Effectiveness of interventions to enhance healing of chronic ulcers of the foot in diabetes: a systematic review

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Summary
The outcome of management of diabetic foot ulcers remains a challenge and there remains continuing uncertainty concerning optimal approaches to management. It is for these reasons that in 2008 and 2012 the International Working Group of the Diabetic Foot (IWGDF) working group on wound healing published systematic reviews 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 June 2010 and June 2014. 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 or hydrotherapy; wound bed preparation using antiseptics, applications and dressing products; resection of the chronic wound; oxygen and other gases, 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 and other systemic therapies which did not fit in the above categories. Heterogeneity of studies prevented pooled analysis of results. Of the 2161 papers identified, 30 were selected for grading following full text review. The present report is an update of the earlier IWGDF systematic reviews and the conclusion is similar: that with the possible, exception of negative pressure wound therapy in post operative wounds, there is little published evidence to justify the use of newer therapies. Analysis of the evidence continues to present difficulties in this field as controlled studies remain few and the majority continue to be of poor methodological quality.

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

Abbreviations: 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; TcPO2 – 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 financial and therapeutic challenge throughout the world. The International Working Group of the Diabetic Foot (IWGDF) has issued guidelines on management since 1999, and systematic reviews to underpin those from 2005. In 2006 the IWGDF Editorial Board invited the IWGDF working group on wound healing to undertake a systematic review of the evidence supporting interventions to enhance the healing of chronic ulcers of the foot in diabetes in order both to inform protocols for routine care and to highlight areas which should be considered for further study. The first review included all papers published up to December 2006 (1) and this was later updated to include all subsequent papers up until June 2010 (2). The working group has now undertaken a further update by considering papers on the interventions to improve the healing of chronic ulcers of the foot in diabetes published between June 2010 and June 2014.

Materials and Methods

Controlled studies which were either prospective or retrospective, published in any language, and which 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, and/or reduction in ulcer area. Search strategies (Appendix A) included selected search terms on study design, patient group, clinical problem and interventions of interest by using Medline (June 2010 to June 2014) and Embase (June 2010 to June 2014). Randomised controlled trials (RCT), case–control studies,

prospective and retrospective cohort studies, control before-and-after (CBA) 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 the following clinical trials registries, the search terms used were: Foot Ulcer; Diabetes Mellitus; Diabetic Foot Ulcer; Diabetic Foot: http://www.controlled-trials.com/, www.clinicaltrials.gov, www.who.int/trialsearch, clinicalstudies.info.nih.gov/,cordis.europa.eu/en/home.html, www.clinicaltrialsregister.eu/, www.pactr.org/, www.anzctr.org.au/, www.canadiancancertrials.ca/, www.fmhs.auckland.ac.nz/sms/oncology/ctnz/default.aspx, www.chictr.org/Default.aspx, cris.nih.go.kr/cris/en/search/basic_search.jsp, registroclinico.sld.cu/, drks-neu.uniklinik-freiburg.de/drks_web/, www.hkclinicaltrials.com/, www.irct.ir/, www.umin.ac.jp/ctr/ www.kctr.se/, clinicaltrials.health.nz/, www.sanctr.gov.za/SAClinicalTrials/tabid/169/Default.aspx, www.slctr.lk/ www.clinicaltrials.in.th/, public.ukcrn.org.uk/search/, www.controlled-trials.com/ukctr/, and attempts were made to contact investigators if there was no evidence of publication of relevant studies.

Two reviewers (FLG and WJJ) 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 or rejected 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 Scottish Intercollegiate Guidelines Network (SIGN) (3). 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 SIGN instrument [3]: (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 conflicts of interest.

Extracted data were summarized in evidence tables on a study-by-study narrative basis. Because of the heterogeneity of study designs, including interventions, follow-up and outcomes, no attempt was made to pool the results. The evidence tables were compiled following collective discussion by the working party, and conclusions were drawn. The papers selected for scoring were divided into the same ten categories as the 2012 review, except that the articles on the use of platelet derived growth factors have now been included in the section on cell therapy (in contrast to the previous allocation to the section on wound biochemistry); the section on oxygen has been expanded to include other gases.

Results

In 2008, a total of 2155 articles were identified from EMBASE and Medline. Of these, 372 were selected for full text review, and 61 were included in the review. In 2012, 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 current update, a total of 2,161 articles were identified in total; 1,501 from Medline and 660 from EMBASE. Forty-three of these were selected for full text review. An additional 7 articles were identified from other sources, either other systematic reviews, or clinical trial databases. Of the total 50 articles, 30 that fulfilled the inclusion criteria as above were included in the review (Figure 1). The selected papers were grouped into ten categories.

1. **Sharp debridement and wound bed preparation with larvae or hydrotherapy** (Tables 1-3)

Sharp debridement

In the 2008 review one study on sharp debridement was identified that was a subgroup analysis of cases from an RCT of another intervention; it reported that

healing at 12 weeks was more likely following a more vigorous debridement (4). One further study was identified but lack of detail meant that it was not included (5).

Larval therapy

In 2008 we selected two studies on the use of larvae. One small, complex non-randomised cohort study reported an apparent significant effect on the appearance of the wound (but not healing) at 2 weeks (6). The second, a case control study in elderly, non-ambulant people with peripheral artery disease, reported an apparent significant decreased time to healing and amputation rates in those patients for whom 6 month follow-up data was available (7). The 2012 review added one further low scoring paper (8) which reported no difference in either healing or amputation rates between those treated with larval therapy and a control group.

The present search selected only one new paper to add to the three previously reported (9). This study was a non -blind, low scoring cohort design subject to further bias as patients were allowed to choose whether to have treatment with larvae or not The lack of baseline data on the type of wounds makes the apparent benefit of larval therapy on healing uninterpretable.

Hydrotherapy

No further studies were identified to add to the one paper in the previous on hydrotherapy (Versajet®) (10) which showed no benefit to healing at 12 weeks in a small study.

Clostridial collagenase

The use of Clostridial collagenase ointment used daily as a debriding agent was examined in one small study (11). This small, moderate scoring but unblinded study of non-ischaemic wounds showed an apparent improvement in area reduction from baseline in the treated group after 4 weeks, whereas there was no improvement seen in the control group. There were no between group comparisons made, however, and the finding that there was an average increase in the area of the wounds in the control group compared to baseline at 4 and 12 weeks suggests that the control group may not have received usual best practice.

2. Wound bed preparation using antiseptics, applications and dressing products (Tables 4-6)

Antiseptics and antimicrobials

In 2008 one study was identified which demonstrated that cadexomer-iodine showed no benefit in cavity wounds when compared with usual care (12). A subsequent large, observer-blinded, RCT of good quality identified in the 2012 review reported no difference between three products: carboxymethylcellulose hydrofibre, a surface antiseptic (Inadine®) and a non-adherent product gauze in terms of healing by 24 weeks (13). The 2008 review also found evidence from a single small study of possible benefit from the use of zinc oxide tape but no subsequent reports have been found (14).

Only one study of the use of honey was identified in the 2012 review, and this was a small, non-blinded and poorly designed controlled study, which reported no difference in outcome between the use of honey and povidone/iodine (15). In the current review, we identified two further studies. The first (16) was a very small, poorly scoring, non-blinded RCT of honey soaked dressings compared with povidone/iodine dressings. Although there was an apparent difference in area reduction at 15 days between the two groups, this result is uninterpretable given the lack of data on the baseline characteristics of the ulcers in the two groups and the probable inappropriate use of parametric statistics. In a second small cohort, study (17) comparing honey dressings with iodine dressings, no differences were found in either the incidence of healing or of amputation at 10 weeks although there was an apparent reduction in time to outcome (healing or amputation) in the honey group. This result is difficult to interpret and the study was of poor methodological quality with few data on the baseline characteristics of the patients. Despite the widespread use of honey dressings in clinical practice, there are no robust data to support their use to enhance the healing of diabetic foot wounds and this reinforces the conclusions of a recent Cochrane review (18).

A single non-blinded RCT on the use of superoxidized solution (DermacynW) was identified in the 2012 review (19), 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. The results of this trial were of doubtful quality given the methodological flaws in the study and no further studies have been identified in this review.

The use of topical antimicrobials (tobramycin beads) on the wound at the time of forefoot amputation was shown in a non-randomised cohort study reported in the 2012 review to have a significant beneficial effect on the need for later surgical revision (20), but no difference in healing times or later transtibial amputation. No further studies on antibiotic impregnated beads or cement have been identified and so the place of these agents in wound healing is yet to be determined.

Alginate and collagen-alginate products

Two small studies of alginate containing products were identified in the 2008 review. Neither showed evidence of improved wound healing either in comparison with saline moistened gauze (21) or Vaseline gauze (22).

Carboxymethylcellulose dressings

We previously identified an RCT which reported improvement with the use of a carboxymethylcellulose hydrofibre dressing in the 2008 review (23). In the 2012 review, however, a further larger RCT with a silver impregnated dressing (24) showed no difference in healing at 8 weeks when compared with an alginate dressing. Another large, observer-blinded, RCT of good quality reported no difference between three products: carboxymethylcellulose hydrofibre, a surface antiseptic (Inadine®) and a non-adherent product gauze in terms of healing by 24 weeks (13). No relevant new studies were identified in the present search.

Topical phenytoin

The 2008 review found one cohort (25) and one small poorly scoring RCT on the use of topical phenytoin (26), both of which reported a positive benefit in terms of ulcer area reduction, but with a high risk of bias. The current search identified two further studies. The first was a small, poorly scoring, open label RCT which reported a significant apparent improvement in ulcer area at 8 weeks when compared with a control group who had just vaseline gauze applied to their ulcers (27). The lack of baseline data on the patients or ulcers and the lack of blinding make this finding

difficult to interpret. The second study was a slightly larger, high scoring, double blind study comparing topical phenytoin with an alginate dressing (28). There was no difference between the two groups in terms of healing at 16 weeks. However, recruitment was incomplete, and so the study was ultimately not powered to show any differences between the two groups.

Hydrogels

We found evidence in the previous reviews from three controlled trials suggesting that hydrogels may hasten healing. One non-blind RCT reported a significant benefit in terms of healing of non-ischaemic foot ulcers when a hydrogel was compared with saline-moistened gauze (29). Two cohort studies were identified, but neither reported any hard data on wound healing and one used no statistical analysis (30,31). No further studies on hydrogels were identified and the place of these products in routine care is still not substantiated.

Herb/bark extracts

In the 2012 review a small study of the use of QRB7 (oak bark extract) in Bensal HP compared to silver sulphadiazine for six weeks showed a significant benefit in terms of healing, but the quality of the study was difficult to assess because of missing details (32).

In the present search a small, non blinded and poorly scoring study of a polyherbal cream compared with application of a silver sulphadiazine cream was identified (33). There was no difference in the time to healing between the two groups. A small, poorly scoring multicentre RCT of a Chinese polyherbal preparation (34) was also identified. Even though the only analysis was *per protocol*, no significant differences were observed between the intervention and control groups in terms of healing or ulcer area reduction up to 24 weeks.

Other

A further small, poorly scoring, non-blinded RCT of bismuth subgallate/borneol with patients randomised in a 2:1 ratio to either topical application of this or of intrasite gel, found no difference in healing at 12 weeks (35). There was, however, a surprisingly high rate of healing in both groups (100%).

There was a single, small but well-designed double blind RCT of NorLeu^3-A(1-7) (an analogue of angiotensin (1-7)), 0.01% or 0.03% versus placebo (36). There was no difference in the proportion of patients healed in either of the two treatment groups, or in reduction in wound area at 12 weeks compared to placebo. At 24 weeks there was a reported significant increase in the proportion of patients healed in the NorLeu^3-A 0.03% group compared to controls but there were a high number of drop outs and only a *per protocol* analysis was reported. Hence the efficacy of this treatment remains unproven.

One small open label cohort study of a microbial cellulose membrane compared to xeroform gauze was identified (37). The two groups were not well matched at baseline in terms of the presence of PAD, gender, age ulcer size and duration and so the positive results (an apparent significant improvement in time to healing and area reduction per week) reported should be interpreted with caution.

A small, double blind, placebo controlled RCT of the daily application of topical insulin cream was found in the current search (38). Although mainly an animal/biochemical study there appeared to be a significant improvement in the length, width and depth of the ulcers in the intervention group when compared to the control group. The analysis was *per protocol*, however, and both this and the lack of clinical baseline characteristics of the patients make the result difficult to interpret.

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

3. Resection of the chronic wound

(Table 7)

The 2008 review included 3 studies relating to excision of plantar ulcers with or without removal of underlying bone. Wide excision of chronic plantar ulcers – combined when indicated with removal of underlying bone – reduced time to healing but had no effect on eventual healing rate (39). Two retrospective cohort studies

looking at either the effect of excising the 5th metatarsal head underlying a chronic ulcer (40) or excising wounds under the interphalangeal joint of the hallux or first metatarsophalangeal joint (41), combined with arthroplasty reported benefit in terms of healing. No further publications on this have been found in either the 2012 or this review.

In summary surgical resection of the chronic wound particularly when combined with underlying bone may have a place in reducing time to healing, although this has not been tested in rigorous randomised and blinded trials of appropriate statistical power.

4. Oxygen and other gases

(Tables 8-10)

Topical

Two studies were identified in the 2008 review, which evaluated the use of topical hyperbaric oxygen therapy (HBOT). One was randomised and reported no apparent reduction in the cross-sectional area of ulcers at either 7 or 14 days (42). The other was only partially randomised but reported an apparent benefit at 4 weeks (43).

The present search identified one further study of topical HBOT. This was a small cohort study (44) and reported an apparent improvement in healing at 90 days in the intervention group, but it was marred by the fact that patients chose the intervention and there were differences between groups in the number of contacts with health care professionals. At present, therefore, the evidence from these three studies does not support the use of topical oxygen therapy to enhance the healing of diabetic foot ulcers.

Systemic

The 2008 review included four RCTs (45-48) which provided some evidence to suggest that systemic HBOT may reduce the rate of major amputation. The strongest data came from a high scoring but rather small, RCT of patients with unreconstructable peripheral artery disease (PAD) (48).

Two further RCTs were included in the 2012 review (49,50), only one of which was

methodically sound (50). This high quality double-blind RCT demonstrated significantly improved outcomes in the intervention group, who were more likely to heal within 12 months. 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 identified in 2008 (48) where only patients with unreconstructable critical limb ischemia were included.

