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REVIEW ARTICLE

A systematic review of interventions to enhance the healing of chronic ulcers of the foot in diabetes

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SUMMARY

The outcome of management of diabetic foot ulcers is poor, and there is continuing uncertainty concerning optimal approaches to management. It was for these reasons that in 2006 the International Working Group of the Diabetic Foot (IWGDF) working group on wound healing undertook a systematic review of the evidence to inform protocols for routine care and to highlight areas which should be considered for further study. The same working group has now updated this review by considering papers on the interventions to improve the healing of chronic ulcers published between December 2006 and June 2010. Methodological quality of selected studies was independently assessed by two reviewers using Scottish Intercollegiate Guidelines Network criteria. Selected studies fell into the following ten categories: sharp debridement and wound bed preparation with larvae and hydrotherapy; wound bed preparation using antiseptics, applications and dressing products; resection of the chronic wound; hyperbaric oxygen therapy (HBOT); compression or negative pressure therapy; products designed to correct aspects of wound biochemistry and cell biology associated with impaired wound healing; application of cells, including platelets and stem cells; bioengineered skin and skin grafts; electrical, electromagnetic, lasers, shockwaves and ultrasound; other systemic therapies which did not fit in the above categories. Heterogeneity of studies prevented pooled analysis of results.
Of the 1322 papers identified, 43 were selected for grading following full text review. The present report is an update of the earlier IWGDF systematic review, but the conclusion is similar: that with the exception of HBOT and, possibly, negative pressure wound therapy, there is little published evidence to justify the use of newer therapies. This echoes the conclusion of a recent Cochrane review and the systematic review undertaken by the National Institute for Health and Clinical Excellence Guidelines Committee in the UK. Analysis of evidence presents considerable difficulties in this field particularly as controlled studies are few and the majority are of poor methodological quality.

Keywords diabetes; diabetic foot; ulcer; wound healing; dressing

Abbreviations ABPI – ankle : brachial pressure index
AKA – above knee amputation
ATA – atmosphere absolute (pressure)
bFGF – basic fibroblast growth factor
BKA – below knee amputation
CBA – control before and after (study)
DFU – diabetic foot ulcer
EGF – epidermal growth factor
GCSF – granulocyte-colony stimulating factor
HBOT – hyperbaric oxygen therapy

IQR – interquartile range
ITS – interrupted time series (study)
ITT – intention to treat (analysis)
NPWT – negative pressure wound therapy
PDGF – platelet-derived growth factor
RCT – randomized controlled trial
rhVEGF – recombinant human vascular endothelial growth factor
SIGN – Scottish Intercollegiate Guidelines Network
SSG – split skin graft
$TcpO_2$ – transcutaneous oxygen tension
UT – University of Texas (wound classification system)
VAS – visual analogue scale

Introduction

The management of foot disease in diabetes remains a major therapeutic challenge throughout the world. The International Working Group of the Diabetic Foot (IWGDF) has issued guidelines on management since 1999, but good evidence is still required to substantiate the roles of particular interventions. It is for this reason that from 2005 the IWGDF established working groups to undertake a series of systematic reviews into aspects of prevention and management of foot disease, including offloading [1], osteomyelitis [2] and chronic ulceration [3]. At the invitation of the IWGDF Editorial Board, the IWGDF working group on wound healing undertook a systematic review of the evidence to inform protocols for routine care and to highlight areas which should be considered for further study, considering all papers published up to December 2006 [3]. The same working group have now updated this review by considering papers on the interventions to improve the healing of chronic ulcers published between December 2006 and June 2010.

Methods

Prospective and retrospective controlled studies, published in any language, that evaluated interventions for the treatment of chronic foot ulcers in people aged 18 years or older with either type 1 or type 2 diabetes mellitus were considered. Studies were included if they concerned agents or interventions that may accelerate the healing process, and the primary outcomes used were clinical: healing, time to healing, reduction in ulcer area or amputation. Search strategies were defined, which included selected search terms on study design, patient group, clinical problem and interventions of interest by using Medline (December 2006 to June 2010) and Embase (December 2006 to June 2010). Randomized controlled trials (RCT), case–control studies, prospective and retrospective cohort studies, control before-and-after (CBA) design and interrupted time series (ITS) designs were included. Bibliography tracking of identified articles was not performed. Previously performed high quality systematic reviews and Cochrane reviews on the topics of interest were searched to determine the need for an extension to the literature search. A later search was made of four clinical trials registries: http://www.controlled-trials.com/isrct/, http://www.clinicaltrials.gov, http://www.anzctr.org.au/ and http://ctrl.nic.in/Clincaltrials/index.jsp, and attempts were made to contact investigators if there was no evidence of any potentially relevant studies being published.

Two reviewers independently assessed all identified references by title and abstract to determine possible eligibility. Full-paper copies of identified articles were retrieved, and eligibility was confirmed by one of four pairs of independent reviewers. Each study was scored for methodological quality using scoring lists specific for each study design and based on checklists developed by the Dutch Cochrane Center (www.cochrane.nl/index.html). Equal weighting was applied to each validity criterion. Findings on data extraction and methodological quality were discussed between co-reviewers and a final decision endorsed by the entire group. Quality items were rated as 'done', 'not done' or 'not reported', and only those rated as 'done' contributed to methodological quality score. This quality score was translated into a level of evidence according to the Scottish Intercollegiate Guidelines Network instrument [4]: (1) RCTs and (2) studies with case–control, cohort, CBA or ITS design. Studies were also rated as ++ (well conducted with very low risk of bias), + (well conducted with low risk of bias) and − (low quality with higher risk of bias). Meta-analyses, other reviews and studies reporting non-analytic case reports and case series were not included. Reviewers did not assess their own work because of potential conflict of interest.

Extracted data were summarized in evidence tables on a study-by-study narrative basis. Because of the heterogeneity of study designs, interventions, follow-up and outcomes, no attempt was made to pool the results. These evidence tables were compiled following collective discussion by the working party, and conclusions were drawn and recommendations formulated. The papers selected for scoring were divided into the same nine categories used in the earlier review, except that the single article on the use of platelets has now been included in the section on cell therapy (in contrast to the previous allocation of platelet supernatant to the section on growth factors). A new tenth category, *other systemic therapies*, was added.

Results

A total of 802 articles were identified from EMBASE and 507 from Medline. Seventy-two of these were selected for full text review. An additional 13 articles were identified from other sources, including other systematic reviews. Of the total 85 articles, 43 were included in the review. The selected papers were grouped into ten categories.

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Sharp debridement and wound bed preparation with larvae and hydrotherapy

The earlier review concluded from three papers that the scientific evidence to confirm the benefit of sharp debridement was not strong. No further studies were identified on this method of wound preparation nor to supplement the weak evidence to support the use of hydrogels reported in the previous review. The results of the present search are summarized in Table 1. There have been a very small number of studies undertaken of newer therapies. The present search selected only one new paper to add to the two previously reported on the use of larvae [5]. This study was of a low-scoring cohort design and reported no significant effect on either healing or amputation following the application of larvae from the Malaysian blowfly, *Lucilia cuprina*. Only one paper was identified in which the use of hydrotherapy using Versajet® was compared with controls [6]. This was a low-scoring RCT, however, and although wound debridement time was shorter with hydrotherapy, no benefit was observed in healing at 12 weeks.

Wound bed preparation using antiseptics, applications and dressing products

The earlier review found evidence from a single small study of possible benefit from the use of zinc oxide tape. A small RCT had also reported improved ulcer healing with the use of a carboxymethylcellulose hydrofibre dressing (Aquacel®). However, in the present search, a large, observer-blinded RCT of good quality was identified that reported no difference between three products: Aquacel®, a surface antiseptic (Inadine®) and a non-adherent product (N-A®) in terms of healing by 24 weeks, as well as of a variety of secondary outcome measures including mean healing time, incidence of major and minor amputation and the incidence of secondary infection [7]. Similarly, another large, but non-blinded, RCT reported no difference between a silver impregnated carboxymethylcellulose hydrofibre dressing (Aquacel Ag®) and an alginate in the incidence of complete healing over 8 weeks, healing velocity, change in ulcer area and time to healing. A weak significant effect was shown on reducing wound depth, but depth was assessed using a relatively imprecise method, and the observers were non-blinded [8]. Thus, the earlier data on the use of hydrofibre dressings has not been confirmed in these more recent, and much larger, studies. In the absence of supportive evidence, the additional expense of the newer hydrofibre product is not justified.

