



Swansea University
Prifysgol Abertawe



Cronfa - Swansea University Open Access Repository

This is an author produced version of a paper published in:

Diabetes/Metabolism Research and Reviews

Cronfa URL for this paper:

<http://cronfa.swan.ac.uk/Record/cronfa48708>

Paper:

Game, F., Apelqvist, J., Attinger, C., Hartemann, A., Hinchliffe, R., Löndahl, M., Price, P. & Jeffcoate, W. (2016). IWGDF guidance on use of interventions to enhance the healing of chronic ulcers of the foot in diabetes.

Diabetes/Metabolism Research and Reviews, 32, 75-83.

<http://dx.doi.org/10.1002/dmrr.2700>

This item is brought to you by Swansea University. Any person downloading material is agreeing to abide by the terms of the repository licence. Copies of full text items may be used or reproduced in any format or medium, without prior permission for personal research or study, educational or non-commercial purposes only. The copyright for any work remains with the original author unless otherwise specified. The full-text must not be sold in any format or medium without the formal permission of the copyright holder.

Permission for multiple reproductions should be obtained from the original author.

Authors are personally responsible for adhering to copyright and publisher restrictions when uploading content to the repository.

<http://www.swansea.ac.uk/library/researchsupport/ris-support/>

IWGDF guidance on use of interventions to enhance the healing of chronic ulcers of the foot in diabetes

Prepared by the IWGDF working group on Wound Healing

F.L. Game¹, J. Apelqvist², C. Attinger³, A. Hartemann⁴, R.J. Hinchliffe⁵, M. Löndahl², P.E. Price⁶, W.J. Jeffcoate⁷; on behalf of the International Working Group on the Diabetic Foot (IWGDF)

¹. Department of Diabetes and Endocrinology, Derby Teaching Hospitals NHS FT, Derby UK

². Department of Endocrinology, Skåne University Hospital, Sweden

³. Department of Plastic Surgery, Medstar Georgetown University. Hospital, Washington, DC, USA

⁴. Pitié-Salpêtrière Hospital, APHP, Paris 6 University, ICAN, France

⁵. St George's Vascular Institute, St George's Healthcare NHS Trust, London, UK

⁶. Vice-Chancellors' Office, Cardiff University, Cardiff, Wales, UK

⁷. Department of Diabetes and Endocrinology, Nottingham University Hospitals NHS Trust, Nottingham UK

Address of correspondence

Dr Fran Game, Department of Diabetes and Endocrinology, Derby Teaching Hospitals NHS FT, Uttoxeter Road, Derby DE22 3NE, UK. Frances.game@nhs.net

Recommendations

1. Clean ulcers regularly with clean water or saline, debride them when possible in order to remove debris from the wound surface and dress them with a sterile, inert dressing in order to control excessive exudate and maintain a warm, moist environment in order to promote healing. (GRADE strength of recommendation: Strong; Quality of Evidence: Low)
2. In general remove slough, necrotic tissue and surrounding callus with sharp debridement in preference to other methods, taking relative contra-indications such as severe ischemia into account. (Strong; Low)
3. Select dressings principally on the basis of exudate control, comfort and cost. (Strong; Low)
4. Do not use antimicrobial dressings with the goal of improving wound healing or preventing secondary infection. (Strong; Moderate)
5. Consider the use of systemic hyperbaric oxygen therapy, even though further blinded and randomised trials are required to confirm its cost-effectiveness, as well as to identify the population most likely to benefit from its use. (Weak; Moderate)
6. Topical negative pressure wound therapy may be considered in post-operative wounds even though the effectiveness and cost-effectiveness of the approach remains to be established. (Weak; Moderate)
7. Do not select agents reported to improve wound healing by altering the biology of the wound, including growth factors, bioengineered skin products and gases, in preference to accepted standards of good quality care. (Strong; Low)
8. Do not select agents reported to have an impact on wound healing through alteration of the physical environment, including through the use of electricity, magnetism, ultrasound and shockwaves, in preference to accepted standards of good quality care. (Strong; Low)

9. Do not select systemic treatments reported to improve wound healing, including drugs and herbal therapies, in preference to accepted standards of good quality care.

(Strong; Low)

Introduction

There is a clear need for evidence to substantiate the use of particular interventions in the management of chronic ulcers of the foot in diabetes. Following the completion of the latest of three systematic reviews undertaken over the last ten years for the International Working Group on the Diabetic Foot (IWGDF) (1-3), the authors have formulated guidance on the use of interventions to enhance the healing of foot ulcers in diabetes, based on the evidence from all three reviews. The guidance is based on the GRADE system of rating both the quality of the evidence and the strength of the recommendations¹. Recommendations can be made to support an intervention, but also against the use of a particular intervention if there is no strong supporting evidence to justify its adoption. The guidance is divided into ten categories – the same as those used to group different types of intervention in the systematic reviews.