This review identified four more studies in this group: three RCTs and a large cohort study. The first was a small, non-blinded, randomised study of poor quality (51). Although apparently showing an improvement in the intervention group at 10 weeks, the lack of blinding and incomplete data on important baseline variables makes this difficult to interpret. The second RCT (52) was an equally small, non-blinded study which appeared to be designed mainly as a biochemical study. The apparent improvement in the group of patients allocated to systemic HBOT compared with either silver impregnated or gauze dressings is surprising given the extremely short follow-up period of 2 weeks. The third was another small and non-blinded RCT that apparently showed inferiority of HBOT over shockwave treatment (53). The results are difficult to interpret as the analysis was *per protocol* throughout and the patients were able to choose a second course of either therapy at the end of 6 weeks. In addition, this study is very similar to one included in the 2012 review by the same authors (54), albeit with slightly higher numbers in the two study arms. It is unclear whether the later paper is an update of the previously reported study or is completely new.

A single, very large, retrospective cohort study of the use of HBOT in a population of patients treated in 83 centres located in 31 states of the USA was reported (55). Patient data were included if patients had poorly healing ulcers and had been treated according to reimbursement guidelines from Centers for Medicare and Medicaid Services which included the need for adequate peripheral perfusion, as defined by the clinician. Using propensity score–adjusted models to adjust for differences in baseline variables compared to a cohort of patients who were not exposed to HBOT, the authors concluded that HBOT did not appear to be useful for the prevention of amputation and did not improve the likelihood that a wound would heal in a cohort of patients selected by the eligibility criteria for reimbursement. This paper has proved

controversial with a number of authors criticising the methodology (56,57). Nevertheless, this report echoes the concerns of other authors that it is not yet possible to define the particular patient group in which this therapy would be effective and cost effective.

The authors of the present review are aware of another large blinded RCT of HBOT which has been completed, but is yet to report its findings (58).

Ozone

One small but high scoring study of topical ozone on healing by 24 weeks was identified in the current search. No difference was reported between the intervention and control groups (59).

5. Compression or negative pressure wound therapy

(Tables 11-13)

Compression

The 2008 review reported a single RCT, which suggested a benefit from compression therapy on post-operative wounds (60). In 2012, however, three further studies (two RCTs and a cohort study) were identified. The first RCT, which excluded patients with neuropathy, reported an apparent reduction in wound area following the use of vacuum compression, but was of poor methodological quality (61). The second investigated large post-operative wounds and, although the results showed a reduction in time to healing in the intervention group, the study was un-blinded (62). The cohort study which showed an apparent significant increase in the number of patients who healed with limbs intact was potentially biased as patients were allowed to choose whether to have the intervention or not (63).

There were no new studies identified in the current search.

Topical Negative Pressure Wound Therapy (NPWT)

The 2008 review also identified three RCTs of NPWT. Two of the three RCTs were very small but reported significant benefits in both healing rate and healing time

(64,65). A third, much larger study reported a significant benefit of NPWT in both time to, and proportion of persons, healing in those who had recently undergone foot surgery (66) even though the definition of 'healing' used included those who healed after repeat surgery, and this weakens the conclusions to be drawn from the results.

The 2012 review included three studies of NPWT, two RCTs and a cohort study. One of the RCTs was too small to draw any firm conclusions (67). The second however methodologically sound study involving the randomisation of 342 patients (68) showed a reduced time to wound closure, an increased incidence of healing by16 weeks, a greater reduction in cross-sectional area by 8 weeks and reduced incidence of minor amputation . The ulcers 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. A cohort study (also identified in the 2012 review) attempted to confirm the effectiveness of NPWT through analysis of reimbursement claims, but the results could potentially be explained (in part) by confounding factors (69).

The present search identified only three more small studies but none of these was of good methodological quality. The first, a small non blind RCT, showed no difference between the two groups in terms of healing at 8 weeks and although there was an apparent reduction in wound area, the lack of information on the baseline areas of the two groups makes this finding uninterpretable (70). The second also included few patients, was non-blinded and compared NPWT with standard wound care. The size of the wounds was quite large at baseline (NPWT group mean 35.7 cm^2 and control group 29.7 cm^2) and it is therefore surprising that the apparent time to healing was less than 4.5 weeks in each group. Although the text of the paper states that the healing rate was faster in the intervention group, this result was not supported by the data given in the table, which suggests that the intervention group took on average 0.6 weeks longer to heal (71). The third paper (72) contained two studies; the first was a small, low scoring, non-blinded RCT comparing the use of NPWT after split skin graft with a non adherent dressing over the graft which suggested that the proportion of the split skin grafts which took successfully was significantly higher in those who had the NPWT. The lack of blinding and information on baseline wound characteristics makes this result difficult to interpret. This novel use of NPWT is, however of interest, even though the study needs confirmation. The second part of

this paper describes a small non blind RCT of infected or surface contaminated chronic wounds and compared the use of NPWT with other advanced wound care products. The definition of healing included those wounds that were surgically closed as well as those which were allowed to heal by secondary intention. Although there was an apparent reduction in the time to healing in the intervention group, the lack of data on the baseline area of the ulcers, the uncertain drop-out rate and the lack of blinding (which could have influenced the decision to surgically close the wound) makes this result difficult to interpret.

In 2012 it was concluded that further high quality evidence was needed to substantiate the place of NPWT in routine clinical practice, but no such evidence has been identified in this latest search.

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

(Tables 14-16)

This section included growth factors in the earlier reviews but these have been included in the following section in this update.

Collagen/oxidised regenerated cellulose

In 2008 the search found one large RCT of a collagen/oxidised regenerated cellulose (ORC) dressing product, but this failed to confirm an effect on healing (73). In 2012 a small non-blind RCT reported a significant benefit when a collagen/ ORC dressing was compared to usual care (74) but was compromised by using *per protocol* analysis. This report included details of a second study which suggested that there may be additional benefit of combining this dressing with autologous platelet supernatant when compared to either treatment alone, but the data were not fully presented and the conclusions are therefore difficult to interpret (75).

The current search identified two further RCTs comparing collagen/ORC dressings with usual care. The first, which also contained silver in the dressing, was of poor quality but found no difference compared to the control group (76). The second was also very small and of poor quality and reported an apparent improvement in wound

healing at 8 weeks. Even though there was a difference in baseline area of the two groups, which would have favoured the intervention (77).

Acellular bioproducts

A single study of an acellular bioproduct derived from the small intestinal submucosa of pigs was identified in the 2008 review (78). When compared with platelet derived growth factor (PGDF), no benefit was observed

In 2012 a further 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 (79). A significant difference in healing and the final wound area 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 (80). A significant difference in healing at 12 weeks was found, but the study was not blinded.

Others

In the 2012 review, a small partial dose ranging study of talactoferrin was identified in (81). The study design was poor, however, and no difference was observed between groups. Topical Chrysalin, a ligand for thrombin binding sites, was studied in a small double-blind placebo-controlled, partial dose-ranging trial (82) and although no statistical analysis was presented, the outcomes appeared similar in the three groups. A small RCT of an extract of the plant Tinaspora cordifolia, applied as an immunomodulator reported a non-significant change in rate of healing (83) was also identified in the same review. No studies of any of these interventions were identified in the current review.

The current search did however identify a high scoring, double blind RCT of daily intramuscular injections of polydeoxyribonucleotide, (a DNA product that is thought to stimulate cellular proliferation) for 5 days a week with additional perilesional injections two days a week for 8 weeks, compared with placebo injections. The study reported a significant improvement in the proportion of ulcers healed at 8 weeks as

well as the time to healing in those that healed, although the healing rate in the control arm appeared quite low for this type of ulcer and there was little information about offloading (84). This interesting finding therefore needs to be confirmed.

7. Application of cells, including platelets and stem cells, and growth factors (Tables 17-19)

Growth factors

One small RCT of basic fibroblast growth factor (bFGF) was identified in the 2008 review, showing no benefit in healing by 12 weeks compared to controls (85). A second high quality, partial dose ranging RCT of bFGF administered in spray form for 8 weeks was identified in the 2012 review. Although a significant difference between the higher dose and placebo in the proportion of ulcers having a reduction in area by >75% was reported, this was only on *per protocol* analysis (86). The authors are aware of another trial of bFGF, the results of which are yet to be published. Preliminary results published in the clinical trial registry suggest there is no difference between intervention and control arms of the study in terms of healing after 12 weeks treatment (87). No further published studies on bFGF were identified in the current search.

In the 2008 review two studies of epidermal growth factor (EGF) were included. The first was a small but high scoring partial dose ranging, double blind RCT of topical EGF cream (88) which showed a significant improvement in healing of the group randomised to the higher dose EGF when compared to placebo at 12 weeks. Another study was less robust and included patients with leg ulcers (89), but there was no difference in the numbers healed by 16 weeks.

In the 2012 review it was concluded that the preliminary findings of two more studies of epidermal growth factor (EGF) were interesting. One double blind RCT, showed no benefit overall (90), although a second (91), high scoring, RCT of intralesional injection of EGF reported a highly significant difference between groups in the prevalence of granulation tissue after just two weeks. Unfortunately, this latter study was marred by switching those in the control group to an intervention arm after the first two weeks. One further small, poor scoring cohort study was identified in the current search. No difference in healing was identified in healing at 8 weeks following weekly application of topical EGF compared with saline moistened gauze (92).

In the 2012 review a small but well-designed double blind RCT (93) assessed the effect of intramuscular injections of a plasmid containing the gene for vascular endothelial growth factor, phVEGF$_{165,}$ and showed that a significantly greater percentage of the intervention group achieved the primary outcome measure of >60% reduction in ulcer area than controls. No further studies on this type of intervention have been identified.

In the 2008 review five studies of granulocyte-colony stimulating factor G-CSF were included. Whilst designed to determine its effect on infection, the five RCTs also assessed wound healing and reduction of amputation as secondary endpoints (94-98). Only one of the five (96) was associated with any apparent benefit. No further studies were identified in either the 2012 or this review.

In 2008 three studies on platelet-derived growth factor (PDGF) were identified. The initial RCT (99) in non-infected neuropathic ulcers indicated a significant effect on healing, and this was confirmed in the later definitive phase III study (100). A further study (101) failed to recruit sufficient numbers and no differences were observed. It is also known to the authors that an equally large but allegedly negative study was never published; despite extensive efforts, no reference to this study, that started in the pre-registration era, could be identified. No studies were identified on PDGF in the 2012 search but two studies were identified, in this review. Both were small and of poor methodological quality. The first was a small three-way comparison between a group of patients treated with topical antiseptics, a group treated with topical HBOT and a group treated with PGDF. Although supposedly showing superiority of PGDF treatment in terms of healing at 10 weeks, the lack of baseline data and the open label design means that the significance of any such effect is difficult to determine (44). The second was a poorly scoring, open label multicentre study which showed no difference in outcome between the two treatment arms (PGDF vs. TheraGauze®) (102).

The 2008 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 (103-107).

It was noted in the 2012 review that products of platelet and platelet-derived products are expensive because of the cost of harvesting autologous platelets. A single study was identified that assessed the use of platelets from ABO and rhesus-matched blood bank samples in a single-blind RCT, reporting a significant improvement in the healing of the intervention group at 12 weeks (108). No further studies of this type were found in the present search.

In the 2012 review we found a single observer-blind, good quality, placebo-controlled RCT of autologous lipoaspirate cells, which reported a significantly higher incidence of healing at 8 weeks as well as a significantly reduced time to healing (109). No further studies of this type of intervention have been found.

In summary the evidence from studies of cell therapy including platelets and stem cells and growth factors to support their use in wound healing is not robust and further rigorously designed blinded trials are needed.

8. Bioengineered skin and skin grafts

(Tables 20-22)

Dermal fibroblast culture

The 2008 review identified three studies of dermal fibroblast culture. One dose-ranging study (110) reported that weekly applications of dermal fibroblast culture improved healing of plantar neuropathic ulcers by 12 weeks, compared with saline-moistened gauze but the results should be viewed with caution given the very low healing rate in the control group (8% at 12 weeks). Another study (111) found no difference between intervention and placebo. Although the third RCT (112) reported that healing by 12 weeks was significantly greater in the intervention arm than in controls, again the healing rate of the control arm was unexpectedly low at 18%.

No further studies of dermal fibroblast culture have been identified.

Fibroblast/keratinocyte co-culture

A single multicentre RCT of fibroblast/keratinocyte co-culture was identified in the 2008 review which showed a significant improvement in both the proportion of ulcers healed at 12 weeks and time to healing in those treated for 4 weeks in the intervention arm compered to a control group treated with saline moistened gauze (113).

One further study was included in the 2012 review. Although well designed, the trial was stopped prematurely when only 72 of 120 planned participants had been enrolled. Although there was an apparent significant improvement in healing at 12 weeks in the intervention group (51.5% vs 26.3% p= 0.049), the failure to complete recruitment casts doubt on the strength of the conclusion that can be drawn and the efficacy of the product (114).

The current review found a single open label study of a 2 stage procedure, cultured autologous fibroblasts and keratinocytes on a hyaluronic acid scaffold (HYAFF autograft) followed by epidermal tissue engineered autografts compared with paraffin gauze. The study was stopped before the planned target of 200 patients was reached due to the long duration of recruitment (>6 years). Although there appeared to be a reduction in the time to 50% area reduction, there was no difference in the numbers of patients healed at 12 weeks (115).

Cultured Keratinocytes

In 2008 a single low scoring RCT reported the use of keratinocytes alone, but few data were presented (116). In the 2012 review a small RCT reported the use of a novel keratinocyte delivery system but was of very poor methodological quality, and the result was inconclusive (117). One small single blind multicentre RCT was found in this search which compared cultured allogenic keratinocytes on paraffin gauze to paraffin gauze alone. A significant improvement in the intervention group was noted at 12 weeks although many participants were lost to follow up (118).

Split skin grafts

In the 2012 review a small case–control study of the use of split skin grafting reported a positive outcome, but the study was of poor methodological quality and susceptible to bias because the patients had the option to select their treatment group (119). In the present search a small cohort study of the use of artificial dermis replacement applied under a split thickness skin graft was identified (120). Although there appeared to be an improvement in the rates of healing at 12 weeks compared to spilt skin grafting alone, the study was non-randomised. There were also differences in the data presented in the text as opposed to the tables, which makes the significance of the

observations difficult to determine.

Amniotic membrane

There has also been a recent small and poor scoring, open label RCT of the use of an amniotic membrane wound graft (121), which reported a significant improvement in healing at 6 weeks. However, the very low healing rate of the ulcers in the control group casts doubt on the significance of this finding.