The previous review found evidence from three controlled trials suggesting that hydrogels also may hasten healing, but no new studies on hydrogels were identified in this search, and the place of these products in routine care is still not substantiated. A small study of the use of QRB7 (oak bark extract) in Bensal HP or silver sulphadiazine

Table 1. Sharp debridement and wound bed preparation with larvae

Reference	Study design and score	Population	Intervention and control management	Outcomes	Differences and statistical results	Level of evidence (SIGN)	Comments
Caputo *et al.* [6]	RCT Open label Study quality, 2/9	41 patients: 54% had DFU, 44% (19) had venous ulcers Intervention, $n = 19$ (11 with DFU); control, $n = 22$ (11 with DFU)	Versajet® hydrosurgery versus standard sharp debridement plus pulse lavage	Wound debridement time Wounds closed at 12 weeks	Intervention: 10.8 min vs control: 17.7 min, $p = 0.008$ Intervention 52.6% vs control 47.4% NS	1–	Outcomes in DFU and venous ulcers not separately described. No difference in healing, but this would not necessarily be expected in a study of this type
Paul *et al.* [5]	Cohort Study quality, 3/8	59 with DFU Intervention, $n = 29$. Control, $n = 30$. Patients with ischaemia (ABPI > 0.75) excluded	Malaysian blowfly (*Lucilia cuprina*) larvae versus standard debridement	'Healing'(suitable for complete closure by self healing or suitable for grafting) Amputation	Intervention: 14/29 Control: 18/30 NS Intervention: 5/29 Control: 11/30 NS	2–	Period of study unclear – ran for 'at least 18 months' Unclear as to whether baseline characteristics of groups similar Unusual definition of healing

SIGN, Scottish Intercollegiate Guidelines Network; DFU, diabetic foot ulcer; ABPI, ankle : brachial pressure index.

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for 6 weeks [9] showed a significant benefit in terms of healing, but the quality of the study was difficult to assess because of missing details. The use of surface antimicrobials (tobramycin beads) on the wound at the time of forefoot amputation was shown in a non-randomized cohort study to have a weak significant effect on the need for later surgical revision. Little can be drawn from this study, however, as the apparent effect could have resulted from confounding influences [10].

Despite its widespread use in clinical practice, it was possible to identify only one study in which the effect of honey was assessed in a controlled study. This study was a small, non-blinded study of poor design and reported no difference between the use of honey and of povidone iodine [11].

A single non-blinded RCT on the use of superoxidized solution (Dermacyn®) was identified [12], which compared the incidence of healing at 6 months after infected surgical wounds of the foot had been irrigated with either the superoxidized solution or with povidone iodine. Although the results suggested an improvement both in healing by 6 months and in time to healing, the study was of poor methodological quality and took no account of any possible adverse effect on healing of the comparator.

In summary, there is little evidence to support the choice of any one dressing or wound application in preference to any other in attempts to promote healing of chronic ulcers of the foot in diabetes (Table 2).

Resection of the chronic wound

The earlier review identified a single study which reported the benefit of complete excision of plantar neuropathic ulcers [13]. No recent publication on this intervention was identified.

Hyperbaric oxygen

The previous review concluded that there were some data to suggest that systemic (but not topical) hyperbaric oxygen (HBO) reduces the rate of major amputation in people who have chronic foot ulcers complicating diabetes. The strongest evidence was provided by a double-blinded, but rather small, RCT of patients with unreconstructable peripheral arterial disease (PAD) [14]. The results of the present search resulted in three further studies being selected (see Table 3). These included ulcers of varying duration and severity and with varying severity of PAD.

One study was a retrospective analysis of 42 people who had been offered HBO, in which the outcome was compared between those who had completed ten or fewer treatments and those that had completed more [15]. A significant difference between groups in terms of the number of major amputations was seen, but the influence of confounders cannot be excluded. In a second, poorly reported RCT of low methodological quality, the intervention group was reported to have a marked improvement in outcome, with healing in 66% versus 0% [16]. Little can be concluded from this non-blinded study because of the choice of primary outcome measure: 'healing without surgical intervention'. The lack of blinding could have resulted in further surgical intervention being chosen for the control group.

The third new study was, however, a high quality double-blind RCT which demonstrated significantly improved outcome in the intervention group [17], who were more likely to heal within 12 months: 25/48 (52%) versus 12/42 (27%); $p = 0.03$. Of note, the intervention group included patients who either had no evidence of PAD or who were deemed unsuitable for vascular reconstruction, unlike the previous RCT by Abidia *et al*. [14], where only patients with unreconstructable critical limb ischaemia were included. Although the limitations of this study have been listed [18], its potential implications are far-reaching, and the study needs to be repeated with full health economic analysis and with an attempt being made to define the population most likely to benefit.

Compression or negative pressure therapy

The earlier review reported a single RCT which suggested a significant benefit of compression therapy on post-operative wounds. The review also identified three RCTs on topical negative pressure wound therapy (NPWT). Two of these were small, but the third suggested benefit, again for post-operative wounds. The results of the present search which resulted in the selection of three studies on compression and three on NPWT are given in Table 4.

One study of vacuum compression therapy was of poor methodological quality but reported a significant reduction in wound area following the intervention [19], and the conclusions that can be drawn from this study are further limited by the fact that patients with neuropathy were excluded. Two other studies which explored the benefit of compression therapy for (predominantly) post-operative wounds were identified. One was a cohort study in which the reported incidence of complete healing was significantly higher and the incidence of major amputation significantly lower in those who received the intervention, but the study was potentially biased as participants were allowed to opt for or against the intervention [20]. The second, randomized, study compared outcome in those with large post-operative wounds on the foot (mean area 3000 and 2668 mm^2 in the intervention and control groups) [21]. The results suggested a significant reduction in time to healing in the intervention group, but the study was non-blinded and of low methodological quality.

Two new studies of NPWT – one small and one large – concluded that the intervention was associated with reduced time to 90% granulation [22], reduced time to wound closure, increased incidence of healing by 16 weeks, greater reduction in cross-sectional area by 8 weeks and reduced incidence of minor amputation [23]. This latter study involved the randomization of

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Table 2. Wound bed preparation using antiseptics, applications and dressing products

Reference	Study design and score	Population	Intervention and control management	Outcomes	Differences and statistical results	Level of evidence (SIGN)	Comments
Jeffcoate *et al*. [7]	RCT with three arms Observer blinded Study quality, 6/9	DFU $N = 317$ randomized to three groups: Non-infected ABPI > 0.7 Duration > 6 weeks Area ≥ 25 and $\leq 2500\,mm^2$ Inadine® $n = 108$ Aquacel®: $n = 103$ N-A® $n = 106$ 88 withdrawals	Three different dressings: Inadine®, Aquacel®, N-A®	Healing by 24 weeks Time to healing Health economics Secondary infection	Inadine® 44.4% N-A®: 38.7% Aquacel®: 44.7% NS Inadine®: 74, 1 (SD 20.6) days N-A®: 75.1 (SD 18.1) Aquacel®: 72.4 (SD 20.6) days NS Mean dressing cost per patient Inadine®: £17.48 N-A®: £14.85 Aquacel®: £43.6 $p < 0.05$ Inadine®: $n = 71$ Aquacel®: $n = 54$ N-A®: $n = 48$ $p < 0.001$	1+	Patients and care providers not blinded. Blinded evaluation. Eventual to change throughout a 24-week period No evidence to suggest that iodine-impregnated dressing reduces the incidence of secondary infection
Jude *et al*. [8]	RCT Open label Study quality, 4/9	DFU $N = 134$ Intervention, $n = 67$ Control, $n = 67$ Lost to follow-up $n = 21$	Aquacel Ag® versus calcium alginate dressing for 8 weeks	% healing Healing velocity Time to healing % reduction in area over 8 weeks Change in ulcer depth	Intervention: 31% Control: 22% NS Intervention: 0.29 (SD 0.33) cm^2/week Control: 0.26 (SD 0.9) cm^2/week NS Intervention: 52.6 (SD 1.8) days Control: 57.7 (1.7) days NS Intervention: 58.1 (53.1)% Control: $60.5 \pm 42.7\%$ NS Intervention: 0.25 (0.49) cm Control: 0.13 (0.37) cm $p = 0.042$	1−	Outcome assessment not blinded No difference in healing Poor method for assessing depth (cotton-tipped swab)
Jacobs and Tomczak [9]	RCT, possibly blinded Study quality, 3/9	Plantar DFU $N = 40$ Non-infected, Wagner I = II, ABPI > 0.75 Duration > 6 weeks Diameter < 3 cm Baseline diameter Intervention: 1.9 (SD 0.76) cm	QRB7 (extract of oak bark) in Bensal HP versus silver sulphadiazine cream Applied daily for 6 weeks	Reduction in diameter	Intervention: 72.5% vs control: 54.7% $p = 0.059$	1−	Study said to be blinded but details not given No details of randomization given

(*continued*)

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Table 2. (Continues)

		Control: 1.6 (SD 0.78) cm					
Krause *et al*. [10]	Cohort Study quality, 3/8	Following transmetatarsal amputation for diabetic foot disease Intervention, $n = 46$ (49 feet) Control, $n = 14$(16 feet)	Antibiotic beads (tobramycin impregnated calcium sulphate) versus no local antibiotics	Time to healing Rate of surgical revision Transtibial amputation at an average follow-up of 28.8 months	Intervention: 10.5 (SD 4.5) weeks Control: 14.5 (SD 3.8) weeks NS Intervention: 8.2% Control: 25% $p < 0.05$ Intervention: 27% Control: 25%	2−	Retrospective study possibly affected by selection bias Outcome reported in only 40 of 60 patients
Piaggesi *et al*. [12]	RCT Non-blinded Study quality, 1/9	Infected surgical wounds $N = 40$: Intervention 20 Control 20 Ulcer size: Intervention: 32.7 (SD 19.8) cm^2 Control: 31.3 (SD 22.4) cm^2	Irrigation with superoxidized solution (Dermacyn®) versus irrigation with 50% povidone iodine	Healing at 6 months Time to healing	Intervention: 90% Control: 55% $p = 0.002$ Intervention: 10.5 (SD 5.9) weeks Control: 16.5 (SD 7.1) weeks $p = 0.007$	1−	Length of intervention unclear Adverse effects of povidone iodine cannot be excluded
Shukrimi *et al*. [11]	RCT Non-blinded Study quality, 1/9	DFU $N = 30$ Wagner II Mean $TcpO_2$39 (36–42) mmHg	Honey plus gauze versus povidone iodine diluted with normal saline plus gauze (changing to saline soaked gauze when wound free from pus) Daily dressings	Time to wound being deemed suitable for surgical closure Follow-up 7–36 days	Intervention: 14.4 (range 7–26) days Control: 15.4 (range 9–36) days NS	1−	Poor description of methodological detail

RCT, randomized controlled trial; DFU, diabetic foot ulcer; ABPI, ankle : brachial pressure index.