¹ Recommendations in this guidance were formulated based on the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system for grading evidence when writing a clinical guideline (4,5). For much of the older data found in the systematic review underlying this guidance we could not calculate or assess for inconsistency, indirectness or imprecision, which are needed to fully assess the quality of evidence. Therefore, we decided to assess the *quality* of evidence on: the risk of bias of included studies, effect sizes, and expert opinion, and rate the quality of evidence as ‘high’, ‘moderate’, or ‘low’. We assessed the *strength* of each recommendation as ‘strong’ or ‘weak’, based on the quality of evidence, balance between benefits and harms, patient values and preferences, and costs (resource utilization). The rationale behind each recommendation is described in this guidance.

Recommendations of specific types of ulcer treatment in the management of diabetic foot ulcers (excluding off-loading)

What is the best way of debriding a diabetic foot ulcer?

1. Clean ulcers regularly with clean water or saline, debride them when possible in order to remove debris from the wound surface and dress them with a sterile, inert dressing in order to control excessive exudate and maintain a warm, moist environment in order to promote healing. (GRADE strength of recommendation: Strong; Quality of Evidence: Low)
2. In general remove slough, necrotic tissue and surrounding callus with sharp debridement in preference to other methods, taking relative contra-indications such as severe ischemia into account. (Strong; Low)

The term debridement is here defined as the removal of surface debris, slough, necrotic and infected matter with the aim of leaving clean, viable tissue. Even though professional opinion is united in support of the use of debridement to clean the surface of the wound when possible, the experimental evidence to justify debridement in general and of any particular method of debridement, is not strong. Debridement may be undertaken using physical (eg surgical, sharp or hydro-debridement), biological (larvae), autolytic (hydrogels) or biochemical (enzymes) methods. There is surprisingly little evidence on sharp or surgical debridement with only a single paper included in one of the previous systematic reviews and that being a subgroup analysis from another trial (6). Despite this the majority of national guidelines emphasise that sharp debridement (7,8,9) is an essential part of good wound care, taking relative contra-indications such as severe ischemia into account.

The available evidence from the three systematic reviews undertaken by the IWGDF, as published earlier in this journal, suggest that the use of hydrogels (10,11,12) as a means of debridement may have some benefit in terms of wound healing when compared to saline moistened gauze, but the risk of bias in the published studies was high – a conclusion supported by a Cochrane review (13). Similarly, the use of enzymatic or hydro-debridement cannot be supported by the available evidence, which is limited to one study on each method that qualified for inclusion (14,15). The use of larval therapy is equally unsupported in these three reviews with only four small studies identified, each of which had a high risk of bias

(16-19). Of interest, two recent large RCTs of the use of larval therapy in venous leg ulcers have failed to demonstrate benefit in terms of healing (20,21).

This does not mean that debridement is ineffective but simply that the studies have not been done that provide robust evidence to support a strong recommendation. In general, however, clinicians should not adopt newer, more expensive, interventions unless they have been shown to have a greater impact on wound healing than existing methods.

What is the best dressing to use?

3. Select dressings principally on the basis of exudate control, comfort and cost. (Strong; Low)
4. Do not use antimicrobial dressings with the goal of improving wound healing or preventing secondary infection. (Strong; Moderate)

The three systematic reviews performed have looked at a number of different topical preparations designed to improve the healing of ulcers of the foot in diabetes. In general, the evidence to support the adoption of any particular intervention is poor, because the available studies are small and at high risk of bias.

The results of an earlier positive study on a carboxymethylcellulose dressing (22) were not born out by a more recent large single blind RCT with low risk of bias (23).

There is increasing interest in the use of surface antiseptics or antimicrobials and although healing may not be the most obvious outcome measure to evaluate these agents, it is important that it is assessed in order to demonstrate the contribution it may make to the healing process. A single study reporting the use of antibiotic beads after transmetatarsal amputation found that this intervention had no impact on the incidence of wound healing (24).

Honey has been used for centuries as an antimicrobial agent and its appeal as a potential target for the management of chronic wounds is obvious. There is, however, little evidence to support its use for either the promotion of healing or the prevention of secondary infection. Over the three systematic reviews, only three small controlled studies on the use of honey were identified and none showed convincing evidence of benefit when compared with an iodine-containing dressing (25-27). A Cochrane review of honey based dressings in all

wound types (28) concluded that health services may wish to consider avoiding routine use of honey dressings until sufficient evidence of effect is available – a conclusion that is endorsed by the results of the current review.