9. Electrical, electromagnetic, lasers, shockwaves and ultrasound (Tables 23-25)

Electrical stimulation

Two RCTs identified in the 2008 review examined electrical stimulation of the feet. The first was methodologically weak and no benefit was observed (122). In contrast, the second reported a non-significant trend towards a greater proportion healing at 12 weeks (123). The 2012 review also identified two studies on electrical therapy. The first, a methodologically weak, cohort study showed no difference in ulcer area reduction at 60 days (124). The second, a small low scoring study (125) compared the use of electrical stimulation with a placebo comprising local warming of the skin. The lack of blinding and other methodological weaknesses cast doubt on the positive finding of a significant reduction in wound area at 4 weeks.

Shockwave therapy

Two trials of shockwave therapy were identified in the 2012 review. The first randomized 30 patients to receive either shockwave therapy to the perimeter of the ulcer each 72 hours or a sham intervention (126). There was no difference in ulcer healing by 20 weeks. The second compared extracorporeal shockwave treatment with hyperbaric oxygen (54). Again methodologically weak, the reporting of a significant difference between the superiority of shockwave therapy over HBOT was based on a curious composite end point of the proportion of ulcers healed, or ‘greater than 50% improved’.

The present search found only one new study on physical methods. This was a randomised trial comparing shockwave therapy with hyperbaric oxygen (53). As noted above, this study was very similar to one included in the 2012 review by the same authors (54) albeit with slightly higher numbers in the two study arms and again

shows an apparent superiority of shock wave therapy in terms of healing. It is unclear whether the later paper is an update of the previously reported study or is completely new.

Normothermic therapy/Magnets/Laser therapy

Small studies of the normothermic (127), magnetic (128) and laser therapy (129) were also identified in the 2008 review, but none reported any convincing evidence of benefit.

10. Other systemic therapies

(Tables 26-27)

Five trials were identified in the 2012 review; one of low molecular weight heparin (130), one of iloprost infusion (131), and three of herbal preparations – administered orally in two (132,133) and intravenously (134) in one. None of the five were of good quality and none showed any major improvement in outcome.

The current search found only two more papers in this category. One, a poor scoring non-blinded study of oral vildagliptin (135), showed an apparent improvement in healing at 12 weeks (31 vs. 15%) but the very low incidence of healing in the control group is surprising for the type of ulcer selected for study and this casts doubt on the likely clinical benefit of this product in routine clinical practice. The paper was also notable for the remarkably good matching of all the baseline clinical measures, especially for a relatively small population.

The second paper reported the use of oral pentoxyfilline in a small cohort study (136). The only results included were the number of patients with a >10x10 mm reduction in ulcer area at 30 days, with no data on the incidence of healing. In addition, no information was provided on adverse events in this paper.

Discussion

The outcome of treatment of ulcers of the foot in patients with diabetes remains a challenge. It is, however, important that the effectiveness and cost effectiveness of new treatments is rigorously assessed, and that the introduction of treatments that lack evidence of effectiveness should be avoided. The present report is an update of earlier

IWGDF systematic reviews in 2007 (published in 2008) and 2011 (published in 2012) (1,2), and the conclusion is similar in that the evidence to support many of the therapies that are in routine use is poor. A systematic review in 2012 (137) as well as that undertaken by the National Institute for Health and Clinical Excellence Guidelines Committee in the UK (138) came to similar conclusions and these have not yet been updated.

There has been little change in the quality of the evidence since the last review. Once again many of the papers selected as abstracts were not included as they were not controlled and even those included were generally of poor methodological quality (see Tables) with, in particular, a general lack of blinded assessments and hence weakened by potential bias. The lack of detail on baseline characteristics made a number of papers difficult to assess and makes it difficult to extrapolate the conclusions drawn from any positive findings difficult to a general clinical population.

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 change in routine clinical practice. There are still no good studies to support the use of topical applications or dressing products, a finding supported by Cochrane reviews (18, 139-142).

The previously earlier positive reports from randomised studies of hyperbaric oxygen have now been countered by a large cohort study (55) which showed little evidence of improvement when used in the patient cohort that qualifies for reimbursement in the USA, which is different from those patients recruited into the RCTs.. Consequently, the question of which patient group would most benefit from this type of intervention remains unanswered.

Despite widespread use there have been no further good studies on the use of NPWT and at present the evidence to support its effectiveness or cost effectiveness in the healing of chronic ulcers of the foot in diabetes – as opposed to post-operative wounds – is not strong, a conclusion echoed in the recent Cochrane review (143).

In the 2012 review we reported on some interesting early studies on epidermal growth

factor (EGF). It is disappointing that no further randomised controlled studies were found in the current search and although a number of uncontrolled cohort studies have been published, there has been no advancement of knowledge on the effectiveness or cost effectiveness of this therapy.

There have been no good quality studies which advance our knowledge of the efficacy of any other growth factors, skin or skin substitutes or any other physical therapies.

Conflict of interest

FG, JA, AH, RH, ML,PP, WJ: None declared relating to the interventions reviewed.
CA: Consultant: Acelity, Integra and Smith and Nephew.

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Appendix A

Search strings for each of the sections

Medline search 'Wound Healing Guidelines'

June 2010 to June 2014

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 Trial”[MeSH]) or (“comparative study”[Mesh]) OR (“Epidemiologic Study Characteristics as Topic”[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 bioengineered skin OR dermagraft OR apligraf OR tendra))

Electromagnetic, laser and ultrasound therapy

((“Electromagnetic Phenomena”[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 Factors ”[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*))

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’

June 2010 to June 2014

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 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 (' bone 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 ('vasculotropin'/exp OR 'vasculotropin') 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)

Table 1: Debridement and Larvae – results from 2008 review (1)

Reference	Study design and score	Population	Intervention and control management	Outcomes	Differences and Statistical results	Level of evidence (SIGN)	Comments
Saap 2002 (4)	Cohort study (5/8)	143 evaluable subjects with neuropathic superficial diabetic foot ulcer followed for 12 weeks in a parent RCT	Assessment of the extent of sharp debridement, on Day 0 using a debridement index	Closure of ulcer	A wound with a debridement index of 3-6 was 2.4 times more likely to heal than one with index of 0-2 (p =0.03).	2+	This was a sub-analysis of a study of the effectiveness of another intervention, (Apligraf) Veves, et al (2001)

Table 2: Debridement and Larvae – results from 2012 review (2)

Paul 2009 (8)	Cohort (3/8)	59 with DFU Intervention n=29 Control n=30 Patients with ischaemia (ABPI>0.75) excluded	I: Malaysian blowfly (*Lucilia cuprina*) larvae *versus* C: standard debridement	"Healing" (suitable for complete closure by self healing or suitable for grafting) Amputation	I: 14/29 C: 18/30 (NS) I: 5/29 C: 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
Caputo 2008 (10)	RCT Open label (2/9)	41 patients: 54% had DFU, 44% (19) had venous ulcers Intervention n=19 (11 with DFU) Control n=22 (11 with DFU)	I: Versajet® hydrosurgery *versus* C: standard sharp debridement plus pulse lavage	Wound debridement time Wounds closed at 12 weeks	I: 10.8 min C: 17.7 min p=0.008 I: 52.6% C: 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.

Table 3: Debridement and Larvae – new results

Wang 2010 (9)	Cohort study (1/8) Unblinded	"pressure ulcers" Ulcer size I: 17.8 cm^2 C: 16.9 cm^2	I: Larval therapy n=13 C: Traditional dressings n=12	Time to healing	I: 26.4 days C: 39.6 days p=0.042	2.0	Small study Patients allowed to chose treatment Limited baseline data
Tallis 2013 (11)	RCT Unblinded (6/10)	48 patients from 7 centres Heel ulcers excluded TcPO2 > 40 mm Hg or TBP>40 mm Hg Mean age I: 58.5 years C: 63.5 years Gender (% male) I:68% C:68% Ulcer size I: 3.0 cm^2 C: 2.4 cm^2	I: Clostridial collagenase ointment, daily treatment, n=24 C: Saline moistened gauze, daily treatment, n=24	Percentage change from baseline area at 4 weeks Percentage change from baseline area at 12 weeks	4 weeks: I: -44.9%, p=0.0016 C: +0.8%, NS I: -53.8%, p=0.0012 C: +8.1%, NS	1.0	No between groups analysis Small number of patients Concern about wound sizes in control group increasing over 12 weeks, suggests control care was not best practice

Table 4: Wound applications and dressings – results of 2008 review (1)

Reference	Study design and score	Population	Intervention and control management	Outcomes	Differences and Statistical results	Level of evidence (SIGN)	Comments
Apelqvist 1996 (12)	RCT (3/9)	41 patients with diabetes > 40 years old, with toe/ankle pressure > 30/80 mmHg, respectively, and with exudating, cavity wounds with an area 1-25cm^2 Intervention group 22, control group 19 Lost to follow-up 5	I: Lodosorb daily initially and then less often for 12 weeks or until the wound was less exudative *versus* C: saline-moistened gauze	Healing and decrease in area >50%	I: 5/17 C: 2/18 (NS)	1-	Primarily a health economic analysis, with limited results presented on clinical outcomes Per protocol analysis; 5 said to be lost to follow-up, but results given on only 35
Apelqvist 1990 (14)	RCT (3/9)	44 patients with necrotic ulcers. Intervention group 22, Control group 22 Followed for 5 weeks Lost to follow-up: 2	I: Adhesive zinc oxide tape *versus* C: hydrocolloid	Necrotic ulcer area reduction greater than 50%	I: 14/21 C: 6/21 ($p<0.025$)	1-	Uncertain numbers of withdrawals
Donaghue 1998 (21)	RCT (5/9)	Patients with non-ischaemic foot ulcers, area >	I: Collagen-Alginate wound dressing *versus*	Ulcer healing, reduction in ulcer area	I: 48% C: 36 % (NS)	1+	Open label study

		1cm^2: Intervention group 50, Control group 25 Followed for 8 weeks Lost to follow-up: 14	C: Saline-moistened gauze		Mean reduction in ulcer area: I: 81% C: 61% (NS)		
Lalau 2002 (22)	RCT (4/9)	77 with both chronic and acute wounds, area >1cm^2 Intervention group 39, Control group 38	I: Calcium alginate *versus* C: Vaseline gauze	>75% wound granulation plus decrease in ulcer area by >40%	Combined endpoint achieved: I: 42.8% C: 28.5% (NS)	1-	Included acute wounds Study duration reduced from 6 weeks to 4 weeks because of high drop-out rate Mean ulcer area at recruitment was very high at 8 cm^2 High % with type I diabetes suggests selected population
Piaggesi 2001 (23)	RCT (3/9)	20 patients with foot ulcers >1cm deep Intervention group 10, Control group 10 Followed for 8 weeks	I: Hydrofibre carboxymethyl cellulose dressing *versus* C: saline-moistened gauze	Days to healing	I: 127 (46 SD) C: 234 (61) ($p < 0.001$)	1-	
Muthukumar-	Cohort	100 patients with	I: Topical phenytoin	Decrease in	Intervention	2-	No statistical

asamy 1991 (25)	(4/8)	type 2 diabetes and Wagner grade 1 or 2 foot ulcers Intervention group 50 (27 M) Control group 50 (27 M)	*versus* C: saline 35 days *versus* C: an occlusive dry dressing	ulcer area and complete healing	group % decrease in area was 88% of baseline versus 50% ($p < 0.005$) 20/50 healed in the intervention group versus 12/50		analysis given for the numbers which healed
Pai 2001 (26)	RCT (5/9)	70 patients with type 2 diabetes and Wagner grade 1 or 2 ulcers Intervention: n=36; mean age 56 years; ulcer area 11.9cm^2; 25M Control: n=34; mean age 60; ulcer are 11.9cm^2; 22M Dropouts: 13	I: Topical phenytoin powder for 6 weeks *versus* C: talc/silicone dioxide	% decrease in cross-sectional area	I: 78.3% C: 73.5% (NS)	1+	
Jensen 1998 (29)	RCT (3/9)	Patients with non–ischaemic foot ulcers; area > 1cm^2 Intervention group 14, Control	I: Hydrogel dressing *versus* C: Saline moistened gauze	Ulcer healing	85% in the intervention group versus 46% in controls ($p<0.05$)	1-	Open label study

		group17 Followed for 20 weeks Lost to follow-up: 0					
Cangialosi 1982 (30)	Prospective cohort series (1/8)	28 diabetics with 37 lower extremity ulcers Intervention group 14, Control group 14 Drop out: unknown. Follow-up: unknown	Hydrogel and sterile gauze	Ulcer healing	Remark: "healing about 33% more rapid in hydrogel group"	2-	No statistical analysis Duration of follow-up and number lost to follow-up not stated Stated results vague
Capasso 2003 (31)	Cohort retrospective (2/8)	50 patients (28 with diabetes) with arterial disease and foot ulcers Intervention group 25, Control group 25 Diabetics 28/50 Follow-up 7 weeks.	I: Amorphous hydrogel *versus* C: Wet or dry sterile gauze	Cost; Wound healing; Time to healing	No differences observed in wound healing Time to heal: p=0.02 in favour of hydrogel	2-	Complex series Primary health economics studies No raw data presented on either wound healing or time to healing
Blackman 1994 (144)	RCT (4/9)	18 patients with diabetes and Wagner grade 1 or 2 ulcers. Intervention group 7 (mean age 51 years; 6M) Control group 11	I: Semi-permeable membrane dressing applied for 2 months *versus* C: wet-to-dry saline gauze; late cross-over for 5/7	Healing by 2 months Change in ulcer area over 2 months	I: 3/11 C: 0/7 (no statistical analysis I: 35±16% C: 105±28%, p=0.03	1-	Further reduction in area in the cross-over group

		(59 years; 11M)	control group	(intervention versus control);			

Table 5: Wound applications and dressings – results of 2012 review (2)

Jeffcoate 2009 (13)	RCT with three arms Observer blinded (6/9)	DFU N=317 randomised to three groups: Non-infected ABPI >0.7 Duration >6 weeks Area ≥25 and ≤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 (Mean dressing cost per patient) Secondary infection	Inadine® 44.4% N-A®: 38.7% Aquacel® : 44.7% (NS) Inadine®: 74,1 (SD20.6) days N-A®: 75.1 (SD 18.1) Aquacel®: 72.4 (SD20.6) days (NS) Inadine®: £17.48 N-A®: £14.85 Aquacel®: £43.6 p<0.05 Inadine®: n=71	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