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Table 3. Hyperbaric oxygen therapy

Chen *et al*. [15]	Cohort Study quality, 5/8	Infected DFU $N = 42$ Wagner III and IV Group 1: $n = 21$, 10 Wagner III, 11 Wagner IV Mean duration of infection 7 (range 1–52) weeks Group 2: $n = 21$, 7 Wagner II, 16 Wagner IV Mean duration of infection 14 (range 2–52) weeks	Group 1: received ten or less sessions of HBOT Follow-up for mean 13.3 (6–29) months follow-up Group 2: received >10 sessions HBOT Follow-up mean 14.8 (6–30) months	Healing with preservation of foot at 6 months 'Failure' = amputation or persistent ulcer with no significant improvement	Group 1: healed: 7 (33.3%); failed 14 (BKA: 9, AKA: 1) Group 2: healed: 16 (76.1%); failed: 5 (BKA: 2, AKA: 2) $p = 0.05$	2+	Retrospective analysis Potential for selection bias
Duzgun *et al*. [16]	RCT Open label Study quality, 2/9	DFU $N = 100$ Wagner II–IV II $n = 18$ III $n = 37$ IV $n = 45$ Present for >4 weeks 50 in each group Follow-up 92 ±12 weeks	Intervention: HBOT plus standard care 2–3 ATA for 2 × 90 min day 1 then 1 × 90 min following day continued for approximately 20–30 days Control: standard care (daily wound care; debridement; amputation when indicated; infection control)	Final healing without any form of surgical intervention	Intervention: 33/50 (66%) Control: 0/50 (0%) Closure by Wagner grade: II: 6/6 (100%) III: 13/19 (68%) IV: 14/25 (56%) $p < 0.05$	1−	No ITT analysis No dropouts or deaths reported Limited details on concomitant therapy Possible selection bias, lack of clarity on baseline ulcer characteristics No comment about vascular status of patients Higher number of females in control group Non-blinding could have led to increased surgical intervention in control group
Löndahl *et al*. [17]	RCT Double-blind Study quality, 7/9	DFU $N = 94$ HBOT: $n = 49$ Control, $n = 45$ Wagner II–IV ulcers present for >3 months; and either with adequate distal perfusion or deemed not suitable for revascularization Toe systolic pressure ≤35 mmHg: HBOT 33% Placebo 29%	HBOT: 2.5 ATA in multiple person chamber for 85 min 5 days a week over 8 weeks plus standard care Control: placebo 2.5 ATA air treatment in same chamber plus standard care	Healing within 12 months and maintained 'to next visit' Death Amputation	ITT Intervention: 25/48 (52%) Control: 12/42 (27%) $p = 0.03$ NNT = 4.2 Per protocol Intervention: 23/38 (61%) Control: 10/37 (27%) $p = 0.009$ NNT = 3.1 Intervention: 1 Control: 3 Intervention: 1 BKA, 2 minor	1++	Dropout from treatment 19/94 10 patients had revascularization during follow-up: 6 in HBOT, 4 in control group (1 healed post procedure in each group)

DFU, diabetic foot ulcer; HBOT, hyperbaric oxygen therapy; BKA, below knee amputation; AKA, above knee amputation; ATA, atmosphere absolute (pressure); NNT, Number needed to treat

Table 4. Compression and negative pressure therapy

Akbari *et al*. [19]	RCT Open label Study quality, 1/9	DFU $N = 18$ UT Grade II No significant loss of protective sensation	Intervention: Vacuum Compression therapy 10 sessions; 1 h per day four times a week plus standard care over 3 weeks Control: standard care (debridement, blood glucose control, systemic antibiotics, saline cleansing, offloading and daily dressing changes)	Reduction in surface area	Intervention: 46.88 (SD 9.24) to 35.09 (SD 4.09) mm^2($p = 0.006$) Control: 46.62 (SD 10.03) to 42.89 (SD 8.1)mm^2 ($p = 0.01$) Comparative reduction: $p = 0.024$ (intervention versus control) Within group improvement judged better for Intervention group: $p = 0.03$	1− Poor description of study Outcome not predefined
Kavros *et al*. [20]	Cohort Study quality, 3/8	Retrospective review of patients 1998–2004 Non-healing toe or amputation wounds for which revascularization was not possible 32/48 of total population had diabetes (67%) Resting ABPI Intervention: 0.55 (IQR 0.44–0.66) Control: 0.52 (IQR 0.45–0.65)	Intermittent pneumatic compression 6 h/day in two 3-h sessions versus standard wound care	Survival at 18 months Complete healing limb intact Below knee amputation	Intervention: 20/24 (83%) Control: 18/24 (75%) NS Intervention: 14/24 (58%) Control: 4/24 (17%) $p < 0.001$ Intervention: 10/24 (42%) Control: 20/24 (83%) $p < 0.001$	2− Only 63% and 71% of the two groups had diabetes, and the results were not described separately from patients without diabetes Mixed population of chronic foot and post amputation wounds with critical limb ischaemia not defined Biased as patients were able to select treatment No details on length of treatment with intervention High amputation rates
Mars *et al*. [21]	RCT Open label Study quality, 3/9	$N = 60$ patients with large post-op DFU (intervention: 3000 mm^2 vs control: 2668 mm^2) following extensive resection for infection which required urgent surgical intervention Results given for Intervention, $n = 28$, control, $n = 29$	Intervention: Compressed air massage at 100 kPa for 15–20 min 5 days a week. Other treatment as for controls Control: specified standard wound care plus antibiotics plus insulin infusion Treatment applied to the foot and tissue around ulcer, not to the wound bed	Time to healing (by secondary intention or by split skin graft Numbers receiving skin grafts Amputations	Intervention: 58.1 (SD 22.3) days Control: 82.7 (SD 30.7) days $p = 0.001$ Intervention: 9/28 Control: 10/29 Intervention: 14/28 Control: 15/29	1− No method of randomization given No data on actual healing incidence No baseline data on neuropathy or arteriopathy Results reported for only 57/60
Sepulveda *et al*. [22]	RCT Single-blind Study quality, 5/9	DFU following transmetatarsal amputation or removal of two or more adjacent toes $N = 22$:11 in each group Mean age Intervention: 61.5 (SD 10) years Control: 62.1 (SD 8) years ABPI:	Intervention: NPWT applied 3–5 days after surgery. Changes each 2–3 days, plus standard care Control: standard care involving moist wound healing including hydrocolloid gel or alginate	Time to 90% granulation	Intervention: 18.8 (SD 6.0) days Control: 32.3 (SD 13.7) days $p = 0.007$	1+ Outcome assessment blinded Control dressing varied by extent of wound exudates Variable follow-up Power calculation given, based on pilot data

		Intervention: 1.05 Control: 1.16					
Blume *et al*. [23]	RCT Open label Study quality, 5/9	DFU Wagner II–III $>2\,cm^2$ Ulcer duration prior to treatment: NPWT: 198.3 (SD 323.5) days Control: 206 (SD 365.9) days ABPI 0.7–1.2; triphasic wave form and/or $TcpO_2$ >30 mmHg 342 patients randomized 335 received treatment	Intervention: NPWT until healing or 16 weeks (112 days) plus standard care Control: standard care (usually involving hydrogels or alginates used according to manufacturer's guidelines)	Healing at 16 weeks (complete epithelialization with no drainage) Reduction in surface area at day 28 (different from baseline) Time to closure Amputation	Intervention: 73/169 (43.2%) Control: 48/166 (28.9%) $p = 0.007$ Intervention: $-4.32\,cm^2$ Control: $-2.53\,cm^2$ $p = 0.021$ Intervention: 96 (75–114) days Control: 'unquantifiable'; $p = 0.001$ LEA Intervention, $n = 7$ Control, $n = 17$ $p = 0.035$	1+	ITT but 30.75% dropout rate Median baseline area of ulcers was large Intervention: 13.5 (18.2) cm^2 Control: 11.0 (12.7) cm^2 Population selection: 79% male Healing may not be the best outcome measure for wounds of this size and may not be the objective of this type of therapy No reported follow-up after 112 days
Frykberg and Williams [24]	Cohort Study quality, 2/8	DFU identified from two groups of reimbursement claims – payers and Medicaid	Retrospective comparison for people receiving NPWT versus people receiving other treatments Data corrected for extent of debridement (as measure of wound severity)and for overall morbidity (as reflected in total reimbursement claim)	Incidence of amputation	Significantly fewer amputations in NPWT group in both reimbursement groups (Payers/Medicaid) when adjusted either for debridement depth (wound severity): Payers: NPWT 26.3% vs non-NPWT 52.7% $p < 0.001$ Medicaid: 18.3% vs 53.3% $p < 0.001$or for overall costs (total morbidity) Payers: NPWT 27.3% vs non-NPWT 45.7% $p = 0.002$ Medicaid 9.1% vs 44.7% $p < 0.001$		Can draw no conclusions about clinical effectiveness Not completely contemporaneous Potential source of bias: data based on out-patient treatment only