Other topical antimicrobials, such as silver or iodine based dressings and applications, are also used frequently. Only one controlled trial of a silver based dressing was identified in all three systematic reviews (29) and this demonstrated no convincing evidence of benefit. Similarly, a recent Cochrane review found no evidence of benefit from the use of antiseptic preparations in terms of either healing or secondary infection in any studies of infected or contaminated wounds (30). Similarly a single large high scoring multicentre RCT which compared a non-adherent dressing with an iodine impregnated dressing and a carboxymethylcellulose hydrofibre dressing was reported in the 2012 review. This showed no difference between the three products either in terms of wound healing or the incidence of new infection (23).

The conclusion for the whole group of topical interventions is that there was either insufficient or no evidence to justify the use of any of the preparations considered in preference to any other. In the absence of any specific indication, practitioners should use the dressing/application with the lowest acquisition cost, but which supports moist wound healing whilst controlling any exudate.

Does systemic hyperbaric oxygen therapy (HBOT) hasten wound healing in diabetic foot ulcers?

5. Consider the use of systemic hyperbaric oxygen therapy, even though further blinded and randomised trials are required to confirm its cost-effectiveness, as well as to identify the population most likely to benefit from its use. (Weak; Moderate)

In our systematic reviews we reported two RCTs (31,32) of methodologically good quality on systemic HBOT. The larger study (32), which included patients both with and without (severe) peripheral arterial disease, demonstrated a significantly improved outcome in the intervention group, who were more likely to heal within 12 months. In a post-hoc analysis ulcer healing in the patients treated with HBOT was associated with baseline trans cutaneous oxygen pressure (TcPO₂) levels, but not with ankle:brachial index (ABI) or toe blood pressure (33). Of note, the second RCT that also observed improved wound healing (31)

included only patients with non-reconstructable critical limb ischemia. It remains therefore to be determined which group of patients will benefit most from systemic HBOT. This is underscored by a large retrospective cohort study of patients treated in 83 centres located in 31 states of the USA (34). Data were included if patients had been treated according to reimbursement guidelines from Centers for Medicare and Medicaid Services which require that patients have “an adequate lower-extremity arterial flow” as determined by the clinician. Using propensity score–adjusted models, 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 these patients. Although the design and inclusion criteria of this study have been criticised, it highlights the need for further studies to determine which patient group might benefit most from this treatment and to establish cost-effectiveness.

Does topical negative pressure wound therapy (NPWT) hasten healing in diabetic foot ulcers?

6. Topical negative pressure wound therapy may be considered in post-operative wounds even though the effectiveness and cost-effectiveness of the approach remains to be established. (Weak; Moderate)

NPWT is a technique for applying continuous or intermittent negative pressure to wounds via a material that fills the wound. Optimal use of this technique requires knowledge of the influence of different pressure levels, the different materials that can be put in the wound and the interface materials (those in direct contact with the wound surface). One theory behind the use of NPWT is that by extracting wound exudate, the frequency of dressing changes can be reduced and, wounds can therefore be kept cleaner, and with reduced malodour. Moreover, NPWT appears to stimulate granulation tissue formation (35,36) and contraction of the wound (35). It is also suggested that NPWT may increase tissue perfusion by mechanical means and may also encourage off-loading by making ambulation difficult (35). NPWT is generally useful in stimulating the healing process, but does not result in complete epithelialisation. Potential adverse effects of NPWT have been described, including wound maceration, retention of dressings and wound infection (36). A number of other potential contraindications to its use have been listed elsewhere (37). Given the relative complexity of this technique and its risks, it requires skills and organization.

There are two distinct types of wounds in which NPWT has been studied in the management of ulcers of the foot in diabetes; the post surgical and the chronic non-surgical wound.

Post surgical wounds:

In earlier systematic reviews we reported on two large RCTs and a small RCT which suggested in post-operative wounds a significant benefit of NPWT in both the time to healing and the proportion of wounds healed (38,39,40). However, there were methodological issues in these studies rendering them subject to bias.

One small study was reviewed in the latest review which compared the use of NPWT on the success of split skin grafting (41). Although apparently improving the number of split skin grafts which took successfully when compared to usual care, the study was of poor methodological quality. A small randomised but single blind study has shown that the qualitative but not quantitative assessment of the graft take improved when NPWT was used in addition to split skin grafting (42) but this was not undertaken in diabetic foot ulcers.

Non-surgical ulcers:

Three small RCTs and one cohort study have been identified on the use of NPWT in chronic DFUs from all three systematic reviews (43-46). All had methodological flaws but showed NPWT was associated with decreased wound volume and depth (43), and decreased time to ulcer healing (44), but these studies were subject to bias and there is, in addition, considerable publication bias in this area (35). It is not possible to make a recommendation on the use of NPWT in non-surgical wounds because of the lack of available evidence.