					N-A®: n=48 Aquacel®: n=54 p<0.001		
Shukrimi 2008 (15)	RCT Non-blinded (1/9)	DFU N=30 Wagner II Mean TcpO2 39 (36-42) mmHg	I: Honey plus gauze versus C: 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	I: 14.4 days (range 7-26) C: 15.4 days (range 9-36) (NS)	1-	Poor description of methodological detail
Piaggesi 2010 (19)	RCT Non-blinded (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	I: Irrigation with superoxidized solution (Dermacyn®) *versus* C: Irrigation with 50% povidone iodine	Healing at 6 months Time to healing	I: 90% C: 55% p=0.002 I: 10.5 (SD 5.9) weeks C: 16.5 (SD 7.1) weeks p=0.007	1-	Length of intervention unclear Adverse effects of povidone iodine cannot be excluded
Krause 2009 (20)	Cohort (3/8)	Following transmetatarsal amputation for diabetic foot disease Intervention: n=46 (49 feet) Control: n=14 (16 feet)	I: Antibiotic beads (tobramycin impregnated calcium sulphate) *versus* C: no local antibiotics	Time to healing Rate of surgical revision Transtibial	I: 10.5 (SD 4.5) weeks C:14.5 (SD 3.8) weeks (NS) I: 8.2% C:25% p<0.05 I: 27%	2-	Retrospective study possibly affected by selection bias Outcome reported in only 40 of 60 patients

				amputation at an average follow-up of 28.8 months	C: 25%		
Jude 2007 (24)	RCT Open label (4/9)	DFU N=134 Intervention: n=67 Control: n=67 Lost to follow-up n=21	I: Aquacel Ag® *versus* C: Calcium alginate dressing for 8 weeks	% healing Healing velocity Time to healing % reduction in area over 8 weeks Change in ulcer depth	I: 31% C: 22% (NS) I: 0.29 (SD 0.33) cm^2/week C: 0.26 (SD 0.9) cm^2/week (NS) I: 52.6 (SD 1.8) days C: 57.7 (SD 1.7) days (NS) I: 58.1% (SD 53.1) C: 60.5% (SD 42.7) (NS) I: 0.25 (0.49) cm C: 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 2008 (32)	RCT Possibly blinded	Plantar DFU N=40 Non-infected,	I: QRB7 (extract of oak bark) in Bensal HP *versus*	Reduction in diameter	I: 72.5% C: 54.7% p=0.059	1-	Study said to be blinded but details not given

	(3/9)	Wagner I=II, ABPI >0.75, Duration >6 weeks Diameter <3cm Baseline diameter Intervention: 1.9 (SD 0.76) cm Control: 1.6 (SD 0.78) cm	C: silver sulphadiazine cream Applied daily for 6 weeks				No details of randomisation given

Table 6: Wound applications and dressings – new results

Rehman 2012 (16)	RCT 2/9 Non-blinded	Wagner 1 or 2 Non infected 60 patients, 30 in each group	I = honey soaked dressing C=povidone/iodine normal dressing	% reduction in wound area at 15 days	I =81% C=59% P<0.001	1.0	Selected/purposive sampling Very few details of baseline characteristics, including absolute area size Use of parametric statistics is questionable
Jan 2012 (17)	Cohort Non randomised 2/8	Mean age 56 years Wagner 1-4	I = honey application (n=50) C= iodine dressing (n=50) 10 week intervention	Healing rate at 10 weeks Amputation rate at 10 weeks Recovery: Healing and/or	I=72% C=66% NS I =28% C =34% NS 2-4 weeks	2.0	Confusing presentation of results Heterogeneous group of patients (Wagner 1-4) No data on baseline characteristics of

				amputation rates	I =60% C=30% Healing and amputation at 5-7 weeks I=94% C=56% Healing and amputation at 8-10 weeks I=100% C=100% Overall p value = 0.0001		patients
Ahmed 2014 (27)	RCT 4/9 Non blind	Wagner grade I or 2 30 patients per group 60% male Baseline area I=1310 mm^2 C=1108mm^2	I=Phenyton+Vaseline gauze C= Vaseline Gauze	% reduction area 8 weeks >50%reduction	I= 66.2% C=46.7% P=0.045 I=70% C=43.3% P=0.037	1.0	Not clear if the >50% reduction is also at 8 weeks Limited information on baseline characteristics. No information on healing.
Shaw 2010 (28)	RCT 8/9 Double blind	ABPI >0.5 Ulcer duration > 4 weeks	I: Phenytoin topical n=31 C: alginate n=34	Complete healing at 16 weeks	I: 62% C:74% NS	1+	Incomplete recruitment hence underpowered.

		Age 61 years 72% males 80% Type 2 diabetes BMI I:28 kg/m2 C: 25 kg/m2 Ulcer area I: 268 mm2 C: 233 mm2					
Viswanathan 2011 (33)	RCT 4/9 Non blinded	Mean age 59 years All type 2 diabetes HbA1c I: 10.5% C: 10.9% Ulcer duration I: 15 days C: 14 days Wagner grade 1 I: 26% C: 31% Grade 2 I:36% C: 37%	I: Polyherbal formulation cream, n=20 C: Silver sulphadiazine cream, n=20	Time to healing	I: 43 days C: 44 days NS	1.0	Small number of patients

		Grade 3 I:37% C:32% PAD I: 26% C: 21%					
Li 2011 (34)	RCT multicentre 4/10 Non blinded for primary outcome	Chronic ulcers N=57 (9 withdrawn) Wagner grade 1-3 ABI ≥0.7 and ≤1.2 Mean age 60 years Gender: 64% male Ulcer area I: 3.8 cm^2 C: 5.4 cm^2	I: Topical herbal ointment every 2-3 days + standard wound therapy (SWT). C: SWT	PP analysis Complete healing 4 weeks 12 weeks 24 weeks Ulcer improvement (decrease in area >50%) 4 weeks 12 weeks 24 weeks	 I: 16.7% C:20.8% NS I: 37.5% C; 33.3% NS I: 79.2% C 58.3% NS I: 25% C: 25% NS I; 62.5% C: 37.5% NS I; 70.8% C: 41.7% P=0.08	1.0	Very small pilot study with few patients from each of the 7 centres No ITT analyses

Wang 2012 (35)	RCT (4/9) Non-blinded	Male gender I: 56% C: 40% Mean age I:63.6 years C: 58.1 years All type 2 diabetes Wagner grade 2 or 3 Infected ulcers excluded ABPI > 0.6 Ulcer area I: 8.22 cm^2 C: 6.13 cm^2 NS	I: Bismuth Subgallate/Borneol dressing, n=25 C: Intrasite gel, n=10	Healing rate at 12 weeks	I: 100% C: 100%	1.0	Surprisingly high healing rates in both groups given baseline size of the ulcers
Balingit 2012 (36)	RCT 8/9 Double blind	Wagner 1,2 Non infected Area reduction of <30% in previous 2 weeks Mean age 55.3 years Baseline area Ia:1.9 cm^2 Ib:2.4 cm^2	Ia=$NorLeu^3$-A(1-7) 0.01% (n=27) Ib= $NorLeu^3$-A (1-7) 0.03% (n=26) C=placebo (n=24) Daily for 4 weeks	Healing by 12 weeks (ITT) Area reduction at 12 weeks Healing at 24	Ia:38% Ib:54% C:33% Ib vsC : NS Ib vs C P=0.037 Ib:73%	1+	No difference between Ia and C in any outcome High drop out rate by 24 weeks Definition of ITT unclear

		C:1.9 cm^2		weeks (PP) Area reduction at 24 weeks(PP)	C: 46% P=0.05 P=0.0001		
Solway 2011 (37)	Parallel open cohort study (2/8)	Males I: 87% C: 53% P<0.04 Mean age I: 55 year C: 69 year P<0.04 Ulcer area I: 3.0 cm^2 C: 5.0 cm^2 Ulcer duration I: 6 weeks C: 15 weeks PAD I: 40% C: 74% p<0.05	I: Microbial cellulose membrane, n=11 C: Xeroform gauze, n=19	Time to healing Area reduction per week	I: 32 days C: 48 days p<0.01 I:5% C:2.9% P<0.001	2.0	Small population size Baseline differences between groups in terms of PAD, age, gender, ulcer size and duration.
Lima 2012 (38)	RCT 5/9 Blinded	Male 14/28 Wagner 1 or 2 Age I:62 years C: 64 years	N=46 Insulin cream n=10 Placebo cream n=15 Daily application	Reduction in ulcer size at 8 weeks (data from graphs no figures given in text) Length	Per protocol analysis only I: 75% C:20% I: 80%	1.0	Very little baseline data Mainly and animal/biochemical study

				Width Depth Absolute healing at 8 weeks	C:25% I:85% C:30% I:4 C:0		

Table 7: Resection of the chronic wound – results of 2008 review (1)

Reference	**Study Design**	**Study population and characteristics**	**Intervention and control conditions**	**Outcome category**	**Results primary outcome + statistic**	**Level of evidence** *SIGN*	**Comments on weaknesses**
Piaggesi 1998 (39)	RCT (5/9)	Patients with plantar diabetic forefoot ulcers Intervention group 21 Control group : 20 Followed for at least 6 months None lost to follow up	I: Ulcer excision with removal of bone and closure of wound *versus* C: conservative treatment	Healing, and time to healing	I: 21/22 C: 19/24 (NS) I: 46 days C: 128 days (p <0.001)	1+	Also recorded incidence of secondary infection per ulcer (not per patient): 3/24 intervention group versus 1/22 (p=0.72)
Armstrong 2005 (40)	Retrospective cohort study (3/8)	40 patients with a chronic ulcer under 5th metatarsal head Intervention group 22, Control group 18	I: 5th MT head resection *versus* C: medical treatment only	Time of ulcer healing	I: 5.8 (2.9) weeks C: 8.7 (4.3) (p < 0.05)	2-	

		Followed for 6 months					
Armstrong 2003 (41)	Cohort study (2/8)	Uninfected, non-ischaemic ulcers under the interphalanageal joint of the hallux or the 1st metatarsophalangeal joint Intervention group 21, Control group 20 Followed for 6 months	I: 1st MTP joint arthroplasty, and resection head of 1st metatarsal *versus* C: Non-surgical management	Time to ulcer healing Ulcer recurrence	I: 24.2 days C: 67.1 days (p=0.0001) I: 4.8% C: 35% (p=0.02)	2-	
Tan 1996 (145)	Cohort study (3/8)	112 patients hospitalized with 164 diabetic foot infections 77 patients had surgery within 3 days 87 had no surgery within 3 days	I: Surgery within 3 days of hospitalization versus C: No surgery within 3 days	Amputation and resolution of infection	I: 77 episodes of infection and 10 major amputations C: 87 infection episodes and 35 major amputations (p<0.01)	2-	Description of outcomes and lesion types is incomplete. The incidence of amputation in the control group was high.

Table 8: Oxygen and other gases – results of 2008 review (1)

Reference	Study design and score	Population	Intervention and control management	Outcomes	Differences and Statistical results	Level of evidence (SIGN)	Comments
Leslie 1988 (42)	RCT (6/9)	28 with diabetic foot ulcers (16 Hispanic, 7 black, 7 white) Intervention group 12, Control group 16	I: Topical HBO *versus* C: Standard care	Change in cross-sectional area at day 7 and 14	Day 7: I: 67.1% C: 69.6% (NS) Day 14: I: 45.6% C: 35.6% (NS)	1+	
Heng 2000 (43)	RCT (3/9)	Intervention group 13, Controls 13 (plus an additional 14 controls who were not randomised) Follow for 4 weeks Lost to follow-up: not clear	I: Topical HBO *versus* C: Standard care	Ulcer healing	I: 90% C: 28%	1-	Complicated data presentation No statistical analysis was presented Not all patients had diabetes
Faglia 1996 (45)	RCT (5/9)	68 diabetic patients with ulcers Wagner grade 2-4 Intervention group 35, Control group 33	I: Systemic HBO (2.5 ATA, 90 minutes daily) continued until healing or amputation *versus* C: standard care	Amputation	30% fewer major amputations in Wagner grade 4 patients ($p<0.016$)	1+	Randomization process unclear Not blinded Time to healing not reported High frequency of vascular surgery after randomization

							Mean age in the Intervention group 61.7 years versus 65.6 years in the control group
Kessler 2003 (46)	RCT (6/9)	28 patients with neuropathic ulcers Wagner grade 1-3 and Duration >3 months Intervention group 15, Control group 13 Followed for 4 weeks Lost to follow-up: 1	I: HBO (2,5 ATA, 90 min bid 5 days a week for 2 weeks) *versus* C: standard care	Reduction in ulcer area at 2 weeks and at 4 weeks	2 weeks: I: 42% C: 21% (p=0.037) 4 weeks: I: 62% C: 55% (NS)	1+	One patient excluded from evaluation due to barotraumatic otitis
Doctor 1992 (47)	RCT (3/9)	30 patients: 23 with gangrene and 5 neuropathic ulcers Intervention group 15, Control group 15	I: Systemic HBO (3 ATA, 45 minutes, 4 sessions – mean 34 treatments) *versus* C: standard care	Amputation	I: 2 C: 7 (p<0.05)	1-	Wound size and depth are not reported No differences in number of healed ulcers Less positive bacterial cultures in HBOT group
Abidia 2003 (48)	RCT (9/9)	18 patients with diabetic ulcers area 1-10 cm^2 and duration >6 weeks Intervention group 9, Control group 9 Lost to follow-up: 2	I: Systemic HBO (2.4 ATA, 90 minutes, 30 sessions) *versus* C: Hyperbaric air (2.4 ATA, 90 minutes, 30 sessions)	Healing Reduction in ulcer area Number healed	I: 5/8 C: 1/8 I: 100% C: 52% (p=0.02) I: 5/8	1++	

				at 12 months	C: 0/8 (p=0,026)		

Table 9: Oxygen and other gases – results of 2012 review (2)

Duzgun 2008 (49)	RCT Open label (2/9)	DFU N=100 Wagner II-IV II n=18 III n=37 IV n=45 Present for >4weeks 50 in each group Follow up 92 ±12 weeks	I: HBO plus standard care; 2-3 ATA for 2 x 90 min day 1, then 1 x 90 min following day; continued for approximately 20-30days *versus* C: standard care (daily wound care; debridement; amputation when indicated; infection control)	Final healing without any form of surgical intervention	I: 33/50 (66%) C: 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 drop-outs 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 2010 (50)	RCT Double blind	DFU N=94 HBOT: n=49	I: HBO 2.5 ATA in multiple person chamber for 85 min 5 days a week over 8	Healing within 12 months, and maintained “to	*ITT* I: 25/48 (52%)	1++	Drop out from treatment 19/94