DFU, diabetic foot ulcer; ABPI, ankle : brachial pressure index; IQR, interquartile range; NPWT, negative pressure wound therapy; LEA, lower extremity amputation

342 patients and was methodologically sound. The ulcers which were selected were $>2\,cm^2$ and had been present for much longer than in other studies (mean 200 days), but it was not stated how many of them had originally been post-operative wounds. Further evidence is needed to substantiate the place of NPWT in routine clinical practice.

There was a single study which attempted to confirm the effectiveness of NPWT through analysis of reimbursement claims, but the results could potentially be explained (in part) by confounding factors [24].

Products designed to correct aspects of wound biochemistry and cell biology associated with impaired wound healing

In the previous review, two small RCTs reported possible benefit following the use of, firstly, lyophilized collagen and, secondly, an acellular bioproduct derived from the small intestinal submucosa of pigs. There had also been a number of studies of specific growth factors as well as of transretinoic acid. A single large study to suggest benefit of platelet-derived growth factor (becaplermin) was identified even though it was known that another, equally large but negative, study had not been published. A single study on basic fibroblast growth factor (bFGF) had shown no benefit, and there had been some early, but inconclusive, work to suggest that there may be a role for epidermal growth factor (EGF). One large RCT on a collagen/oxidized regenerated cellulose dressing product (Promogran®), which is believed to modify the balance between matrix metalloproteinases and their tissue inhibitors, failed to confirm an effect on healing.

Trials on granulocyte-colony stimulating factor (GCSF) were included in the following section in the earlier review. There had been a small number of high quality trials which had been of good quality, even though they had been directed primarily at the eradication of infection. They were included, however, because amputation was recorded as an end point, and an apparent trend towards limb salvage had been noted in a separate meta-analysis [25]. No further studies of GCSF were detected in the current search, in contrast to new studies that have examined the efficacy of EGF, bFGF, vascular endothelial growth factor (VEGF), protease modulating dressings, talactoferrin, acellular regenerative tissue matrix and chrysalin (a ligand for thrombin binding sites) (Table 5).

There are some data to suggest that EGF may hasten healing. A double-blind RCT examined the effect of twice daily topical application administration of rhEGF gel to non-ischaemic ulcers of 2–3 weeks' duration [26]. The study was weakened by the use of *per protocol* analysis, and although a significant benefit was reported for a subgroup *post hoc* analysis of ulcers with an area exceeding $6\,cm^2$, the overall results of the trial were essentially negative. A second large, placebo-controlled and partial dose-ranging RCT reported a highly significant difference between groups in the prevalence of granulation tissue after just 2 weeks (73.1% and 70.8% in the two intervention groups and 39.6% in the control arm: $p = 0.000015$). It is to be regretted that the results of later observations in this 8-week study were adversely affected by the insistence of the ethical committee that those in the control group switch to an intervention arm after the first 2 weeks [27]. More studies are needed to seek confirmation of these promising findings.

Uchi and colleagues [28] have recently reported the results of a methodologically high quality, partial dose-ranging RCT of bFGF administered in spray form for 8 weeks. The ulcers selected were rather small. The authors reported a significant difference between the higher dose used and placebo in the percentage having a reduction in area by >75%, but this was only on *per protocol* analysis. There was no difference in numbers healed. As the difference was non-significant when intention to treat (ITT) analysis was used, this would confirm the earlier negative finding of Richard and colleagues [29].

A well-designed double-blind RCT assessed the effect of intramuscular injections of a plasmid containing the gene for $phVEGF_{165}$ [30]. In the subgroup of patients with diabetic foot ulcers, a significantly greater percentage of the intervention group achieved the primary outcome measure of >60% reduction in ulcer area than controls (33% vs 0%).

A small non-blinded RCT of 40 non-infected diabetic foot ulcers reported a significant benefit in the numbers healed and in time to healing within 6 weeks, when a protease modulating dressing was compared with usual care but was compromised by using *per protocol* analysis [31]. A second study suggested that there may be an additional benefit to the use of a protease modulating dressing when added to autologous platelet supernatant compared with either treatment alone [32], but the data were not fully presented and are therefore difficult to interpret.

A single placebo-controlled, partial dose-ranging study of talactoferrin, a recombinant human form of the breast milk protein lactoferrin, was identified [33]. The study design was poor, however, and no difference was observed between groups.

Two RCTs of an acellular dermal regenerative tissue matrix were identified.

The first, a small non-blinded RCT of poor quality combined an acellular dermal regenerative tissue matrix with a mineral oil-soaked dressing [34]. A significant difference in healing and the final wound areas was shown when compared with the control group, but no data were provided on area at baseline. The second was also of poor methodological quality and compared a single application of an acellular dermal regenerative tissue matrix combined with a silver impregnated dressing, with usual wound care [35]. A significant difference in healing at 12 weeks was found, but the study was not blinded.

Topical Chrysalin, a ligand for thrombin binding sites, was studied in a double-blind placebo-controlled, partial dose-ranging trial of 60 participants [36]. Few details were provided, and statistical analysis was not undertaken, but the incidence of wound closure at 20 weeks appeared similar in the three groups. A double-blind controlled trial of an extract of the plant *Tinaspora cordifolia*, applied as an immunomodulator to 50 patients with large foot ulcers, reported a non-significant change in rate of healing [37].

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Table 5. Products designed to correct aspects of wound biochemistry and cell biology associated with impaired wound healing

Viswanathan *et al*. [26]	RCT Double-blind Study quality, 6/9	DFU*N* = 60 Ulcers 2–3 weeks duration Area 2–50 cm^2 ABPI ≥ 0.753 dropouts	rhEGF 150 mcg/g in 30 g tubes administered topically as a gel twice daily until healing or to 15 weeks versus placebo	Healingby 15 weeks Time to healing	Intervention: 25/29 Control: 14/28 No statistical analysis or comment on difference in the text Post hoc analysis showed numbers healing in those with area >6 cm^2 was significantly greater $p < 0.002$ Intervention: Mean: 9.6 (SD 11.3) Median 8.5 weeks Control: Mean: 14.9 (SD 4.1) Median 14.9 weeks No statistical results given	1+	Actual dose given not clear Per protocol analysis Data in intervention group not normally distributed and yet parametric stats used Little evidence to support statement in the Abstract that 'the study demonstrated the . . .efficacy of rhEGF in accelerating healing'
Fernandez-Montequin *et al*. [27]	RCT Double-blind Study quality, 6/9	DFU *N* = 149 Wagner III–IV 49 lost to follow-up Follow-up to 12 months	Intralesional injections of rhEGF Total intervention phase 8 weeks Group 1: 25 mcg per treatment (*n* = 53) Group 2: 75 mcg (*n* = 48) Group 3: placebo(*n* = 48)	Change in area % granulation at 2 weeks Partial (>50%) and complete granulation at 8 weeks Weeks to complete response (>75% granulation)	No results given Group 1: 73.1% Group 2: 70.8% Group 3: 39.6% $p = 0.000015$ Group 1: 86.8% Group 2: 70.8% Group 3: 58.3% $p = 0.005$ Group 1:3 weeks Group 2: 3 weeks Group 3: 5 weeks 1 vs 3 $p = 0.006$ 2 vs 3 $p = 0.031$	1+	Ethics committee insisted that non-responders received intervention after only 2 weeks:4 in Group 1 switched to Group 2; 5 in Group 3 switched to Group 2 No detail on % granulation at recruitment Significance of results difficult to interpret
Uchi *et al*. [28]	RCT Double-blinded Study quality, 8/9	DFU Non-infected Wagner grade II Area <900 mm^2 ABPI > 0.9 or palpable pulses *N* = 150 Three groups A Placebo *n* = 49 B 0.001% bFGF *n* = 51 C 0.01% bFGF *n* = 50	Partial dose-ranging placebo-controlled study bFGF sprayed on as 5 puffs daily 5 cm from target area for 8 weeks	≥75% ulcer area by 8 weeks Healing ≤ depth by 8 weeks	A 27/47 (57.5%) B 34/47 (72.3%) C 37/45 (82.2%) C versus A $p = 0.025$ A 22/47 (46.8%) B 27/47 (57.4%) C 30/45 (66.7%) p = NS A 26/47 (55.3%) B 29/47 (61.7%) C 32/45 (71.1%) p = NS	1++	Per protocol analysis. Small ulcers at baseline Overlap between primary and secondary outcome measures
Kusumanto *et al*. [30]	RCT Double-blinded Study quality, 7/9	54 patients with CLI: 27 in each group. Subset with DFU: Intervention: 21 Control: 17	Intramuscular injection of $phVEGF_{165}$ gene carrying plasmid 2000 mcg on days 0 and 28 versus saline control Follow-up over 100 days	Improvement in ulcer (decrease in ulcer area by >60%) Major amputation	Intervention: 7/21 (33%) Control: 0/17 $p = 0.01$ Intervention: 3/27 (11%) Control: 6/27 (22%) NS	1++	Not clear if the subset with DFU were comparable between groups at baseline Data on amputation not cited separately for the population with DFU
Lázaro-Martínez *et al*. [31]	Non-blinded RCT	DFU *N* = 40	Protease modulating dressing changed each	Healing	Per protocol analysis only Intervention: 12/19 (63%)	1−	Small study Per protocol

