AND analys*[Title/Abstract])) OR (meta[Title/Abstract] AND analyt*[Title/Abstract]))) OR (((review*[Title/Abstract] OR overview*[Title/Abstract]) AND ((evidence[Title/Abstract] AND based[Title/Abstract]))))
#15	Search (#21 AND #22)
#16	Search (#13 AND #20) Filters: Meta-Analysis
#17	Search (#13 AND #20) Filters: Meta-Analysis; Systematic Reviews
	Search (#13 AND #20) Filters: Meta-Analysis; Systematic Reviews; Technical Report
	Search (#26 OR #23)
	Search (#26 OR #23) Filters: published in the last 5 years

Medline (PubMed) nach Leitlinien am 25.03.2014

Suchschritt	Suchfrage
#1	wound healing[MeSH Terms]
#2	leg ulcer[MeSH Terms]
#3	pressure ulcer[MeSH Terms]
#4	((chronic wound*[Title/Abstract]) OR nonhealing wound*[Title/Abstract]) OR non healing wound*[Title/Abstract] OR hard to heal wound*[Title/Abstract]
#5	(wound*[Title/Abstract]) AND (((((((care[Title/Abstract]) OR management[Title/Abstract]) OR treatment[Title/Abstract]) OR therapy[Title/Abstract]) OR therapies[Title/Abstract]) OR therapeutic[Title/Abstract]) OR healing[Title/Abstract])
#6	((pressure ulcer*[Title/Abstract]) OR decubitus[Title/Abstract]) OR bed sore*[Title/Abstract] OR bed sore*[Title/Abstract] OR pressure sore*[Title/Abstract]
#7	((varicose ulcer*[Title/Abstract]) OR stasis ulcer*[Title/Abstract]) OR venous ulcer*[Title/Abstract] OR arterial ulcer*[Title/Abstract] OR ulcus cruris[Title/Abstract]
#8	((leg ulcer*[Title/Abstract]) OR foot ulcer*[Title/Abstract]) OR diabetic foot[Title/Abstract] OR diabetic feet[Title/Abstract]
#9	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8
#10	((Guideline[Publication Type]) OR Practice Guideline[Publication Type]) OR Consensus Development Conference[Publication Type] OR Consensus Development Conference, NIH[Publication Type]) OR guideline*[Title]
#11	(#9) AND #10
#12	(#11) AND ("2009/02/01"[PDAT] : "2014/03/25"[PDAT])
#13 (Update zu DMP Wunde 2013	(#11) AND ("2013/08/14"[PDAT] : "2014/03/25"[PDAT])

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Voigt J, Wendelken M, Driver V, Alvarez OM. Low-frequency ultrasound (20-40 kHz) as an adjunctive therapy for chronic wound healing: a systematic review of the literature and meta-analysis of eight randomized controlled trials. *Int J Low Extrem Wounds* 2011; 10 (4): 190-9.

Anhang:

Studienqualität	Qualitätsstufe in GRADE	Empfehlung	Beschreibung	Symbol
Systematische Übersichtsarbeit (Meta-Analyse) oder RCT (Therapie)	High	A	„Soll“	↑ ↑
RCT mit mittlerem Risiko für systematische Fehler	Moderate	B	„Sollte“	↑
RCT mit hohem Risiko für systematische Fehler	Low	0	„Kann“	↔

Abbildung 1: aus DGfW 2012

Table 1 Definition of categories to grade the strength of evidence of effect

Levels of evidence of effect	Criteria
1. Strong evidence of effect	Significant results in favour of new treatment, based on pooled data of trials totalling over 100 patients
2. Strong evidence of no effect	Significant results in favour of control treatment or non-significant differences, based on pooled data of studies totalling over 100 patients
3. Limited evidence of effect	Significant results in favour of new treatment, based on one or more large (over 100 patients) but unpoolable studies, or pooled results from small studies totalling less than 100 patients
4. Limited evidence of no effect	Significant results in favour of control treatment or non-significant difference, based on one or more large (over 100 patients) but unpoolable studies, or pooled results from small studies totalling less than 100 patients
5. Neither strong nor limited evidence of effect	No large or poolable trials available. These small trials may show: <ul style="list-style-type: none"> a) Significantly positive treatment effect (++) b) Trend towards positive treatment effect (+) c) No significant differences (0) d) Trend towards negative treatment effect (-) e) Significantly negative treatment effect (--)

Abbildung 2: aus Brolmann 2012