	(7/9)	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%	weeks plus standard care *versus* C: placebo 2.5 ATA air treatment in same chamber plus standard care	next visit" Death Amputation	C:12/42 (27%) p=0.03 NNT=4.2 *Per Protocol* I: 23/38 (61%) C: 10/37 (27%) p=0.009 NNT=3.1 I:1 C:3 I: 1 BKA, 2 minor		10 patients had revascularization during follow-up: 6 in HBOT, 4 in control group (1 healed post procedure in each group)
Chen 2010 (146)	Cohort (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	Group 1: received ten or less sessions of HBO Follow-up for mean 13.3 (6-29) months 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

		infection 14 (range 2-52) weeks					

Table 10: Oxygen and other gases – new results

Blackman 2010 (44)	Controlled Cohort 4/8	At least Grade 2A of UT classification ABPI >0.5 Baseline area: I: 4.1cm^2 C:1.4cm^2 p=0.02 Ulcer duration I:6.1months C:3.2months	I = topical wound O2 therapy (daily Monday – Friday) (n=17) C= Advanced Moist wound therapy (n=11)(dressing changed at least x2 weekly)	Healing at 90 days Median Time to complete closure	I: 82% C: 46% P=0.004 I: 56days C: 93days (p value not provided)	2.0	Patients allocated by choice and availability of therapy Misleading detail in abstract Variable amount of contact with health care professionals
Khandelwal 2013 (51)	RCT 1/9 Non blinded	Diabetic foot ulcers Duration > 8 weeks Age 35-65 years Male gender Group 1 n=11 Group 2 n=10 Group 3 n=11 Ulcer area at baseline unclear	Group 1 Topical antiseptics, n=20 Group 2 HBO, n=20 Group 3. Platelet derived growth factor, n=20	Mean ulcer healing time Healing at 10 weeks	G1. 6.75 weeks G2. 6.83 weeks G3. 7.6 weeks NS G1:40% G2:60% G3:80% p=0.0348	1.0	Paper unclear and hard to follow. Insufficient baseline data to interpret results
Ma 2013 (52)	RCT	In-patients	Systemic HBOT twice	Reduction in		1.0	Open label

	4/9 Non blinded	unhealed after >2 months standard care N=36 18 in each group Wagner 1-3 Wagner Grade 3 I: 10/18 C: 7/18 Palpable pulses Normal Doppler scan Mean$TcpO_2$ I: 37.06 mmHg C: 35.61 mmHg Baseline area I: 4.21 cm^2 C: 4.35 cm^2 Duration of wound I: 11.3 months C: 14.3 months	daily 2.5 atm for five days in two consecutive weeks Standard care: silver impregnated dressings if infected; absorbent cotton if not infected	ulcer area at: Day 7 Day 14	 I: 15% C: 12.3% NS I:42.4% C: 18.1% P<0.05		Small sample size Short duration of intervention Greater number with grade 3 ulcers in HBO group Mainly a biochemical study
Wang 2011 (53)	RCT 3/9 Non blinded	Non-healing DFU For > 3 months 45 HBO 43 Shockwave	HBO 2.5 atm Daily for 5 times a week for 20 treatments Compared with shockwave therapy (SWT) 2 treatments twice a week for three weeks or a total of 6 treatments but with	All PP analysis Completely healed ≥ 50% improved	 HBO 25% SWT 57% P=0.003 HBO 15% SWT32% P=0.071	1.0	Possible carry-over of initial HBO therapy from first course because of short interval before second treatment PP analysis

			option for a later treatment (clinical choice with patient consent)	Additional following further treatment HBO n=17 Shockwave n=14 Total healed	HBO:1 SWT:7 P=0.005		Analysis by ulcer rather than patient No data about follow-up Second phase treatment subject to greater potential bias
Margolis 2013 (55)	Cohort study 3/8	Plantar ulcers Non ischemic Area not reduced by 40% in 4 weeks run-in Age I:61.6 years C: 63.7 years P=0.0004 Ulcer area: I: 1.9 cm2 C: 1.6 cm2 P<0.0001 Wagner grade>2 I: 45.7% C: 18.4% P<0.0001	I. Hyperbaric Oxygen, n=793 C: Usual Care, n=5466	Healing by 16 weeks All amputation by 16 weeks Major amputations by 16 weeks	I: 43.2% C: 49.6% p<0.0001 I: 6.7% C: 2.1% p<0.0001 I:3.28% C: 1.28% P<0.0001	2.0	Data based on a CMS database Data about definition of PAD is lacking Higher prevalence of Wagner>2 in intervention group (p<0.0001) Difference in wound duration and gender distribution between groups. although adjusted for in model Healing includes healing with surgery
Wainstein 2011 (59)	RCT (8/9)	Age 62.6 years	I: Topical ozone therapy, 4 times a week for 4 weeks	Healing at 24 weeks	I: 44% C: 31%	1.0	High drop-out rate

	Blinded	97% type 2 diabetes Male gender I: 54% C: 66% ABPI 0.65-0.8 I: 25% C: 28% 0.8-1.0 I: 16% C: 31% >1.0 I: 53% C: 38% Ulcer size I: 4.9 cm^2 C: 3.5 cm^2	(96% O2 and 4% ozone) or up to 50% granulation, and then twice weekly (98% O2 and 2% ozone) for up to 12 weeks, n=32 C: sham treatment with room air, n=29		NS		

Table 11: Compression or Negative pressure wound therapy – results of 2008 review (1)

Reference	Study design and score	Population	Intervention and control management	Outcomes	Differences and Statistical results	Level of evidence (SIGN)	Comments
Armstrong 2000 (60)	RCT (6/9)	115 patients with postoperative infected diabetic neuropathic foot ulcers Intervention group 52, Control group 45 Followed for 12 weeks Lost to follow-up: 18	I: Pneumatic foot compression device *versus* C: Placebo non functioning device	Wound healing	I: 39/52 C: 23/45 ($p<0.02$) OR: 2.9 (1.2 – 6.8)	1+	In addition there was a difference in the intervention group between those who were and were not compliant
McCallon 2000 (64)	RCT (4/9)	Non-healing ulcers of duration >1 month Intervention group 5, Control group 5 Followed until healing Lost to follow-up: 0	I: NPWT therapy *versus* C: Saline moistened gauze	Time to ulcer healing	I: 22.8 days C: 42.8 days (NS)	1-	Small numbers

Eginton 2003 (65)	RCT (4/9)	10 patients with non-ischaemic foot ulcers Followed for 4 weeks Lost to follow-up: 4	Cross-over design Randomly allocated to start with either I: NPWT for 2 weeks or C: saline-moistened gauze for 2 weeks	Reduction in ulcer volume	I: 59% C: 0.1% (p<0,05)	1-	Small numbers and with 40% dropout rate
Armstrong 2005 (66)	RCT (5/9)	162 patients with residual wounds of mean duration 1.5 months after foot surgery Intervention group 77, Control group 85 Followed for 16 week and lost to follow-up: 38	I: NPWT *versus* C: Standard dressings	Healing (but including those unhealed and rendered suitable for surgical closure	I: 56% C: 39% (p=0.04)	1+	This study was of wounds after diabetic foot amputation, rather than chronic foot ulcers. It was also marred by a high rate of drop-out. The strength of the observation is weakened by the definition of healing used

Table 12: Compression or Negative pressure wound therapy – results of 2012 review (2)

Akbari 2007 (61)	RCT Open label (1/9)	DFU N=18 UT Grade II No significant loss of protective sensation	I: VAC Therapy 10 sessions; 1h per day four times a week plus standard care over 3 weeks C: Standard care (debridement, blood glucose control, systemic antibiotics, saline cleansing, offloading and daily dressing changes)	Reduction in surface area	I: 46.88 (SD 9.24) to 35.09 (SD 4.09) mm^2 (p=0.006) C: 46.62 (SD 10.03) to 42.89 (SD 8.1) mm^2 (p=0.01) Comparative reduction: p=0.024 (I. vs. C.) Within group improvement judged better for Intervention group: p=0.03	1-	Poor description of study Outcome not predefined
Mars 2008 (62)	RCT Open label (3/9)	N=60 patients with large post-op DFU (Intervention: 3000 mm^2 versus Control: 2668 mm^2) following extensive resection for infection which required urgent surgical	I: Compressed air massage at 100kPa for 15-20 mins 5 days a week. Other treatment as for controls *versus* C: Specified standard wound care plus antibiotics plus insulin infusion	Time to healing (by secondary intention or by split skin graft Numbers receiving skin grafts Amputations	I: 58.1 (SD 22.3) days C: 82.7 (SD 30.7) days p=0.001 I: 9/28 C: 10/29 I: 14/28 C: 15/29	1-	No method of randomization given. No data on actual healing incidence No baseline data on neuropathy or arteriopathy

		intervention Results given for Intervention: n =28, Control: n=29	Treatment applied to the foot and tissue around ulcer not to the wound bed				Results reported for only 57/60
Kavros 2008 (63)	Cohort (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)	I: Intermittent pneumatic compression 6 h/day in two 3 h sessions *versus* C: standard wound care	Survival at 18 months Complete healing limb intact Below knee amputation	I: 20/24 (83%) C: 18/24 (75%) (NS) I: 14/24 (58%) C: 4/24 (17%) p<0.001 I: 10/24 (42%) C: 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
Sepulveda 2009 (67)	RCT Single blind	DFU following transmetatarsal	I: NPWT applied 3-5 days after surgery. Changes	Time to 90% granulation	I: 18.8 (SD 6.0) days	1+	Outcome assessment blinded

	(5/9)	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: 1.05 Control: 1.16	each 2-3 days, plus standard care *versus* C: Standard care involving moist wound healing including hydrocolloid gel or alginate		C: 32.3 (SD 13.7) days p=0.007		Control dressing varied by extent of wound exudates Variable follow-up Power calculation given, based on pilot data
Blume 2008 (68)	RCT Open label (5/9)	DFU Wagner II-III >2cm^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 TcpO2 >30mmHg 342 patients randomised 335 received	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	I: 73/169 (43.2%) C: 48/166 (28.9%) p=0.007 I: -4.32 cm^2 C: -2.53 cm^2 p=0.021 I: 96 (75-114) days C: "unquantifiable"; p=0.001	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

		treatment		Amputation	I: n=7 C: n=17 p=0.035		of this type of therapy No reported follow-up after 112 days
Frykberg 2007 (69)	Cohort (2/8)	DFU identified from two groups of reimbursement claims – payers and Medicaid	Retrospective comparison for I: NPWT *versus* C: 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 : I: 26.3% C: 52.7% p<0.001 Medicaid: I: 18.3% C: 53.3% p<0.001 Overall costs (total morbidity) Payers: I: 27.3% C: 45.7% p=0.002		Can draw no conclusions about clinical effectiveness Not completely contemporaneous Potential source of bias: data based on out-patient treatment only

					Medicaid: I: 9.1% C: 44.7% p<0.001		

Table 13: Compression or negative pressure wound therapy – new results

Reference	Study design and score	Population	Intervention and control management	Outcomes	Differences and Statistical results	Level of evidence (SIGN)	Comments
Nain 2011 (70)	RCT (1/9) None blind	Age: I: 61 years C: 55 years Gender I: 80% C: 86% Ulcer area between 50 and 200 cm^2	I: NWPT C: saline gauze, twice a day Total population 30	Healing with or without surgery at 8 weeks Ulcer area reduction at 8 weeks	I: 80% C: 60% p=0.10 I: 16 cm^2 C: 6 cm^2 p<0.05	1.0	No data about randomisation procedure No data about PAD No data on baseline ulcer area in each group
Karatepe 2011 (71)	RCT (3/9) None blind	Age I: 68 years C: 66 years Ulcer area I: 35.7 ± 6.4 cm^2 C: 29.7 ± 5.2 cm^2 Type of Diabetes: >99% Type 1	I:NPWT n=30 C: standard wound care n=37	Median time to healing	C: 3.9 weeks I: 4.4 weeks p< 0.005	1.0	Surprisingly short time to healing given baseline wound size. Controls healed faster than intervention

		ABPI >0.7 I: 28/30 C : 34/37					
Dalla Paola 2010 (72)	RCT (1) 3/9 None blind	Age I: 64 years C: 61 years PVD I: 23/35 C: 21/35 TcPO2 I: 42 C:43	I: Surgical debridement +split skin graft+NPWT (n=35) C: Surgical debridement +split skin graft (n=35)	Complete graft take rate	I: 80% C: 68% p=0.05	1.0	Small study. No detail on baseline area
	RCT (2) 3/9 None blind	Age I: 65years C:64,5 years PVD I: 53/65 C: 58/65 Neuropathy I: 61/65 C: 58/65 TcPO2 I: 45.3 C: 44.9	I: Surgical debridement +NPWT (n=65) C: surgical debridement +advanced wound therapy (n=65)	Time to healing Days to infection control	I:65 +/- 16 days C:98+/- 45 days P=.0005 I:10 C:19 P=0.005	1.0	Lack of data on the baseline area of the ulcers, Uncertain drop-out rate. Definition of wound healing includes surgical closure

Table 14: Products designed to correct aspects of wound biochemistry and cell biology associated with impaired wound healing – results of 2008 review (1)

Reference	Study design and score	Population	Intervention and control management	Outcomes	Differences and Statistical results	Level of evidence (SIGN)	Comments
Veves 2002 (73)	RCT (2/9)	276 diabetic foot ulcers Intervention group 138, Control group 138 Followed for 12 weeks Loss to follow-up: 27%	I: Hydrofibre (cellulose/ collagen dressing) *versus* C: Saline moistened gauze	Healing by 12 weeks	I: 37.0% C: 28.3% (NS)	1-	High drop-out rate Suboptimal off-loading strategy
Niezgoda 2005 (78)	RCT (3/9)	98 with diabetic foot ulcers Intervention group 37, Control group 36 Followed for 12 weeks Lost to follow up: 25 patients (25%)	I: Acellular wound care product *versus* C: becaplermin (PDGF)	Healing at 12 weeks, time to healing	I: 49% C: 28% (NS) I: 67 days C: 73 days (NS)	1-	Unexplained high drop out rate
Richard 1995 (85)	RCT (6/9)	17 patients with diabetic foot ulcers Intervention group 9, Control group 8 Followed for 12 weeks	I: Fibroblast growth factor (bFGF) *versus* C: Placebo vehicle	Ulcer healing Reduction in ulcer area	I: 5/9 C: 3/8 (NS) I: 47.2% C: 35.8% (NS)	1+	Small sample size