	Study quality, 3/9	Non-infected neuropathic $TcpO_2$ >30 mmHg Intervention, $n = 20$ Control, $n = 20$ One drop-out from each group	day until healing or 42 days	Time to healing	Control: 3/19 (15%) $p < 0.03$ Intervention: 23.3 (SD 9.9) days Control: 40.6 (SD 1.15) $p < 0.01$		analysis. Some wounds post-surgical
Kakagia *et al*. [32]	RCT Single-blind Study quality, 4/9	DFU $N = 54$ >3 months >2.5 cm^2 post debridement 3 lost to follow-up Not clear how many in each group	Group 1: Protease modulating dressing versus autologous platelet supernatant over 8 weeks Group 2: Protease modulating dressing versus Group 3: both	Healing at 8 weeks % change in length % change in width % change in depth	Group 1: $n = 2$ Group 2: $n = 2$ Group 3: $n = 2$ Group 1: −18.6% Group 2: −14.3% Group 3: −33.8% $p < 0.01$ Group 1: −23.9% Group 2: −17.4% Group 3: −46.1% $p < 0.01$ Group 1: −35.5% Group 2: −34.9% Group 3: −551% $p < 0.01$	1−	Description of methods incomplete Results difficult to interpret because data not fully presented Small sample size
Lyons *et al*. [33]	RCT Single-blind Partial dose-ranging Study quality, 2/9	DFU $N = 46$ 2.5% gel ($n = 15$) 8.5% gel ($n = 15$) Placebo ($n = 16$)	Talactoferrin alpha (recombinant human lactoferrin) gel Topical administration twice daily for 30 days 2.5%, 8.5% versus placebo	75% reduction ulcer size at 12 weeks Complete wound healing at 90 days Combined intervention groups versus placebo	2.5% gel: 7 patients (47%) 8.5% gel: 8 patients (53%) Placebo: 4 patients (25%) NS Intervention: 30% Control: 19% $p = 0.09$	1−	Surrogate outcome measure but no difference
Brigido [34]	RCT Open label Study quality, 2/9	DFU $N = 28$ Wagner II >6 weeks (plus one leg ulcer) Palpable/audible pulses Non-infected	Human acellular regenerative tissue matrix (Graftjacket) Single application with mineral oil-soaked fluff versus wound gel and gauze	Healing Final ulcer area	Intervention 12/14 (85.7%) Control: 4/14 (28.6%) $p = 0.006$ Intervention: 1.0 (SD 2.57) cm^2 Control: 31.14 (SD 43.74) cm^2 $p = 0.005$	1−	No data on baseline ulcer area and yet gross difference between groups in final area Non-blinded Limited information on co-morbidity
Reyzelman *et al*. [35]	RCT Open label Study quality, 3/9	DFU $N = 86$ UT grade 1 or 2 Size 1–25 cm^2 $TcpO_2 > 30$ ABPI 0.7–1.2 Intervention, $n = 47$ Control, $n = 39$	Single application Acellular dermal regenerative tissue matrix plus silver NA dressing versus standard moist wound care	Healing at 12 weeks Time to complete healing	Intervention: 32 (69.6%) Control: 18 (46.2%) $p = 0.03$ Intervention: 5.7 (SD 3.5) weeks Control: 6.8 (SD 3.3) weeks	1−	Unblinded Combined intervention tissue matrix plus silver
Fife *et al*. [36]	RCT Double-blind Partial dose-ranging study Study quality, 3/9	Patients with leg or foot ulcer: $N = 60$ DFU: $n = 35$ Present >8 weeks Wagner 1–III $TcpO_2 \geq 20$ mmHg Mean ulcer area	Chrysalin (TP508): ligand for thrombin binding sites. Total population Group 1: 1 mcg $n = 21$, 12 with DFU Group 2: 10 mcg $n = 18$,	Complete closure within 20 weeks	DFU: Group 1: 9/12 (75%) Group 2: 7/10 (70%) Group 3: 4/13 (31%) Group 1 versus Group 3 $p < 0.05$ Group 1 and Group 2 combined	1−	Limited information about treatment application Limited information about baseline co-morbidities High dropout rate Group 1: 5 Group 2: 3

(*continued*)

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Table 5. (Continues)

			Group 1: 3.59 (SD 5.31) cm^2 Group 2: 315 (SD 3.2) cm^2 Group 3: 4.11 (SD 5.99) cm^2	10 with DFU Group 3: placebo (saline) $n = 21$, 13 with DFU Twice weekly visits up to 20 weeks or until healing	Median time to closure	versus Group 3 $p < 0.05$ Group 1: Total 122 days; DFU 94 days Group 2: Total 87 days; DFU 71.5 days Group 3: >140 days Group 2 versus Group 3 $p < 0.05$	Group 3: 6 25% were ulcers of lower leg
Purandare and Supe [37]	RCT Double-blind Study quality, 4/9	DFU $N = 50$ 5 lost to follow-up Intervention, $n = 23$ Control, $n = 22$ Ulcers >4 cm^2 diameter Wagner I or II Digital ray or forefoot amputations or chronic non-healing ulcers 18 month follow-up	Topical application aqueous plant extract *Tinospora cordifolia* versus standard therapy and debridements	Rate of change of ulcer area (cm^2/day) Change of ulcer perimeter (mm/day)	Intervention: −0.15 cm^2/day Control: −0.07 cm^2/day $p = 0.145$ Intervention: −0.09 mm/day Control: −0.07 mm/day $p = 0.09$	1– 	Intervention unclear Standard therapy unclear No details on arteriopathy or neuropathy Actual healing incidence not given

DFU, diabetic foot ulcer; ABPI, ankle : brachial pressure index; bFGF, basic fibroblast growth factor; NA,non-adherent; CLI, critical limb ischaemia

Application of cells, including platelets and stem cells

The previous review identified five papers reporting the use of platelet-derived products, but all were limited by methodological problems, and no firm conclusion could be drawn, although there were data to suggest possible benefit. Other work on stem cells had been restricted to uncontrolled and observational studies. The present search revealed one further study of the use of platelets as well as two further studies. The details are presented in Table 6.

One major reason for limited adoption of platelet and platelet-derived products is the cost of harvesting autologous platelets. One group has, however, now assessed the use of platelets from ABO and rhesus-matched blood bank samples in a single-blind RCT of good quality [38]. They reported a significant improvement in the healing of the intervention group at 12 weeks compared with controls. The report gave no details of the inclusion criteria, but given that 38 of the 52 in the intervention group had exposed bone at baseline, the incidence of healing was surprisingly high.

A retrospective comparison of fibroblast allograft recipients and controls was reported by Seung-Kyu and colleagues [39]. A significant improvement in healing at 8 weeks in the 37 recipients who opted to have the treatment when compared with 18 controls who did not was reported. Selection bias could have influenced the results.

An observer-blind good quality RCT comparing autologous lipoaspirate cells or placebo was identified [40]. The intervention group had a significantly higher incidence of healing at 8 weeks as well as a significantly reduced time to healing.

Bioengineered skin and skin grafts

The earlier review noted that both dermal fibroblast culture and fibroblast/keratinocyte co-culture were associated with improved healing of clean neuropathic ulcers when compared with placebo, although the strength of the observation was weakened by variable rates of healing in the placebo groups. A single RCT reported the use of keratinocytes alone, but few data were presented. The present search identified two further papers reporting the use of skin substitutes, as well as one on the use of skin grafts. The details are given in Table 7.

A recently reported RCT was identified, which reported the results of a well-designed multicentre RCT undertaken some years earlier, in which the 12-week healing associated with the use of fibroblast/keratinocyte co-culture (Apligraf®) was compared with polyamide and saline moistened gauze [41]. The study had been stopped prematurely for reasons unrelated to the conduct of the trial, when only 72 of 120 participants had been randomized, and data were reported on 71 of these. Even though healing occurred in 51.5% of the intervention group compared with 26.3% of controls ($p = 0.049$), the failure to complete the study casts doubt on the significance of the difference observed and adds little to the available evidence.