Is there a place for the use of other topically applied treatments?

7. Do not select agents reported to improve wound healing by altering the biology of the wound, including growth factors, bioengineered skin products and gases, in preference to accepted standards of good quality care. (Strong; Low)

Four studies of collagen/oxidised regenerated cellulose dressing were identified in the three systematic reviews (47-50). The largest of these failed to show an effect on healing (49). Small, poor quality studies have reported the use of an acellular dermal regenerative matrix and an acellular bioproduct from pig intestine but they provided no good data to support the use of these products in routine care (51-53).

The latest search also identified a single study of perilesional injections of polydeoxyribonucleotide (54). Although a high scoring RCT, there are concerns about the poor healing rate in the control arm, the lack of detail concerning offloading and lack of health economic data. Earlier reports have suggested promise of some other agents (acellular bioproduct derived from the porcine small intestinal submucosa, acellular dermal regenerative tissue matrix, talactoferrin, chrysalin) that alter wound biochemistry and cell biology. The studies identified have provided no firm evidence to justify the use of any intervention listed.

Platelet concentrates and platelet derived growth factors have been of interest as a therapeutic target for a number of years. The earliest study identified was of autologous platelet factor (55) but was limited by being undertaken in both leg and foot ulcers and not all patients had diabetes. A later study on platelet concentrate (56) reported an apparent improvement in wound healing but was marred by a high number of drop-outs and the use of per protocol analysis. The problem of the volume of blood required for the preparation of autologous platelet gel or fluid was overcome in a later RCT by the use of blood bank derived platelets (57). Although the study reported positive results, few details were provided on study inclusion criteria. As this product was used in uninfected, non-ischemic, non-necrotic wounds, this represents a minority of patients with foot ulcers. In addition, the use of non-autologous platelets is potentially associated with adverse effects such as infection.

The use of recombinant platelet derived growth factor has also been assessed. Six RCTs were identified (58-63) that either showed no improvement in healing between intervention and control groups or were marred by significant methodological problems. Given the cost of the product, firm data are required for both its effectiveness and its cost effectiveness before it is considered for use in routine care.

Other recombinant growth factors have also been the subject of studies, and these include basic fibroblast growth factor (bFGF), epidermal growth factor vascular endothelial growth factor. Two studies of bFGF (64,65) do not support the use of this agent in clinical practice. Despite the widespread use of EGF in some countries, only three moderately to high scoring RCTs have been identified, with conflicting results (66-68). Hence no clear outcomes in terms of healing or area reduction have been demonstrated. One study of intramuscular

injections of a plasmid containing the gene for vascular endothelial growth factor (69), has shown some promising results on reduction in wound area but needs confirmation before this therapy could be recommended in clinical practice. There is currently little evidence to suggest that any single growth factor should be considered for adoption in the management of foot ulcers that fail to heal with standard good care.

Several early studies of cultured dermal fibroblasts, keratinocytes or fibroblast/keratinocyte co-culture were marred either by methodological problems or by low healing rates in the control groups (70-74). Only one well designed RCT later reported a significant improvement in healing in a group of patients who were otherwise well managed (75) but the trial was stopped prematurely and the result is that the effectiveness and cost effectiveness of this type of therapy remains to be confirmed. One promising study of co-cultured keratinocytes in combination with fibroblasts followed by epidermal tissue engineered autograft (76) requires confirmation. There are several concerns related to these products such as the complex application process, costs as well as suboptimal quality of the skin after healing and the potential of (slow-virus). For this reason we feel that higher level of evidence is needed to justify its routine use. Split skin grafting is widely used for various kinds of non-infected, non-ischemic, non-necrotic wounds, including diabetic foot ulcers. Surprisingly, only one study of split skin grafting (77) has been identified which for methodological reasons does not provide support for the use of split skin grafting to improve healing of diabetic foot ulcers.

The evidence to justify the use of the various products available has been well reviewed in the three earlier IWGDF reviews, as published earlier, and the evidence to justify the use of any is inconclusive. It is for this reason that the routine use of any such product is not currently recommended.

Is there a place for other local therapies to improve wound healing in the diabetic foot?

8. Do not select agents reported to have an impact on wound healing through alteration of the physical environment, including through the use of electricity, magnetism, ultrasound and shockwaves, in preference to accepted standards of good quality care.
(Strong; Low)

Studies on the use of electrical stimulation (78-80), ultrasound (81), normothermic therapy (82), magnetism (83) and laser therapy (84) have reported no convincing evidence of benefit. Reports of apparent superiority of shockwave therapy over HBO treatment are marred by the use of per protocol analysis and other methodological problems (85,86). There is no evidence to justify the recommendation for the adoption of any reported physical therapies in routine practice.