Tsang 2003 (88)	RCT (7/9)	61 patients with neuropathic diabetic foot ulcers Intervention groups 0.02% 21, 0.04% 21 Control group 19 Followed for 12 weeks	I1: Dose ranging study of epidermal growth factor (EGF) 0.02% *versus* I2: EGF 0.04% *versus* C: Placebo	Proportion of healing at 12 weeks	I1: 12/21 I2: 20/21 C: 8/19 (p=0.0003 for 0.04% gel)	1+	Small sample size
Afshari 2005 (89)	RCT (4/9)	50 patients, including 25% with a leg ulcer Intervention group 30, Control group 20 Followed for 4 weeks Lost to follow-up: 0	I: Topical epidermal growth factor *versus* C: Placebo	Proportion healed by 4 weeks; >70% reduction in ulcer area	No difference in proportion of ulcers healed. I: 50% C: 15% (p=0.05)	1-	Reduction in ulcer area adopted as an endpoint retrospectively after no difference found in primary end point
Steed 1995 (99)	RCT (2/9)	118 subjects with diabetic foot ulcers Intervention group 61, Control group 57 Followed for 20 weeks Lost to follow-up: 3	I: Recombinant Platelet derived growth factor *versus* C: Placebo gel	Proportion of patients healed at 20 weeks	I: 29/61 (48%) C: 14/57 (25%) (p=0.01)	1-	Details of treatment in the two arms unclear Although only 3 were lost to follow-up, total withdrawals were quite high, with only 86/118 completing the study
Wieman 1998 (100)	RCT (6/9)	Uninfected non-ischaemic ulcers present for 8 weeks or more	I: dose ranging becaplermin gel applied daily *versus* C: placebo gel	Proportion healed at 20 weeks, time to healing, reduction in	100 mcg/g associated with 50% *versus* 35% placebo	1+	Details of randomization not specified, nor the blinding of the assessor

		Intervention groups: (30 mcg/g) 132 (100 mcg/g) 123 Placebo gel 127 Followed up to 20 weeks Lost to follow-up: 73/382		ulcer area	(p=0.007) Time to healing 100mcg/g 86 days *versus* 127 placebo (p=0.013) No differences between 30 mcg/g and placebo		
Robson 2005 (101)	RCT (4/9)	146 neuropathic plantar foot ulcers, duration > 4 weeks Intervention group 74, control group 72 Lost to follow up: 3	I: 0.01% becaplermin (PDGF) *versus* C: an adaptive dressing	Healing at 20 weeks, time to healing	I: 42% C: 35% (NS) Time to healing (NS) (no data reported)	1-	Only 146 enrolled of target of 340
Krupski 1991 (103)	RCT (8/9)	18 non-healing ulcers of both leg and foot (14 had diabetes) Followed for 12 weeks Lost to follow-up: 0	I: Autologous platelet factor *versus* C: saline	Healing and reduction in area	I: 24% C: 33% I: 4.3 cm^2 C: 1.9 cm^2 (NS)	1++	Both diabetic and non-diabetic patients Outcomes were for wounds and per patient
Steed 1992 (104)	RCT (6/9)	13 subjects with neuropathic diabetic foot ulcers Intervention group	I: Platelet derived wound healing formula (CT-102) *versus* C: normal saline	Proportion of healing and area reduction	I: 5/7 C: 1/6 (p<0.05) I: 6.2	1+	Definition of healing unclear (3 subjects still needed dressings in one treatment arm)

		7, Control group 6 Followed for 20 weeks			mm^2/day C: 1.8 mm^2/day ($p<0.05$)		
Margolis 2001 (105)	Retrospective Cohort (5/8)	20347 patients with neuropathic ulcers identified from the database of the Citizen Health System Followed for 20 weeks	Platelet Factor given to 6252 patients within 12 weeks	Proportion healed	I: 50% C: 41% RR: 1.38 (1.33 – 1.42)	2+	Retrospective analysis of treatment given in practice: Inconsistent dose and duration of treatment. Selected population
Driver 2006 (106)	RCT (7/9)	72 (out of 129 screened) people with diabetes (type 1 or 2) and uninfected ulcers (UT 1A) of more than 4 weeks duration Intervention: mean age 56 years; 32 M; mean ulcer area 3.2 cm^2; Control: mean age 58 years; 27 M; mean ulcer area 4.0 cm^2	I: Platelet autogel for 12 weeks *versus* C: Placebo gel, with 11 weeks follow-up	Proportion healed (confirmed at 1 week) and time to healing	I: 13/16 C: 8/19 Time to healing significantly shorter in the intervention group ($p=0.018$)	1+	Very high exclusion rate necessitated per protocol analysis. High percentage of heel ulcers
Feng 1999 (107)	Cohort (2/8)	78 cases with diabetes and ulcers of the leg, foot (and elsehwere); 62 on the foot.	I: EGF or PDWHF administered daily *versus* C: Saline control administered daily	Wound closure index at 6 weeks	Closure index higher in both the EGF and PDWHF groups when	2-	Incomplete reporting of results. Mean duration of the ulcers was short at 8.9 days.

		Mean ulcer area 10.7 cm^2; mean ulcer duration 8.9 days		% healed at 2, 4, 6 and 8 weeks	compared with placebo (p<0.01) % healed higher in EGF and PDWHF groups (p<0.01)		
Di Mauro 1991 (147)	RCT (3/9)	20 patients (6 with ischaemic, 4 with neuropathic, and 9 with neuro-ischaemic ulcers Followed until healing Lost to follow-up: 0	I: Lyophilized collagen *versus* C: Hyaluronic acid medicated gauze	Time to healing	I: 32 days C: 49 days (p<0.001)	1-	One ulcer was a wrist ulcer
Tom 2005 (148)	RCT (7/9)	24 subjects with neuropathic diabetic foot ulcers Intervention group 13, Control group 11 Followed for 16 weeks Lost to follow-up: 2	Solution of topical Tretinoin (retinoin A-) versus placebo saline solution applied for 4 weeks	Proportion healed by 16 weeks, Reduction in ulcer area and depth	I: 6/13 C: 1/11 (p = 0.03) Reduction in area (p<0.02), and depth (p<0.01) greater in intervention group	1+	Details of the analysis are not clear

Table 15: Products designed to correct aspects of wound biochemistry and cell biology associated with impaired wound healing – results of 2012 review (2)

Lazaro-Martinez 2007 (74)	RCT Non-blinded (3/9)	DFU N=40 Non-infected neuropathic TcpO2 >30 mmHg Intervention n=20 Control n=20 One drop-out from each group	Protease modulating dressing changed each day until healing or 42 days	Healing Time to healing	Per protocol analysis only I: 12/19 (63%) C: 3/19 (15%) p<0.03 I: 23.3 (SD 9.9) days C: 40.6 (SD 1.15) p<0.01	1-	Small study Per protocol analysis Some wounds post-surgical
Kakagia 2007 (75)	RCT Single blind (4/9)	DFU N=54 >3 months >2.5cm^2 post debridement 3 lost to follow up Not clear how many in each group	G1: Protease modulating dressing versus autologous platelet supernatant over 8 weeks G2: Protease modulating dressing versus G3: Both	Healing at 8 weeks % change in length % change in width % change in depth	G1: n=2 G2: n=2 G3: n=2 G1: -18.6% G2: -14.3% G3: -33.8% p<0.01 G1:-23.9% G2:-17.4% G3:- 46.1% p<0.01 G1:-35.5% G2:-34.9% G3:-551% p<0.01	1-	Description of methods incomplete Results difficult to interpret because data not fully presented Small sample size

Brigido 2006 (79)	RCT Open label (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	I: 12/14 (85.7%) C: 4/14 (28.6%) p=0.006 I: 1.0 (SD 2.57) cm^2 C: 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 comorbidity
Reyzelman 2009 (80)	RCT Open label (3/9)	DFU N=86 UT grade 1 or 2 Size 1-25 cm^2 TcpO2 >30 ABPI 0.7-1.2 Intervention: n=47 Control: n=39	I: Single application Acellular dermal regenerative tissue matrix plus silver NA dressing *versus* C: Standard moist wound care	Healing at 12 weeks Time to complete healing	I: 32 (69.6%) C: 18 (46.2%) p=0.03 I: 5.7 (SD 3.5) weeks C:6.8 (SD 3.3) weeks	1-	Non-blinded Combined intervention tissue matrix plus silver
Lyons 2007 (81)	RCT Single blind Partial dose-ranging (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 I1: 2.5% I2: 8.5% C: placebo	75% reduction ulcer size at 12 weeks Complete wound healing at 90 days Combined intervention groups versus	I1: 7 patients (47%) I2: 8 patients (53%) C: 4 patients (25%) (NS) I: 30% C:19% p=0.09	1-	Surrogate outcome measure but no difference

				placebo			
Fife 2007 (82)	RCT Double blind Partial dose-ranging study (3/9)	Patients with leg or foot ulcer: N=60 DFU: n=35 Present >8 weeks Wagner 1-III $TcpO_2$ ≥20 mmHg Mean ulcer area Group 1: 3.59 (SD 5.31) cm^2 Group 2 315 (SD 3.2) cm^2 G3: 4.11 (SD 5.99) cm^2	Chrysalin (TP508): ligand for thrombin binding sites. Total population Group 1: 1 mcg n=21, 12 with DFU Group 2: 10 mcg n=18, 10 with DFU; Group 3: placebo (saline) n=21, 13 with DFU Twice weekly visits up to 20 weeks or until healing.	Complete closure within 20 weeks Median time to closure	G1: 9/12 (75%) G2: 7/10 (70%) G3: 4/13 (31%) G1 versus G3 p<0.05 G1 and G2 combined versus G3 p<0.05 G1: Total 122 days; DFU 94 days G2: Total 87 days; DFU 71.5 days G3: >140 days G2 versus G3 p<0.05	1-	Limited information about treatment application. Limited information about baseline comorbidities High drop out rate Group 1: 5 Group 2: 3 Group 3: 6 25% were ulcers of lower leg
Purandare 2007 (83)	RCT Double blind	DFU N=50 5 lost to follow-up Intervention: n=23	I: Topical application aqueous plant extract Tinospora cordifolia	Rate of change of ulcer area (cm2/day)	I: -0.15 cm2/day C: -0.07	1-	Intervention unclear Standard therapy

	(4/9)	Control: n=22 Ulcers >4cm2 diameter Wagner I or II Digital ray or forefoot amputations or chronic non-healing ulcers 18 month follow-up	versus C: standard therapy and debridements	Change of ulcer perimeter	cm2/day p=0.145 I: -0.09 mm/day C: -0.07 mm/day p=0.09		unclear No details on arteriopathy or neuropathy Actual healing incidence not given
Uchi 2009 (86)	RCT Double blinded (8/9)	DFU Non-infected Wagner grade II Area <900mm^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 5cm 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	1++	Per protocol analysis Small ulcers at baseline Overlap between primary and secondary outcome measures

					(71.1%) p= (NS)		
Viswanathan 2006 (90)	RCT Double blind (6/9)	DFU N=60 Ulcers 2-3 weeks duration Area 2-50 cm^2 ABPI ≥0.75 3 drop-outs	I: rhEGF 150mcg/g in 30g tubes administered topically as a gel twice daily until healing or to 15 weeks *versus* C: Placebo	Healing by 15 weeks Time to healing Change in area	I: 25/29 C: 14/28 No statistical analysis or comment on difference in the text Post hoc analysis showed numbers healing in those with area >6cm^2 was significantly greater $p<0.002$ I: Mean – 9.6 (SD 11.3) weeks C: Mean – 14.9 (SD 4.1) weeks No statistical results given No 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 2009	RCT Double blind	DFU N=149 Wagner III-IV	I: Intralesional injections of rhEGF	% granulation at 2 weeks	G1: 73.1% G2: 70.8%	1+	Ethics committee insisted that non-

(91)	(6/9)	49 lost to follow-up Follow-up to 12 months	Total intervention phase 8 weeks G1: 25mcg per treatment (n=53) G2: 75mcg (n=48) G3: placebo (n=48)	Partial (>50%) and complete granulation at 8 weeks Weeks to complete response (>75% granulation)	G3: 39.6% p=0.000015 G1: 86.8% G2: 70.8% G3: 58.3% p=0.005 G1: 3 weeks G2: 3 weeks G3: 5 weeks 1 versus 3 p=0.006 2 versus 3 p=0.031		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
Kusumanto 2006 (93)	RCT Double blinded (7/9)	54 patients with CLI: 27 in each group. Subset with DFU: Intervention: 21 Control:17	I: Intramuscular injection of phVEGF$_{165}$ gene carrying plasmid 2000mcg on days 0 and 28 *versus* C: Saline control Follow up over 100 days	Improvement in ulcer (decrease in ulcer area by >60%) Major amputation	I: 7/21 (33%) C: 0/17 p=0.01 I: 3/27 (11%) C: 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

Table 16: Products designed to correct aspects of wound biochemistry and cell biology associated with impaired wound healing- new results

Gottrup 2013 (76)	RCT 4/9 Non-blinded	Non infected, >30 days duration Area: I=2.1cm^2 C=4.4cm^2 Ulcer duration: I=12.9months C=16.9months Toe Pressure I=96mmHg C=83 mmHg	I= Collagen/Oxidized regenerated cellulose/Silver (n=24) C=Foam/absorbant dressing (n=15) 4 weeks treatment	>50% area reduction by week4 Healed by week 14 Withdrawal due to infection	I: 79% C: 43% P=0.035 I :52% C: 31% NS I: 0% C:31% P=0.012	1.0	Unequal size groups: Small sample size No definition of infection. Use of parametric statistics is questionable.
Motzkau 2011 (77)	RCT (2/9) Single blind	Age I 61 years C: 58 years HbA1c I: 7.4% C: 7.6% Ulcer area: I: 225 mm^2 C: 816 mm^2	I: Collagen/ORC, n=13 C: standard care (soft silicon wound contact layer), n=6	Healing Change in ulcer area by 5 days	I: 8/13 by 26 days C: 0 by 19 days I: 17% decrease C: 9% decrease p=0.03	1.0	Very small population Baseline wound size appear not to be the same Short and variable follow-up time
Squadrito 2014 (82)	RCT (9/9) Double blind	Ulcer duration > 4 weeks TcPO2>50mmHg Wagner grade 1 and 2 Age I: 66 years	I: Polydeoxyribonucleotide daily intramuscular injections 5 days a week + perileisonal injections 2 days a week for 8 weeks, n=106 C: Placebo injections, n=110	Ulcer healing at 8 weeks Median time to healing	I: 37% C: 19% p=0.0027 I: 30 days C: 49 days p=0.027		Low healing rate in control arm. Little information about off-loading