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Table 6. Application of cells, including platelets and stem cells

Jeong *et al*. [38]	RCT Single-blind Study quality, 6/9	DFU $N = 100$ Intervention, $n = 52$ Control, $n = 48$ Wagner I–II Mean area 5.7 (SD 3.6) cm^2 Duration >4 weeks: mean 12.4 (SD 5.6) weeks	Intervention: blood bank platelet concentrate (ABO and Rh compatible) with fibrinogen (activator) and thrombin (sealant) Applied following debridement on 2 occasions, 3–4 days apart Control: fibrinogen plus thrombin	Healing at 12 weeks Time to healing % reduction in area Satisfaction (VAS)	Intervention: 41:52 (79%) versus control: 22:48 (46%) $p < 0.05$ Intervention: 7.0 (SD 1.9) weeks vs 9.2 (SD 2.2) $p < 0.05$ Intervention: 96.3 (SD 7.8) vs control: 81.6 (SD 19.7) $p < 0.05$ Intervention: 7.6 ± 1.6 vs control: 5.3 (SD 1.4) $p < 0.05$	1+	Inclusion/exclusion criteria not clear 38/52 in the Intervention group had exposed bone: surprisingly high rate of healing
Seung-Kyu *et al*. [39]	Case–control Study quality, 2/7	Non-infected DFU $N = 55$ Without severe arteriopathy Intervention, $n = 37$ Control, $n = 18$ $TcpO_2$ >30 mmHg ABPI > 0.5	Intervention: fresh human fibroblast allograft with fibrinogen and local thrombin Control: fibrinogen and thrombin without fibroblasts	Healing at 8 weeks Time to healing in those who healed	Intervention: 83% ($n = 37$) Control: 50% ($n = 18$) ($p < 0.05$) Intervention: 31 days Control: 42 days ($p < 0.05$)	2−	Retrospective analysis Selection bias as intervention group comprised those accepting fibroblast treatment, whereas controls did not accept this treatment No details on arterial status
Seung-Kyu *et al*. [40]	RCT Single-blind Study quality, 6/9	DFU $N = 54$ Non-ischaemic non-infected Wagner I or II At least 6 weeks duration Intervention, $n = 28$ Control, $n = 26$ Mean duration: Intervention: 12.5 (SD 5.6) weeks Control: 12.5 (SD 5.5) weeks Area: Intervention: 4.3 cm^2 Control: 4.0 cm^2	Intervention: single treatment human lipoaspirate cells autograft, tegaderm as dressing. Control: the same cell carrier without lipoaspirate cells	Healing at 8 weeks Time to healing	Intervention: 26/26 Control: 16/26 $p < 0.05$ Intervention: 33.8 (SD 11.6) days Control: 42.1 (SD 9.5) days $p < 0.05$	1+	Patient groups very similar at baseline Outcome assessments (but not patients) blinded to group allocation

DFU, diabetic foot ulcer; ABPI, ankle : brachial pressure index; VAS, visual analogue scale

Table 7. Bioengineered skin and skin grafts

Edmonds [41]	RCT Open label Study quality, 5/9	DFU $N = 72$ from 20 centres Neuropathic non-infected ulcers Intervention, $n = 33$ Control, $n = 39$	Intervention: Apligraf™ (living keratinocytes and fibroblasts) Control: polyamide and saline moistened gauze	Healing at 12 weeks	Intervention: 17/33 (51.5%) Control: 10/38 (26.3%) $p = 0.049$	1+	Prematurely stopped by sponsor for non-safety reasons (original aim 120 patients per arm) Low healing rate in the control group but median ulcer duration prior to recruitment was long: Intervention: 1.1 Control: 1.2 years
Moustafa *et al*. [42]	RCT Open label Study quality, 3/9	DFU $N = 12$ Wagner I	Intervention: dressing with autologous keratinocytes once a week during 12 weeks Control: dressing without cells during 6 weeks then one treatment once a week during 6 or 12 weeks	Healing	Intervention: 4/7 Control: 1/5	1−	Weak design. Very small sample size, inconclusive result
Mahmoud *et al*. [43]	Case–control Study quality, 3/7	DFU $N = 100$ Intervention, $n = 50$ Control, $n = 50$ ABPI ≥ 0.4 DFU $\geq 2\,cm^2$ Ulcer area and duration equivalent in the two groups	Intervention: skin graft Control: paraffin gauze	Median healing time Mean hospital stay Ulcer recurrence	Intervention: 34 days Control: 145 days $p = 0.03$ Intervention: 6 days Control: 18 days $p < 0.05$ Intervention: 8% Control: no result given	2−	Biased as patients allowed to choose treatment group Few data on baseline characteristics of groups All patients eventually healed, but no data on how healing confirmed

DFU, diabetic foot ulcer; ABPI, ankle : brachial pressure index.

Equally, the very small RCT that reported the use a novel keratinocyte delivery system was of very poor methodological quality, and the result was inconclusive [42].

Mahmoud and colleagues reported a case–control study with 50 having their foot ulcer managed by split skin graft and 50 having paraffin gauze dressings [43]. The authors reported a significant difference in median healing time between groups, but the study was of poor methodological quality and susceptible to bias because the patients had the option to select their treatment group.

Electrical, electromagnetic, lasers, shockwaves and ultrasound

The previous review described reports on the use of electrical stimulation, ultrasound, normothermic therapy, magnets and laser therapy but found no convincing evidence of clear benefit of any. The present search resulted in the selection of four further papers on physical methods, and the details are given in Table 8.

A cohort study investigated reduction in ulcer area following rhythmical electrical stimulation of the edge of the ulcer on alternate days over 1 month [44]. The study was methodologically weak, however, and the means of allocation to groups was not clear. Although there was an apparently greater reduction in ulcer area at 45 days, this was not maintained at 60 days.

A second study [45] compared the use of electrical stimulation with a placebo comprising local warming of the skin. Although a significant reduction in ulcer area in the intervention group was seen at 4 weeks, the study was very small and methodologically weak, and the lack of blinding throws doubt on the significance of the difference described.

No studies on shockwave therapy were included in the earlier review, but the present search yielded two trials. The first randomized 30 patients to receive either shockwave therapy to the perimeter of the ulcer each 72 h or a sham intervention [46]. There was no difference in healing by 20 weeks, although the time to healing in the small number who were healed was reported to be significantly shorter. The strength of the statistical significance is surprising for such small numbers and may relate to the inappropriate use of parametric statistics.

The second compared extracorporeal shockwave treatment with hyperbaric oxygen [47]. Again methodologically weak, the reporting of a significant difference between the two groups was based on a curious composite end point of the proportion of ulcers healed, or 'greater than 50% improved'. Our reworking of the statistics based on the raw data given in the paper casts doubt on even these results.

Other systemic therapies

Five trials were identified, which did not fit into any of the categories used in the earlier review. The details are given in Table 9.

A double-blind RCT of up to 3 months treatment with a low molecular weight heparin, bemiparin, reported a statistically significant difference in the size or Wagner grade of uncomplicated foot ulcers, although there was no difference in the percentage healing in the intervention and control groups (35.1% vs 33.3%, respectively) [48].

A small poor quality RCT of iloprost infusion was conducted with the main aim of investigating changes in endothelial function in patients with severe peripheral ischaemia and Wagner grade III–IV foot ulcers, but the incidence of amputation at 30 days was also reported [49]. The intervention group received treatment for ten consecutive days, whereas controls had no treatment; the study was unblinded. There was no apparent difference in the incidence of major and minor amputations between the intervention groups.

In a study of a Chinese herbal preparation, 80 participants with necrotic/gangrenous ulcers who had previously been deemed to require amputation of the digit were randomized to receive either the herbal formulation or placebo in a patient-blinded RCT [50]. There was no difference between groups in the primary end point, which was time to ulcer granulation sufficient to enable skin grafting. There was similarly no difference in the incidence of amputation.

In another study of a herbal extract ANGIPARS™, 21 participants were randomized in a three-way trial comparing the reduction in wound surface area at 6 weeks following treatment with (1) twice daily oral administration of the herbal extract, (2) oral administration plus topical application of the extract to the wound surface and (3) standard care [51]. Significant reductions in surface area were reported within group for the two treatment groups but not for the control. No between-group comparisons were reported. The quality of the trial methodology was low scoring.

The same preparation which was reported above is also available for intravenous administration and was the basis of another small and methodologically weak RCT [52]. Intravenous herbal extract was administered daily for 28 days, and the primary outcome measure was change in ulcer area over the same period. A highly significant change in area was reported in the intervention group, but the change in the (smaller number of) controls was not significant. There also appeared to be a difference between the groups in terms of the ulcer area at baseline (intervention 479.9 vs 766 mm^2).