Is there a place for other systemic therapies, including drugs and herbal therapies, in improving wound healing in the diabetic foot?

9. Do not select systemic treatments reported to improve wound healing, including drugs and herbal therapies, in preference to accepted standards of good quality care.
(Strong; Low)

Trials of low molecular weight heparin (87), iloprost infusion (88), and of herbal preparations – (administered orally in two studies and intravenously in one) (89-91) were of poor quality and none showed any major improvement in outcome. One recent study of the use of oral vildagliptin (92), reported apparent improvement in healing at 12 weeks in one recent study but the very low incidence of healing in the control group casts doubt on the likely clinical benefit of this product if used in addition to good clinical care. There is no evidence to justify the recommendation for the adoption of any other systemic therapy to enhance the healing of DFUs in routine practice.

Considerations

Our recommendations are derived from critical systematic review of all relevant publications but this process has its limitations and these must be borne in mind. The first is that the reviews sought evidence specifically that an intervention may improve healing (and only of foot ulcers complicating diabetes – and not of other wounds, whether acute or chronic). As, however, the process of healing is a highly complex one, involving the interaction of many different cell types and signalling pathways, it is likely that the benefit of the majority of specific interventions is limited to a particular type of wound and to a particular phase in the healing process. As the process tends to last for weeks or months, this means that the impact of any beneficial effect of a therapy may not be apparent. It is also important to consider whether the benefit of a therapy has been demonstrated in people who are also receiving

usual best care, including adequate offloading in those with ulcers on weight bearing areas of the foot.

If, however, studies are of insufficient duration to assess complete healing of an ulcer as an outcome measure, it may be possible to use a surrogate measure – such as percentage reduction in wound area over four weeks, which has been shown to correlate with, and to be predictive of, the incidence of eventual healing (93). The adoption of such a surrogate measure will reduce the chance of a short term response to an intervention being obscured by the complexity of the overall healing process. Demonstration of benefit in such short duration studies could then be used as the foundation for further work designed to determine the specific population and circumstances in which the use of the intervention is likely to be beneficial.

Ultimately, however, the clinical endpoint of care is to accelerate complete healing of chronic ulcers of the foot in diabetes and this must be demonstrated if any treatment is to be generally recommended. Hitherto, such recommendation has not been possible because of the limitations both in extent and, in many cases, in quality of reported studies.

KEY UNRESOLVED ISSUES

1. Overall low evidence base for the assessment of interventions

With the exception of off-loading (not considered in this review), the field remains blighted by the poor level of evidence to justify the use of any particular therapy in the management of ulcers. There is little evidence that the number of high-quality studies is increasing.

2. The contribution made by difficulties of trial design in the continuing low output of high quality research in the field

One particular aspect of trial design may be having a major impact on the poor evidence base for specific interventions and this relates to the choice of outcome measure for intervention studies. The difficulty derives from the fact that the best measure of efficacy of an intervention in this field is the demonstration of an effect on ulcer healing, and yet ulcer healing may take many weeks. If, however, an intervention is only effective at a particular stage of wound healing or under a particular set of clinical circumstances, then it is difficult to demonstrate its benefit in a conventionally designed trial.

3. Very few data on effectiveness and cost-effectiveness

Even though there are a small number of studies suggesting efficacy of particular interventions, there are very few studies confirming effectiveness (and, thereby, of cost-effectiveness) of any particular intervention in routine care.

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.

References

1. Hinchliffe RJ, Valk GD, Apelqvist J, Armstrong DG, Bakker K, Game FL, Hartemann-Heurtier A, Løndahl M, Price PE, van Houtum WH, Jeffcoate WJ. A systematic review of the effectiveness of interventions to enhance the healing of chronic ulcers of the foot in diabetes. *Diabetes Metab Res Rev* 2008; 24 Suppl 1 S119-144.
2. Game FL, Hinchliffe RJ, Apelqvist J, Armstrong DG, Bakker K, Hartemann A, Løndahl M, Price PE, Jeffcoate WJ. A systematic review of interventions to enhance the healing of chronic ulcers of the foot in diabetes. *Diabetes Metab Res Rev*. 2012; 28 Suppl 1: 119-41
3. Game FL, Hinchliffe RJ, Apelqvist J, Armstrong DG, Bakker K, Hartemann A, Løndahl M, Price PE, Jeffcoate WJ. A systematic review of interventions to enhance the healing of chronic ulcers of the foot in diabetes. *Diabet Metab Res Rev* 2015.
4. Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, Schünemann HJ; GRADE Working Group. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *Brit Med J* 2008; 336(7650): 924-6
5. http://essentialevidenceplus.com/product/ebm_loe.cfm?show=grade (accessed 31st March 2015)
6. Saap LJ, Falanga V. Debridement performance index and its correlation with complete closure of diabetic foot ulcers. *Wound Repair Regen* 2002; 10: 354-9
7. Centre for Clinical Practice at NICE (UK). Diabetic Foot Problems: Inpatient Management of Diabetic Foot Problems. National Institute for Health and Clinical Excellence (UK); 2011 National Institute for Health and Clinical Excellence: Guidance
8. Ottawa (ON): Canadian Agency for Drugs and Technologies in Health Procedures for Managing Diabetic Foot Ulcers: A Review of Debridement, Clinical Effectiveness, Cost-effectiveness, and Guidelines 2014
<http://www.ncbi.nlm.nih.gov/books/NBK253769/pdf/TOC.pdf> (accessed December 2014)
9. Bergin SM, Gurr JM, Allard BP, Holland EL, Horsley MW, Kamp MC, Lazzarini PA, Nube VL, Sinha AK, Warnock JT, Alford JB, Wraight PR; Australian Diabetes Foot Network. Australian Diabetes Foot Network: management of diabetes-related foot ulceration - a clinical update. *Med J Aust* 2012; 20;197: 226-9