		C: 63 years Type 2 diabetes I: 66% C: 73% Ulcer area I: 1.7 cm^2 C: 1.6cm^2					

Table 17: Application of cells, including platelets and stem cells and growth factors – results of 2008 review (1)

Reference	Study design and score	Population	Intervention and control management	Outcomes	Differences and Statistical results	Level of evidence (SIGN)	Comments
Gough 1997 (94)	RCT (9/9)	Patients with foot ulcers complicated by sift tissue infection Intervention group 20, Control group 20 Followed for 7 days Lost to follow-up: 0	I: G-CSF administered sc daily for 7 days *versus* C: saline injections sc	Ulcer healing	I: 4/20 C: 0/20 (p=0.09)	1++	This was primary a study of the eradication of infection and not powered for ulcer healing Short duration of intervention
De Lalla 2001 (95)	RCT (4/9)	Patients all with osteomyelitis. Intervention group 20, Control group 20 Followed for 6 months.	G-CSF sc and conventional treatment versus conventional treatment alone	Cure, improvement of infection, failure, amputation	No significant differences were reported	1-	All dropouts were in the intervention group The use of composite endpoints makes interpretation

		20 in each group. Lost to follow-up: 4					difficult
Yonem 2001 (96)	RCT (3/9)	Patients with ulcers Wagner grade 2 complicated by soft tissue infection (inflammation >2cm) Intervention group 15, Control group 15 Lost to follow-up: Nil	I: G-CSF given sc *versus* C: standard treatment for 10 days	Duration of hospital admission Time to infection resolution Proportion of amputation	I: 26.9 days C: 28.3 (NS) I: 23.6 days C: 22.3 (NS) I: 13.3% C: 20% (NS)	1-	No data regarding healing rate No information given on blinding
Kastenbauer 2003 (97)	RCT (7/9)	Patient with foot ulcers complicated by cellulitis Intervention group 20, Control group 17 Followed for 10 days Lost to follow-up: 0	I: G-CSF sc daily for 10 days *versus* C: saline sc	Ulcer volume reduction	I: 59% C: 35% (NS)	1+	Primary endpoint was eradication of infection (study not powered for volume reduction)
Huang 2005 (98)	RCT (4/9)	Patients with ischaemic ulcers Intervention group 14, Control group 14. Followed for 3 months	I: IM administration of autologous monocytes following G-CSF sc for 5 days *versus* C: iv administration of prostaglandin E2	Ulcer healing	I: 14/18 C: 7/18 (p=0.016)	1-	The primary endpoint was improvement of limb ischemia Ulcers were analysed instead of patients

		Lost to follow-up: 0					

Table 18: Application of cells, including platelets and stem cells and growth factors – results of 2012 review (2)

Jeong 2010 (108)	RCT Single blind (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	I: blood bank platelet concentrate (ABO and Rh compatible) with fibrinogen (activator) and thrombin (sealant) Applied following debridement on 2 occasions, 3-4 days apart C: fibrinogen plus thrombin	Healing at 12 weeks Time to Healing % reduction in Area Satisfaction VAS	I: 41:52 (79%) C: 22:48 (46%) p<0.05 I: 7.0 (SD 1.9) weeks C: 9.2 (SD 2.2) p<0.05 I: 96.3 (SD 7.8) C: 81.6 (SD 19.7) p<0.05 I: 7.6 (SD 1.6) C: 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 2010 (109)	RCT Single blind (6/9)	DFU N=54 Non-ischaemic non-infected Wagner I or II	Intervention: single treatment human lipoaspirate cells autograft, tegaderm as dressing Control: the same cell	Healing at 8 weeks Time to healing	I: 26/26 C: 16/26 p<0.05 I: 33.8 (SD 11.6) days	1+	Patients groups very similar at baseline Outcome assessments (but not patients) blinded

		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: 4.3cm^2 Control: 4.0 cm^2	carrier without lipoaspirate cells		C: 42.1 (SD 9.5) days p<0.05		to group allocation
Seung-Kyu 2009 (149)	Case control (2/7)	Non-infected DFU Without severe arteriopathy N=55 Intervention: n=37 Control: n=18 TcpO2 >30mmHg 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	I: 83% (n=37) C: 50% (n=18) (p<0.05) I: 31 days C: 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

Table 19: Application of cells, including platelets and stem cells and growth factors – new results

Khandelwal 2013 (51)	RCT (1/9) Non-blinded	Diabetic foot ulcers Duration > 8 weeks Age 35-65 years	Group 1 Topical antiseptics, n=20 Group 2 HBO, n=20 Group 3. Platelet derived growth factor, n=20	Mean ulcer healing time	G1: 6.75 weeks G2: 6.83 weeks G3: 7.6	1.0	Paper unclear and hard to follow. Insufficient baseline data to interpret

		Male gender Group 1: n=11 Group 2: n=10 Group 3 :n=11 Ulcer area at baseline unclear		Healing at 10 weeks	weeks NS G1: 40% G2: 60% G3: 80% p=0.0348		
Singla 2012 (92)	Cohort 2/8 Non-blind	Wagner Grade 1 and 2 Fasting blood glucose ≥7 mmol/L Male gender I: 60% C:70% ABPI "reduced" I: right leg- 15% left leg -60% C: right leg-65% left leg-70%	I: EGF applied topically weekly for 8 weeks (n=20) C: saline moistened gauze (n=20)	Healing at 8 weeks	I: 16/20 C: 7/20 P=0.54	2.0	Lack of detail of baseline ulcers including size. Possible higher numbers of patients with ischaemia in control group.
Landsman 2010 (102)	RCT Multi-centre (1/10) Non blinded	Wagner grade 1 or 2 fore- or midfoot ulcer Total number of patients unknown Ulcer area 1-8 cm^2 Able to tolerate off-loading Non-ischemic Non-infected	I: Platelet derived growth factor (Becaplermin 0.01% daily) plus Theragauze C: Theragauze 32 wounds altogether	Healing at 12 weeks Healing at 20 weeks	I: 46.2% C: 46.2% I:69.2% C: 61.5%	1.0	Unclear study design with missing detail Number of patients not stated

Table 20: Bioengineered skin and skin grafts – results of 2008 review (1)

Reference	Study design and score	Population	Intervention and control management	Outcomes	Differences and Statistical results	Level of evidence (SIGN)	Comments
Gentzkow 1996 (110)	RCT (6/9)	Patients with non-ischaemic plantar foot ulcers Intervention groups: 1: 12 2: 14 3: 11 C: 13 Followed for 12 weeks Lost to follow-up: 0	1: application of 1 piece of Dermagraft weekly, 2: 2 pieces of Dermagraft every 2 weeks 3: 1 piece of Dermagraft every 2 weeks C: saline-moistened gauze	Proportion with ulcer healing	1: 50 % 2: 21 % 3: 18 % C: 8 % (Group 1 versus controls, p< 0.05)	1+	The percentage of controls healing at 12 weeks was very low
Naughton 1997 (111)	RCT (3/9)	281 Patients with non-ischaemic plantar neuropathic ulcers of duration >2 weeks and area >1cm^2 Intervention group 139 Control group 142 Followed for 12 weeks Lost to follow-up: 46 (17.4%)	I: Dermal fibroblast culture weekly for 8 weeks *versus* C: standard care	Healing at 12 weeks	I: 38.5% C: 31.7% (NS)	1-	Per protocol analysis The data were also re-analysed on the basis of perceived metabolic inactivity of some batches of Dermagraft Short ulcer duration before study
Marston 2003	RCT	245 patients with	I: Dermal fibroblast	Healing at 12	I: 30%	1+	90% of patients

(112)	(5/9)	non-ischaemic plantar neuropathic ulcers of duration >2 weeks and area >1 cm^2 Intervention group 130, Control group 115 Lost to follow-up : 46 (19%)	culture weekly for up to 8 treatments *versus* C: conventional therapy	weeks, time to healing	C: 18% (p=0.023) RR = 1.6 Time to healing: p=0.04 in favor of the intervention group		were male, suggesting selection bias No raw data on time to healing Short ulcer duration before study
Veves 2001 (113)	RCT (5/9)	277 patients with non-ischaemic plantar neuropathic ulcers of duration >2 weeks and area >1cm^2 Intervention group 112, Control group 96 69 were excluded and ITT analysis performed on remaining 208 44 withdrawals (21%)	I: Tissue engineered sheet of fibroblasts /keratonicyte co-culture once a week for 12 weeks *versus* C: saline-moistened gauze	Numbers healed at 12 weeks, days to healing	I: 56% C: 38% (p=0.004) OR = 2.14 (95% CI 2.3-3.74) Median time to healing I: 65 days C: 90 days (p=0.003)	1+	Suboptimal offloading strategy Open study (difficult to blind) Large number of exclusions and withdrawals
Bayram 2005 (116)	RCT (0/9)	40 patients with Wagner grade 2 and 3 foot ulcers Intervention group 20, Control group 20 Followed for 1 year	I: Keratinocyte loaded microcarrier *versus* C: microcarrier placebo	Ulcer healing, reduction of ulcer area and wound condition	Reduction in ulcer area: I: 92% C: 32% Wound condition: I: 5.86	1-	Ulcer healing: no data given Missing data make interpretation difficult

		Lost to follow-up: unknown			C: 2.85 (p<0.001)		
Puttirutvong 2004 (150)	RCT (3/9)	80 patients with infected ulcers of both legs and feet Intervention group 36, Control group 44	I: Meshed skin graft *versus* C: split thickness graft	Time to healing	I: 19.8 days C: 20.4 days (NS)	1-	Inconsistency between patient numbers in the abstract and the text

Table 21: Bioengineered skin and skin grafts – results of 2012 review (2)

Edmonds 2009 (114)	RCT Open label (5/9)	DFU N=72 from 20 centres Neuropathic non-infected ulcers Intervention: n=33 Control: n=39	I: Apligraf ™ (living keratinocytes and fibroblasts) *versus* C: polyamide and saline moistened gauze	Healing at 12 weeks	I: 17/33 (51.5%) C: 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 2007 (117)	RCT Open label (3/9)	DFU N=12 Wagner I	I: Dressing with autologous keratinocytes once a week during 12 weeks C: Dressing without cells during 6 weeks then one treatment once a week	Healing	I: 4/7 C: 1/5	1-	Weak design Very small sample size, inconclusive result

			during 6 or 12 weeks				
Mahmoud 2008 (119)	Case control (3/7)	DFU N=100 Intervention: n=50 Control: n=50 ABPI ≥0.4 DFU ≥ 2cm^2 Ulcer area and duration equivalent in the two groups.	I: Skin graft C: Paraffin gauze	Median healing time Mean hospital stay Ulcer recurrence	I: 34 days C: 145 days p=0.03 I: 6 days C: 18 days p< 0.05 I: 8% C: no result given	2-	Bias 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

Table 22: Bioengineered skin and skin grafts – new results

Uccioli 2011 (110)	RCT (4/9) None blinded	Age I: 61 years C: 62 years Type 2 diabetes I: 86% C: 92% $TcPO_2$ I: 36.5 mmHg C: 36.0 mmHg ABPI I: 0.9 C: 0.9	I: 2 step, cultured autologous fibroblasts sad keratinocytes on a hyaluronic acid scaffold (HYAFF autograft) followed by epidermal tissue engineered autograft, n=80 C: paraffin gauze, n=80	Healing at 12 weeks Healing at 20 weeks Time to healing Time to 50% ulcer area reduction	I: 24% C: 21% p=0.85 I: 50% C: 43% P=0.344 I: 50 days C: 58 days NS I: 40 days C: 50 days p=0.018	1.0	Inclusion stopped prematurely Inclusion period 1999-2006

		Ulcer area I:8.8 cm^2 C: 6.7 cm^2 p=0.016 Ulcer duration I: 7.4 months C: 7.3 months Plantar ulcers I: 66% C: 61% All ulcers non-infected					
You 2012 (118)	RCT (6/9) Single blind	Age I: 63.5 years C: 62.4 years Male gender I: 65% C: 73% TcPO2 I: 50 mmHg C: 54 mmHg Ulcer size: I:4.0 cm^2 C: 5.2 cm^2 Wagner grade 1 I: 35% C: 35%	I: Cultured allogenic keratinocytes, n=27 C: paraffin gauze, n=32	Ulcer healing at 12 weeks Mean time to healing	ITT I: 85% C: 59% p<0.05 PP I: 100% C: 69% P<0.05 ITT I: 41.6 days C: 43.6 days P=0.78 PP I: 41.5 days C: 42.6 days P=0.9	1.0	13 lost to follow-up

		Wagner grade 2 I: 65% C: 65%					
Jeon 2013 (120)	Cohort study (2/9)	Type 2 diabetes Chronic foot ulcers UT grading 1a n=9 2a n=51 Ulcer area I: 29 cm^2 C: 26.3 cm^2	I: Artificial dermis replacement+ split thickness skin graft, n=30 C: split thickness skin graft, n=30	Length of hospital stay Time to complete wound epithelialisation Number completely healed at 12 weeks Elasticity ratio of the skin	I: 7.52 weeks C: 9.22 weeks p<0.05 I: 8.61 weeks C: 12.94 weeks p<0.05 I: n=28 C: n=24 P<0.05 I: 0.72 C: 0.19 P<0.01	2.0	Different outcome data in text and tables Unexpected results given interruption between interface and skin graft. Long in-hospital stay
Zelen 2013 (121)	RCT (4/9) None blind	Age I: 56 years C: 62 years Male gender I: 69% C: 58% Ulcer size I: 2.8 cm^2 C: 3.4 cm^2 All ulcers	I: Amniotic membrane wound graft, n=13 C: moistened wound therapy with the use of silver, n=12 Both groups compression dressings	Healing at 4 weeks Healing at 6 weeks Ulcer area reduction at 4 weeks	I: 77% C: 0% P<0.0001 I: 92% C: 8% P<0.0001 I: 97.1% C: 32% p<0.001	1.0	Small pilot study Open label study Unexpectedly low healing rate in control group

		non/infected TcPO2>30 mm Hg ABPI 0.7-1.2 or biphasic signals at the ankles		Ulcer area reduction at 6 weeks	I: 98.4% C: -1.8% P<0.0001		

Table 23: Electrical, electromagnetic, lasers, shockwaves and ultrasound – results of 2008 review (1)