Discussion

The response to treatment of many diabetic foot ulcers is poor, and this tempts clinicians to try any therapy which may hasten healing. It is, however, important that the effectiveness of different treatments is rigorously assessed, and treatments that lack evidence of effectiveness should not be used. The present report is an update of an earlier IWGDF systematic review in 2007[3], and the conclusion

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Table 8. Electrical, electromagnetic, lasers, shockwaves and ultrasound

Margara *et al*. [44]	Cohort Study quality, 3/8	DFUs $N = 30$ Intervention, $n = 16$ Control, $n = 14$ Not infected Baseline ulcer area: Intervention: 8.08 (SD 2.36) cm^2 Control: 8.01 (SD 2.23) cm^2	Frequency rhythmic electrical modulation applied to edge of ulcer for 30-min sessions alternate days for 1 month Control: dressing at least weekly Follow-up 2 months	Reduction in ulcer area at 30, 45 and 60 days as % baseline	30 days Intervention: 33 (SD 22)% Control: 14 (SD 10)% $p < 0.05$ 45 days Intervention: 65 (SD 14)% Control: 51 (SD 14)% $p < 0.05$ 60 days Intervention: 93 (SD 1)% Control: 83 (SD 15)% NS	2−	Means of allocation not clear Not randomized Possible less than adequate management of control group No difference in long-term outcome
Petrofsky *et al*. [45]	RCT Open label Study quality, 3/9	DFU $N = 20$ Wagner II Baseline area Intervention: ($n = 10$) 24.1 (SD 6.2) cm^2 Control: ($n = 10$) 28.2 (SD 5.7) cm^2	Electrical stimulation and local heat (infrared lamp) 30 min 3 times a week for 4 weeks versus infrared lamp alone	Reduction in wound area at 4 weeks determined by length and width multiplied; digital images Wound volume at 4 weeks	Intervention: 68.4 (SD 28.6)% Control: 30.1 (SD 6.7)% $p < 0.05$ Intervention: 69.3 (SD 27.1)% Control: 22.3 (SD 5.3)% $p < 0.05$	1−	Assessment difficult because of much missing data Small sample size Rate of healing surprisingly high considering the baseline wound area
Moretti *et al*. [46]	RCT Open label Study quality, 5/9	DFU $N = 30$ Intervention, $n = 15$ Control, $n = 15$ Neuropathic ABPI > 0.7 Baseline mean wound area: Intervention: 297.8 (SD 129.4) mm^2 Control: 245 (SD 100.9) mm^2	Extracorporeal shockwave therapy 3 sessions each 72 h with 100 pulses per cm^2 to perimeter of ulcer versus standard care	Healing at 20 weeks Time to healing Index of epithelialization	Intervention: 8/15 Control: 5/15 NS Intervention: 60.8 (SD 4.7) days Control: 82.2 (SD 4.7) days $p < 0.001$ Intervention: 2.97 mm^2/day Control: 1.3 mm^2/day $p < 0.001$	1+	Non-blinded. No detail on index of epithelialization No detail on frequency of follow-up Very small numbers Possible inappropriate use of parametric statistics
Wang *et al*. [47]	RCT Non-blinded Study quality, 3/9	DFU $N = 74$ present for >3 months 4 lost to follow-up 35 in each group Mean ABPI: Intervention: 1.22 Control: 1.26	Extracorporeal shockwave treatment each 2 weeks for three treatments, repeated if necessary Controls received HBO daily for 20 treatments Mean follow-up Intervention: 11.64 (6–14) months Control: 12.14 (6–14) months	Composite end point: Complete healing/more than 50% improved or unchanged	$p = 0.001$ for composite: Healing Intervention: 11/36 ulcers Control: 8/36 Improved Intervention: 21/36 Control: 18/36 Unchanged Intervention: 4/36 Control: 10/36	1−	Unusual choice of composite end point The stated level of significance seems high, given the apparent small difference in outcome between groups

DFU, diabetic foot ulcer; ABPI, ankle : brachial pressure index; HBO, hyperbaric oxygen.

Table 9. Other systemic therapies

Rullan *et al*. [48]	RCT Double-blind Study quality, 6/9	Patients $N = 70$ with leg ($n = 18$) and DFU ($n = 52$) DFU: Wagner grade I–II Intervention, $n = 37$ Control, $n = 33$	Bemiparin 3500 IU/day for 10 days followed by 2500 IU/day for up to 3 months versus saline control	Composite primary outcome: Decrease in ulcer area by ≥50% or reduction in Wagner grade at 3 months Secondary outcome: healing by 3 months	Intervention: 70.3% vs control: 45.5% ($p = 0.035$) Post hoc analysis of DFU group 72.4% vs 47.8% (CI −1.5–50.7) Intervention: 35.1% vs control:33.3% ($p = 0.874$)	1+	Sample size powered to detect a difference of 30% (65% vs 35%) Composite end point DFU subgroup subjected to post hoc analysis with no significant difference between groups but no details given
Sert *et al*. [49]	RCT Open label Study quality, 3/9	DFU $N = 60$ Wagner III–IV Severe peripheral ischaemia without possibility for vascular intervention Intervention, $n = 30$ Control, $n = 30$	Intervention: iloprost (prostacyclin) 0.5 to 2 ng/kg/min over 6 h for 10 consecutive days Control: no iloprost	Amputation rate at 30 days	Intervention: 25/30 amputations (12 minor and 13 major) Control: 29 /30 amputations (12 minor and 17 major) (NS)	1−	Study was primarily designed to investigate endothelial function Results regarding healing are inconclusive
Leung *et al*. [50]	RCT Single-blind Study quality, 4/9	DFU $N = 80$ Necrotic and/or infected ulcers 47% gangrenous toes deemed requiring amputation Unhealed ulcers for up to 25 weeks Intervention, $n = 40$ Control, $n = 40$	Intervention: Chinese oral herbal formulation Control: oral placebo	Time to ulcer granulation to enable skin grafting Amputation first 4 weeks Eventual amputations	Intervention: 5.9 weeks Control: 9.2 weeks NS Intervention: 3 Control: 3 Intervention: 3 Control: 9 $p = 0.057$	1−	Patient blind but probably not investigator or observer blind only Time to total amputations not known Amputation is not defined as major/minor Study was for 4 weeks, but all patients received study drug at 4 weeks if no healing or improvement
Bahrami *et al*. [51]	RCT Single-blind Study quality, 4/9	DFU $N = 21$ No improvement in 2 weeks Wagner grade I–II Total 21: G1: 6 G2: 6 G3: 9I	Intervention: ANGIPARS™ herbal extract plus standard care 1 oral 100 mg bd for 6 weeks 2 oral as above plus 3% gel to wound Control: standard wound care (specified in general terms)	% wound surface change at 6 weeks 'Improvement' on 4-point scale 'Complete' = >70% improved Relative improvement = 10–70%	G1: 375 (SD 118) mm^2 to 41.7 (SD 33.7) mm^2 (88% reduction) $p = 0.04$ G2: 916.7 (SD 228.6) to 137.5 (SD 41.7)mm^2 (84%reduction) $p = 0.01$ G3: 766.3 (SD 320.2 to 689.1 (SD 329.1) mm^2 (25% reduction) $p = 0.076$ Complete improvement: Group 1: 5 Group 2: 6 Group 3: 2 Group 1: 1 Group 2: 0 Group 3: 1	1−	Large difference in baseline area between G2 and G3 ? inappropriate use of parametric statistics No between-group comparisons

(*continued*)

Table 9. (Continues)

Larijani *et al.* [52]	RCT Blinding uncertain Study quality, 3/9	DFU 25 >2 weeks without improvement Intervention: 16 Control: 9	Intervention: ANGIPARS™ IV 4 mL in 50–100 mL saline daily for 28 days plus standard wound care Control: placebo plus standard wound care	Change in ulcer area at 4 weeks	Intervention: 479.9 (SD 379.8) mm^2 to 198.9 (SD 143.8) mm^2 (64% reduction) $p = 0.000$ Control: 766 (SD 960.5) mm^2 to 689.1 (SD 846.7) mm^2 (25% reduction) $p = 0.076$ 64% vs 25% reduction $p = 0.015$	1–	Blinding uncertain Primary outcome healing at 4 weeks but no data given Control group have larger wounds at baseline Small sample size Unequal distribution between groups

DFU, diabetic foot ulcer

is similar: that with the exception of hyperbaric oxygen therapy (HBOT) and, possibly, negative pressure wound therapy, there is little published evidence to justify the use of more recent therapies. This echoes the conclusion of a recent Cochrane review [53] and the systematic review undertaken by the National Institute for Health and Clinical Excellence Guidelines Committee in the UK [54].

Analysis of evidence presents considerable difficulties in this field. The number of controlled studies is small, and the majority are of poor methodological quality. Moreover, the complexity of the clinical condition and its frequently slow response to intervention pose particular problems in trial design. Of these, the most important relates to the selection of the primary outcome measure. The most clinically relevant measures are healing, time to healing, avoidance of amputation and survival, but these may not necessarily reflect the effect of a chosen intervention. Thus, a therapy or dressing may have a significant stimulatory effect for only a finite period during the course of the life span of the ulcer being treated. Antibiotics may have a clear benefit in the management of any ulcer that is infected but may not influence the overall rate of healing if this is critically affected by other factors, such as poor peripheral circulation. Nevertheless, these problems do not mean that studies of effectiveness should not be undertaken: they just need to be designed with great care.