10. Jensen JL, Seeley J, Gillin B. Diabetic foot ulcerations. A controlled randomized comparison of two moist wound healing protocols: carrasyn Hydrogel Wound dressing and wet-to-moist saline gauze. *Adv Wound Care* 1998; 11: S1–S4.
11. Cangialosi CP. Synthetic skin. A new adjunct in the treatment of diabetic ulcers. *J Am Podiatry Assoc* 1982; 72: 48–52
12. Capasso VA, Munro BH. The cost and efficacy of two wound treatments. *AORN J* 2003; 77: 984–992.
13. Dumville JC, O'Meara S, Deshpande S, Speak K. Hydrogel dressings for healing diabetic foot ulcers. *Cochrane Database Syst Rev* 2013 Jul 12;7
14. Tallis A, Motley TA, Wunderlich RP, Dickerson JE Jr, Waycaster C, Slade HB; Collagenase Diabetic Foot Ulcer Study Group. Clinical and economic assessment of diabetic foot ulcer debridement with collagenase: results of a randomized controlled study. *Clin Ther* 2013; 35:1805-20
15. Caputo WJ, Beggs DJ, DeFede JL, Simm L, Dharma H. A prospective randomised controlled trial comparing hydrosurgery debridement with conventional surgical debridement in lower extremity ulcers. *Int Wound J* 2008; 5: 288–94
16. Sherman RA. Maggot therapy for treating diabetic foot ulcers □unresponsive to conventional therapy. *Diabetes Care* 2003; 26: □446 – 451.
17. Armstrong DG, Sala P, Short B, et al. Maggot therapy in “lower- □extremity hospice” wound care. *J Am Podiatr Med Assoc* 2005; 95: 254-57
18. Paul AG, Ahmad NW, Ariff AM, Saranum M, Naicker AS, Osman Z. Maggot debridement therapy with *Lucillia cuprina*: a comparison with conventional debridement in diabetic foot ulcers. *Int Wound J* 2009; 6: 39–46
19. Wang SY, Wang JN, Lv DC, Diao YP, Zhang Z. Clinical research on the bio-debridement effect of maggot therapy for treatment of chronically infected lesions. *Orthop Surg* 2010; 2: 201-6
20. Davies C, Woolfrey G, Hogg N, Dyer J, Cooper A, Waldron J, Bulbulia R, Whyman M, Poskitt K. Maggots as a wound debridement agent for chronic venous leg ulcers under graduated compression bandages: a randomised controlled trial. *Health Technol Assess* 2009; 13: 1-182
21. Dumville JC, Worthy G, Soares MO, Bland JM, Cullum N, Dowson C, Iglesias C, McCaughan D, Mitchell JL, Nelson EA, Torgerson DJ; VenUS II team. VenUS II: a randomised controlled trial of larval therapy in the management of leg ulcers. *Health Technol Assess*. 2009 Nov;13(55):1-182