Reference	Study design and score	Population	Intervention and control management	Outcomes	Differences and Statistical results	Level of evidence (SIGN)	Comments
Baker 1997 (122)	RCT (3/9)	80 people with 114 chronic ulcers randomised to one of four groups: three with different amounts of stimulation and one control	I: Electrical stimulation for four weeks and then follow-up for an unspecified period	Ulcer healing Compliance with treatment	No difference between Intervention and Control groups	1-	Post hoc analysis with stratification by compliance, and combination of one of the treatment groups into the controls suggested a statistically significant difference of uncertain meaning
Peters 2001 (123)	RCT (9/9)	40 people with uninfected ulcers (UT Grade 1A-2A) and $TcpO_2$ >30mmHg Intervention: 21 (mean age 54 years; 19M)	I: Electrical stimulation	Healing Time to healing	I: 13/21 (65%) C: 7/20 (35%); p=0058 No difference in time to	1++	The difference between groups was significant when adjusted post hoc for compliance

		Controls: 20 (59.4 years; 16M) Lost to follow-up: 5			healing		
Alvarez 2003 (127)	RCT (5/9)	20 patients with neuropathic DFU I: 10 C: 10 12 weeks follow-up Lost to follow-up: 0	I: Non contact thermal wound care system *versus* C: saline dressing	Ulcer healing at 12 weeks	I: 70% C: 40% (p=0.069).	1+	Interim analysis
Szor 2002 (128)	RCT (4/9)	56 subjects of whom completed the study (19 in the intervention group and 18 controls)	Magnetic stimulation: magnets implanted into insoles held on by stockinette for 12 h (overnight), for a total of 8 weeks	Wound healing	None reported	1-	Sample required was 70 Insufficient evaluable patients for results to be analysed
Chiglashvili 2004 (129)	Cohort (1/8)	46 people with diabetes 28 Intervention 18 controls Lost to follow up: 0	Complex intervention involving the administration of antioxidant and immunomodulatory agents, combined with laser therapy	Time to elimination of debris and fibrin Time to wound healing	12.6±2.1 days vs 16.3±2.6 days 27.3±2.8 vs 36.4±3,9 days	2-	No clear description of the patient groups, the intervention or trial design. No statistical analysis
Ennis 2005 (151)	RCT (6/9)	133 neuropathic DFU (Wagner 1), duration >30 days Follow-up 12 weeks. Number of patients lost to follow up: 24 (+ 12 study	I: Ultrasound versus C: Sham therapy	Ulcer healing	Analysis of 133 patients: no data (p=0.69) Per protocol: I: 41% C: 14%	1+	Data only given on the 55 patients who did not violate the protocol or drop out in some way Number of patients randomised to each

		violations) leaving only 97 then a further 42 had study violation (leaving only 55 assessed)			(p=0.04)		arm not given

Table 24: Electrical, electromagnetic, lasers, shockwaves and ultrasound – results of 2012 review (2)

Margara 2008 (124)	Cohort (3/8)	DFUs N=30 Intervention, n=16 Control, n=14 Not infected Baseline ulcer area: I: 8.08 (SD 2.36) cm^2 C: 8.01 (SD 2.23) cm^2	I: Frequency rhythmic electrical modulation applied to edge of ulcer for 30 minute sessions alternate days for 1 month. C: dressing at least weekly Follow up 2 months	Reduction in ulcer area at 30, 45 and 60 days as % baseline	30 days I: 33 (SD 22)% C: 14 (SD10) % p<0.05 45 days I: 65 (SD 14) % C: 51 (SD14) % p<0.05 60 days I: 93% (SD1) C: 83% (SD15) (NS)	2-	Means of allocation not clear Not randomised Possible less than adequate management of control group No difference in long term outcome
Petrofsky 2009 (125)	RCT Open label (3/9)	DFU N=20 Wagner II Baseline area I: (n=10) 24.1 (SD	I: Electrical stimulation and local heat (infrared lamp) 30 min 3 times a week for 4 weeks	Reduction in wound area at 4 weeks determined by length and width	I: 68.4 (SD 28.6)% C: 30.1 (SD 6.7)% p<0.05	1-	Assessment difficult because of much missing data Small sample size

		6.2) cm^2 C: (n=10) 28.2 (SD 5.7) cm^2	*versus* C: infrared lamp alone	multiplied; digital images Wound volume at 4 weeks	 I: 69.3 (SD 27.1)% C: 22.3 (SD 5.3)% p<0.05		Rate of healing surprisingly high considering the baseline wound area
Moretti 2009 (126)	RCT Open label (5/9)	DFU N=30 Intervention n=15 Control n=15 Neuropathic ABPI> 0.7 Baseline mean wound area: I: 297.8 (SD 129.4) mm^2 C: 245 (SD 100.9) mm^2	I: Extracorporeal shockwave therapy 3 sessions each 72 hrs with 100 pulses per cm^2 to perimeter of ulcer *versus* C: standard care	Healing at 20 weeks Time to healing Index of epithelialisation	I: 8/15 C: 5/15 (NS) I: 60.8 (SD 4.7) days C: 82.2 (SD 4.7) days p<0.001 I: 2.97 mm^2/day C: 1.3 mm^2/day p<0.001	1+	Non-blinded No detail on index of epithelisation No detail on frequency of follow-up Very small numbers Possible inappropriate use of parametric statistics
Wang 2009 (54)	RCT Non-blinded (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	I: Extracorporeal shockwave treatment each 2 weeks for three treatments, repeated if necessary. C: HBO daily for 20 treatments Mean follow up: I: 11.64 (6-14) months C: 12.14 (6-14) months	Composite endpoint: 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	1-	Unusual choice of composite endpoint The stated level of significance seems high, given the apparent small difference in outcome between groups

					Control: 18/36 Unchanged Intervention: 4/36 Control: 10/36		

Table 25: Electrical, electromagnetic, lasers, shockwaves and ultrasound – new results

Wang 2011 (53)	Open label RCT 3/9	Non-healing DFU For > 3 months 45 HBO 43 Shockwave 38 HBO 39 Shockwave	HBO 2.5 atm Daily for 5 times a week for 20 treatments Compared with shockwave therapy 2 treatments twice a week for three weeks or a total of 6 treatments but with option for a later treatment (clinical choice with patient consent)	Completely healed ≥50% improved Additional following further treatment	All PP analysis HBO 25% Shockwave 57% P=0.003 HBO 15% Shockwave 32% P=0.071 HBO (n=17) I healed Shockwave (n=14) 7 healed P=0.005	1.0	Possible carry-over of initial HBO therapy from first course because of short interval before second treatment PP analysis Analysis by ulcer rather than patient No data about follow-up Second phase treatment subject to greater potential bias

Table 26: Other systemic therapies – results of 2012 review (2)

Reference	Study design and score	Population	Intervention and control management	Outcomes	Differences and Statistical results	Level of evidence (SIGN)	Comments
Rullan 2008 (130)	RCT Double blind (6/9)	Patients N=70 with leg ulcer (n=18) and DFU (n=52) DFU: Wagner grade I-II Intervention: n=37 Control:n=33	I: Bemiparin 3500 IU/day for 10 days followed by 2500 IU/day for up to 3 months *versus* C: 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	I: 70.3% C: 45.5% (p=0.035) Post hoc analysis of DFU group 72.4% versus 47.8% (CI -1.5-50.7) I: 35.1% C: 33.3% (p=0.874)	1+	Sample size powered to detect a difference of 30% (65% versus 35%) Composite endpoint DFU subgroup subjected to post hoc analysis with no significant difference between groups but no details given
Sert 2008 (131)	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	I: iloprost (prostacyclin) 0.5 to 2 ng/kg/min over 6 h for 10 consecutive days C: no iloprost	Amputation rate at 30 days	I: 25/30 (12 minor and 13 major) C: 29/30 (12 minor and 17 major) (NS)	1-	Study was primarily designed to investigate endothelial function. Results regarding healing are inconclusive
Leung 2008 (132)	RCT Single blind (4/9)	DFU N=80 Necrotic and/or infected ulcers 47% gangrenous	I: Chinese oral herbal formulation C: oral placebo	Time to ulcer granulation to enable skin grafting	I: 5.9 weeks C: 9.2 weeks (NS)	1-	Patient blind but probably not investigator or observer blind only

		toes deemed requiring amputation Unhealed ulcers for up to 25 weeks Intervention: n=40 Control: n=40		Amputation first 4 weeks Eventual amputations	I:3 C: 3 I :3 C: 9 p=0.057		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 2008 (133)	RCT Single blind (4/9)	DFU N=21 No improvement in 2 weeks Wagner Grade I-II Total 21: I1:6 I2:6 C:9	I: ANGIPARS™ herbal extract plus standard care I1: Oral 100mg bd for 6 weeks I2: Oral as above plus 3% gel to wound C: Standard wound care (specified in general terms)	% wound surface change at 6 weeks	I1: 375 (SD 118) mm^2 to 41.7 (SD 33.7) mm^2 (88% reduction) p=0.04 I2: 916.7 (SD 228.6) to 137.5 (SD 41.7)mm^2 (84%reduction) p=0.01 C: 766.3 (SD 320.2 to 689.1 (SD 329.1) mm^2 (25%reduction) p=0.076	1-	Large difference in baseline area between I2 and C Inappropriate use of parametric statistics No between group comparisons

				Improvement on 4 point scale "Complete"= >70% improved Relative improvement = 10-70%	Complete improvement: I1: 5 I2: 6 C: 2 I1: 1 I2: 0 C: 1		
Larijani 2008 (134)	RCT Blinding uncertain (3/9)	DFU 25 >2 weeks without improvement Intervention: 16 Control: 9	I: ANGIPARS IV 4mL in 50-100mL saline daily for 28 days plus standard wound care C: placebo plus standard wound care	Change in ulcer area at 4 weeks	I: 479.9 (SD 379.8) mm^2 to 198.9 (SD 143.8) mm^2 (64% reduction) p=0.000 C: 766 (SD960.5) mm^2 to 689.1 (SD 846.7) mm^2 (25%reduction) p=0.076 64 versus 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

Table 27: Other systemic therapies – new results

Marfella 2012 (135)	RCT (4 /9) Non blinded	N=106 53 in each group At least one foot ulcer ≥3 months duration Age I:64 years C:63 years Diabetes duration I: 17 years C:16 years Gender I: 35/53 men C:34/53 men Area I: 4.3 cm^2 C: 4.1 cm^2	I :Vildagliptin 50mg bd in addition to other hypoglycaemic agents for 3 months C: Other hypoglycaemic agents without DPPIV inhibitor	Healing at 12 weeks Wound area after treatment	I: 31% C: 15% P<0.05 I: 1.2cm^2 C: 3.6cm^2	1.0	Surprisingly equal allocation the two groups for each baseline characteristic No between group comparison – only within group – for decrease in ulcer area Insufficient detail on other wound care
Rewale 2014 (136)	Cohort (3/8) Non-blinded	N=67 Divided into two “identical” groups: I: 30 C: 32 5 lost to follow-up DFU Wagner 1,2	Pentoxyfylline 400mg tds for 30 days with bed rest and usual care. Control group managed with bed rest and usual care.	Number with > 10mm x 10mm improvement at 30 days	I:76.6% C: 53.1% P=0.09	2.0	Small study 5 lost to follow-up; no mention of possible adverse effects

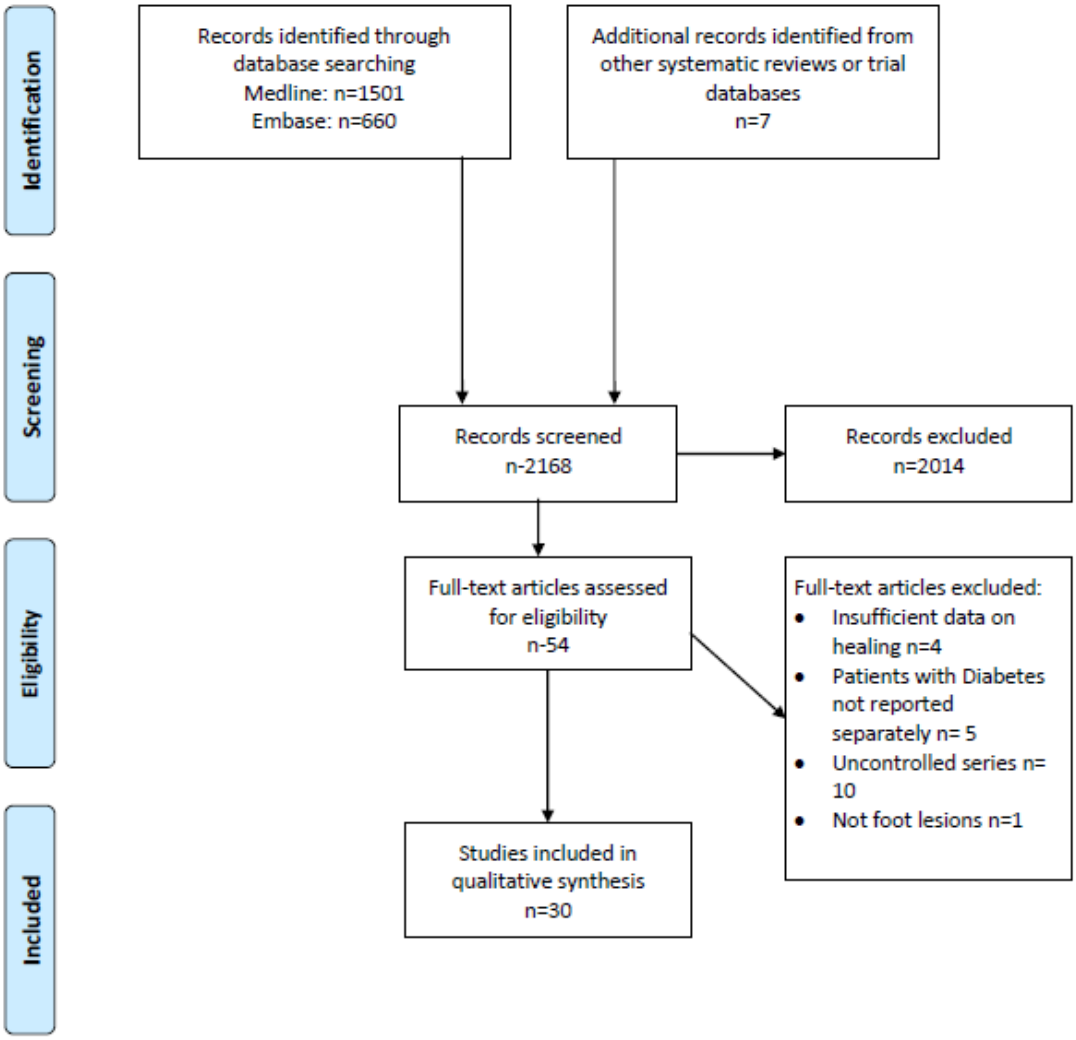

Figure 1. PRISMA Flow diagram 2015 review