New evidence of effectiveness of tested interventions

When the results of this updated review are taken together with those of the earlier report, they provide limited evidence to justify a change in routine clinical practice. With the exception of a new RCT on HBO and a further study reporting a weakly significant benefit of negative pressure therapy, all either showed lack of effect and/or were of questionable methodological quality.

Scoring of published articles

The chosen scoring system is primarily based on aspects of trial design, whereas the concern of clinicians is with both study design and conduct. This can lead to some anomalies, with relatively poor studies scoring highly on the basis of stated design.

Aspects of trial design and choice of end points

Trial design is very difficult in this field because the population (of both people and ulcers) is heterogeneous, with multiple factors contributing to both ulcer onset and failure to heal. As an intervention is likely to be directed at only one of these factors, it is poss xible that an agent can have an effect, but this may be hidden. As ulcers also typically take many weeks to heal, it is likely that the factor

most responsible for healing delay may be different at different stages of the process, and this means that an agent may be effective at one stage but not necessarily all the time. This leads to uncertainty concerning the choice of end points. Clinically relevant end points (such as ulcer healing or amputation) may mean more in practice but may be only partially dependent on any effect of the chosen intervention. On the other hand, surrogate end points (such as change in wound bed appearance or in ulcer area) may be more closely related to the effect of the product being tested but have little relevance to clinical outcome.

Ulcer characterization

One surprising feature of selected articles is the widespread reliance on the Wagner classification of wound type. This method is widely regarded as being relatively imprecise and has been to a large extent rejected by many experts in the field. More recent options (such as University of Texas, "PEDIS" and "SINBAD" [55]) should be used in future studies.

Appendix A Search strings for each of the sections

Medline search 'Wound Healing Guidelines'

Dec 2006 to June 2010

Basic search was combined with searches for specific interventions of interest by adding the search term AND

Basic search

((("Diabetes Mellitus"[MeSH]) OR (Diabetes Mellitus) OR (Diabetes)) AND (("Clinical Trials"[MeSH]) or ("comparative study"[Mesh]) OR ("epidemiologic study characteristics"[Mesh]) OR (Clinical Trial*) OR (case-control stud*) OR (case control stud*) OR (cohort stud*) OR (Comparative stud*)) AND (("Foot Ulcer"[MeSH]) OR (Foot Ulcer) OR (Ulcer) OR (diabetic foot)))

Dressings

(("Biological Dressings"[MeSH] OR "Occlusive Dressings" [MeSH] OR "Bandages, Hydrocolloid"[MeSH]) OR (film* OR foam* OR hydrogel* OR hydrocolloid* OR alginat* OR hydrofib* OR dressing*))

Debridement

(("Debridement"[MeSH]) OR (debrid* OR larv* OR enzym* OR surgic* OR topical OR silver* OR iodin* OR mechanic* OR biologic* OR autol*))

Bioengineered skin and skin grafts

(("Skin Transplantation"[MeSH]) OR (skin graft OR bio engineered skin OR bioengineered skin OR bio-engineered skin OR dermagraft OR apligraf OR tendra))

Electromagnetic, laser and ultrasound therapy

(("Electromagnetics"[MeSH] OR "Lasers"[MeSH] OR "Ultrasonic Therapy"[MeSH]) OR (Electromagnetic* OR Laser* OR Ultrasonic Therap* OR ultrasonic OR magnetic))

Stem cell therapy

(("Stem Cells"[MeSH] OR "Stem Cell Transplantation" [MeSH]) OR (Stem Cell* OR Stem Cell therapy OR marrow OR GCSF OR granulocyte colony stimulating factor*))
((("Growth Substances"[MeSH] OR "Endothelial Growth Factors"[MeSH] OR "Fibroblast Growth Factors"[MeSH] OR "Hematopoietic Cell Growth Factors"[MeSH] OR "Vascular Endothelial Growth Factors"[MeSH] OR "Epidermal Growth Factor"[MeSH] OR ("Fibroblast Growth Factor 2"[MeSH] OR "Fibroblast Growth Factor 1"[MeSH] OR "Granulocyte-Macrophage Colony-Stimulating Factor" [MeSH]) OR "Platelet-Derived Growth Factor"[MeSH]) OR (Growth Substance* OR Endothelial Growth Factor* OR Fibroblast Growth Factor* OR Hematopoietic Cell Growth Factor* OR Vascular Endothelial Growth Factor* OR Epidermal Growth Factor* OR Fibroblast Growth Factor 2 OR Fibroblast Growth Factor 1 OR Granulocyte-Macrophage Colony-Stimulating Factor OR Platelet-Derived Growth Factor) OR (Growth Factor OR Growth)) OR (matrix replacement OR hyalofil* OR collagen* OR emdogain OR hyaluronic acid OR metalloproteinase inhibitor*) OR (tissue enzym* OR timp* OR promogran* OR tissue inhibitor* OR metalloproteinase*) OR (angiogenesis OR gene therap* OR vascular endothelial growth factor* OR VEGF))

Tissue oedema

((vac OR vacuum assisted closure OR vacuum* OR kerraboot OR compress*) OR ("Bandages"[MeSH]) OR (stocking* OR elastic OR bandage*))

DOI: 10.1002/dmrr

Hyperbaric oxygen

(("Hyperbaric Oxygenation"[MeSH]) OR (hyperbar* OR oxygen*))

Resection of the chronic wound/ surgical procedures

((surgic* OR resect* OR remov* OR excisi*) OR ("Surgical Procedures, Operative"[MeSH]) OR ("surgery"[Subheading]))

Embase search 'Wound Healing Guidelines'

Dec 2006 to June 2010

Basic search was combined with searches for specific interventions of interest by adding the search term AND

Basic search

((((('observational study'/exp OR 'observational study') AND [embase]/lim) or (('experimental study'/exp OR 'experimental study') AND [embase]/lim) or (('controlled study'/exp OR 'controlled study') AND [embase]/lim) or (('comparative study'/exp OR 'comparative study') AND [embase]/lim)) and (('diabetes mellitus'/exp/mj OR 'diabetes mellitus') AND [embase]/lim)) and ((('foot ulcer'/exp/mj OR 'foot ulcer') AND [embase]/lim) or (('diabetic foot'/exp OR 'diabetic foot') AND [embase]/lim))

Dressings

(('bandages and dressings'/exp OR 'bandages and dressings') AND [embase]/lim) or (film* OR foam* OR hydrogel* OR hydrocolloid* OR alginat* OR hydrofib* AND [embase]/lim)

Debridement

(('debridement'/exp OR 'debridement') AND [embase]/lim) or (debrid* OR larv* OR enzym* OR surgic* OR ('topical'/exp OR 'topical') OR silver* OR iodin* OR mechanic* OR biologic* OR autol* AND [embase]/lim)

Bioengineered skin and skin grafts

(('skin transplantation'/exp OR 'skin transplantation') AND [embase]/lim) or (('skin graft'/exp OR 'skin graft') OR 'bioengineered skin' OR 'bio engineered skin' OR 'bio-engineered skin' OR dermagraft OR apligraf OR tendra AND [embase]/lim)

Electromagnetic, laser and ultrasound

(('electromagnetic radiation'/exp OR 'electromagnetic radiation') AND [embase]/lim) or (('ultrasound therapy'/exp OR 'ultrasound therapy') AND [embase]/lim) or (electromagnetic* OR laser* OR 'ultrasonic therap' OR ('ultrasonic'/exp OR 'ultrasonic') OR magnetic AND [embase]/lim)

Stem cell therapy

(('stem cell'/exp OR 'stem cell') AND [embase]/lim) or (('stem cell transplantation'/exp OR 'stem cell transplantation') AND [embase]/lim) or (('stem cell therapy'/exp OR 'stem cell therapy') OR 'stem cell' OR ('marrow'/exp OR 'marrow') OR gcsf OR 'granulocyte colony stimulating factor' AND [embase]/lim)

Abnormalities of wound biology and gene therapy

(('growth factor'/exp OR 'growth factor') AND [embase]/lim) or ('matrix replacement' OR hyalofil* OR collagen* OR emdogain OR ('hyaluronic acid'/exp OR 'hyaluronic acid') OR ('metalloproteinase inhibitor'/exp OR 'metalloproteinase inhibitor') OR 'tissue enzym' OR timp* OR promogran* OR 'tissue inhibitor' OR metalloproteinase* OR ('angiogenesis'/exp OR 'angiogenesis') OR 'gene therap' OR ('vegf'/exp OR 'vegf') AND [embase]/lim)

Tissue oedema

(('compression therapy'/exp OR 'compression therapy') AND [embase]/lim) or (('vacuum assisted closure'/exp OR 'vacuum assisted closure') OR vacuum* OR kerraboot OR compress* OR stocking* OR elastic OR bandage* AND [embase]/lim)

Hyperbaric oxygen

(('hyperbaric oxygen'/exp OR 'hyperbaric oxygen') AND [embase]/lim) or (hyperbar* OR oxygen* AND [embase]/lim)

Resection of the chronic wound/ surgical procedures

(('orthopedic surgery'/exp OR 'orthopedic surgery') AND [embase]/lim) or (resect* OR surgic* OR remov* OR excisi* AND [embase]/lim)

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Conflict of Interest

None declared.

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