22. Piaggese A, Baccetti F, Rizzo L, Romanelli M, Navalesi R, Benzi L. Sodium carboxyl-methyl-cellulose dressings in the management of deep ulcerations of diabetic foot. *Diabet Med* 2001; 18: 320–324
23. Jeffcoate WJ, Price PE, Phillips CJ, et al. Randomised controlled trial of the use of three dressing preparations in the management of chronic ulceration of the foot in diabetes. *Health Technol Assess* 2009; 13: 1–86
24. Krause FG, de Vries G, Meakin C, Kalia TP, Younger AS. Outcome of transmetatarsal amputations in diabetics using antibiotic beads. *Foot Ankle Int* 2009; 30: 486–93
25. Shukrimi A, Sulaiman AR, Halim AY, Azril A. A comparative study between honey and povidone iodine as dressing solution for Wagner type II diabetic foot ulcers. *Med J Malaysia* 2008; 63: 44–6
26. Rehman E-U, Afzal M.O., Ali A., Qureshi A.-R.Z.-U.-R., Rashid M. Comparison between honey and povidone-iodine / normal saline dressing for management of Wagner grades I & II diabetic foot ulcers. *Pak J Med Health Sci* 2013; 7/4:1082-108.
27. Jan WA, Shah H, Khan M, Fayaz M, Ullah N. Comparison of conventional pyodine dressing with honey dressing for the treatment of diabetic foot ulcers. *J Postgrad Med Inst* 2012; 26: 402-7
28. Jull AB, Walker N, Deshpande S. Honey as a topical treatment for wounds. *Cochrane Database Syst Rev* 2013; 28; 2
29. Jude EB, Apelqvist J, Spraul M, Martini J. Prospective randomized controlled study of Hydrofiber dressing containing ionic silver or calcium alginate dressings in non-ischaemic diabetic foot ulcers. *Diabet Med* 2007; 24: 280-8
30. Vermeulen H, van Hattem JM, Storm-Versloot MN, Ubbink DT, Westerbos SJ Topical silver for treating infected wounds (Review) *Cochrane Database of Systematic Reviews* 2007, Issue 1. Art. No.: CD005486. DOI: 10.1002/14651858.CD005486.pub2.
31. Abidia A, Laden G, Kuhan G, et al. The role of hyperbaric oxygen therapy in ischaemic diabetic lower extremity ulcers: a double-blind randomised controlled trial. *Eur J Vasc Endovasc Surg* 2003; 25: 513–8
32. Löndahl M, Katzman P, Nilsson A, Hammarlund C. Hyperbaric oxygen therapy facilitates healing of chronic foot ulcers in patients with diabetes. *Diabetes Care* 2010; 33: 998-1003
33. Löndahl M, Katzman P, Hammarlund C, Nilsson A, Landin-Olsson M.

34. Relationship between ulcer healing after hyperbaric oxygen therapy and transcutaneous oximetry, toe blood pressure and ankle-brachial index in patients with diabetes and chronic foot ulcers. *Diabetologia*. 2011 Jan;54(1):65-8.
35. Margolis DJ, Gupta J, Hoffstad O, Papadopoulos M, Glick HA, Thom SR, Mitra N. Lack of Effectiveness of hyperbaric oxygen therapy for the treatment of diabetic foot ulcer and the prevention of amputation. A cohort study. *Diabetes Care* 2013; 36: 1961-6
36. Dumville JC, Hinchliffe RJ, Cullum N, Game F, Stubbs N, Sweeting M, Peinemann F. Negative pressure wound therapy for treating foot wounds in people with diabetes mellitus. *Cochrane Database Syst Rev* 2013 Oct 17;10:CD010318. doi: 10.1002/14651858.CD010318.pub2
37. FDA 2011 US Food, Drug Administration. FDA Safety Communication: Update on serious complications associated with negative pressure wound therapy systems. <http://www.fda.gov/downloads/drugs/drugsafety/postmarketdrugsafetyinformationforpatientsandproviders/ucm142821.pdf> (Accessed December 2014)
38. Strohal, R., Apelqvist, J., Dissemond, J. et al. EWMA Document: Debridement. *J Wound Care*. 2013; 22 (Suppl. 1): S1–S52.
39. Armstrong DG, Lavery LA, Diabetic Foot Study Consortium. Negative pressure wound therapy after partial diabetic foot amputation: a multicentre, randomised controlled trial. *Lancet* 2005; 366: 1704-10
40. Blume PA, Walters J, Payne W, Ayala J, Lantis J. Comparison of negative pressure wound therapy using vacuum- assisted closure with advanced moist wound therapy in the treatment of diabetic foot ulcers. *Diabetes Care* 2008; 31: 631-6
41. Sepulveda G, Espindola M, Maureira A, et al. Negative-pressure wound therapy versus standard wound dressing in the treatment of diabetic foot amputation. A randomised controlled trial. *Cirurg Espanola* 2009; 86: 171-77
42. Dalla Paola L, Carone A, Ricci S, Russo A, Ceccacci T, Ninkovic S. Use of vacuum assisted closure therapy in the treatment of diabetic foot wounds. *J Diabet Foot Complications* 2010; 2; 33-44
43. Moisidis E, Heath T, Boorer C, Ho K, Deva AK. A prospective, blinded, randomized, controlled clinical trial of topical negative pressure use in skin grafting *Plast Reconstr Surg* 2004; 114: 917-22

44. Eginton MT, Brown KR, Seabrook GR, Towne JB, Cambria RA. A prospective randomized evaluation of negative-pressure wound dressings for diabetic foot wounds. *Ann Vasc Surg* 2003; 17: 645-49
45. McCallon SK, Knight CA, Valiulus JP, Cunningham MW, McCulloch JM, Farinas LP. Vacuum-assisted closure versus saline-moistened gauze in the healing of postoperative diabetic foot wounds. *Ostomy Wound Manage* 2000; 46: 28–32
46. Frykberg RG, Williams DV. Negative-pressure wound therapy and diabetic foot amputations. *J Am Podiatr Assoc* 2007; 97: 351-59
47. Peinemann F, McGauran N, Sauerland S, Lange S. Negative pressure wound therapy: potential publication bias caused by lack of access to unpublished study results data. *BMC Medical Research Methodology* 2008; 8: 4
48. Veves A, Sheehan P, Pham HT. A randomized, controlled trial of Promogran (a collagen/oxidized regenerated cellulose dressing) vs standard treatment in the management of diabetic foot ulcers. *Arch Surg* 2002; 137: 822-27
49. Lázaro-Martínez JL, García-Morales E, Beneit-Montesinos JV, Martínez-de-Jesis FR, Aragón-Sánchez FJ. Randomized comparative trial of a collagen/oxidized regenerated cellulose dressing in the treatment of neuropathic diabetic foot ulcers. *Cirurg Espanola* 2007; 82: 27–31
50. Gottrup F, Cullen BM, Karlsmark T, Bischoff-Mikkelsen M, Nisbet L, Gibson MC. Randomized controlled trial on collagen/oxidized regenerated cellulose/silver treatment. *Wound Rep Reg* 2013; 21: 216-25
51. Motzkau M, Tautenhahn J, Lehnert H, Lobmann R. Expression of matrix-metalloproteases in the fluid of chronic diabetic foot wounds treated with a protease absorbent dressing. *Exp Clin Endocrinol Diabetes* 2011; 119: 286-90
52. Niezgodá JA, Van Gils CC, Frykberg RG, Hodde JP. Randomized clinical trial comparing OASIS Wound Matrix to Regranex Gel for diabetic ulcers. *Adv Skin Wound Care* 2005; 18: 258-66
53. Brigido SA. The use of an acellular dermal regenerative matrix in the treatment of lower extremity wounds: a prospective 16-week pilot study. *Int Wound J* 2006; 3: 161-7
54. Reyzelman A, Crews RT, Moore L, et al. Clinical effectiveness of an acellular dermal regenerative tissue matrix compared to standard wound management in healing diabetic foot ulcers: a prospective, randomised, multicentre study. *Int Wound J* 2009; 6: 196–208

55. Squadrito F, Bitto A, Altavilla D, Arcoraci V, De Caridi G, De Feo ME, Corrao S, Pallio G, Sterrantino C, Minutoli L, Saitta A, Vaccaro M, Cucinotta D. The effect of PDRN, an adenosine receptor A2A agonist, on the healing of chronic diabetic foot ulcers: results of a clinical trial. *J Clin Endocrinol Metab* 2014; 99: E746-53
56. Krupski WC, Reilly LM, Perez S, Moss KM, Crombleholme PA, Rapp JH. A prospective randomized trial of autologous platelet-derived wound healing factors for treatment of chronic nonhealing wounds: a preliminary report. *J Vasc Surg* 1991; 14: 526-32
57. Driver VR, Hanft J, Fylling CP, Beriou JM, Autologel Diabetic Foot Ulcer Study Group. A prospective, randomized, controlled trial of autologous platelet-rich plasma gel for the treatment of diabetic foot ulcers. *Ostomy Wound Manage* 2006; 52: 68-70
58. Jeong S-H, Han S-K, Kim W-K. Treatment of diabetic foot ulcers using a blood bank concentrate. *Plast Reconstr Surg* 2010; 125: 944-52
59. Niezgodna JA, Van Gils CC, Frykberg RG, Hodde JP. Randomized clinical trial comparing OASIS Wound Matrix to Regranex Gel for diabetic ulcers. *Adv Skin Wound Care* 2005; 18: 25866
60. Steed DL, Diabetic Ulcer Study Group. Clinical evaluation of recombinant human platelet-derived growth factor for the treatment of lower extremity diabetic ulcers. *J Vasc Surg* 1995; 21: 71-8
61. Wieman TJ, Smiell JM, Su Y. Efficacy and safety of a topical gel formulation of recombinant human platelet-derived growth factor-BB (becaplermin) in patients with chronic neuropathic diabetic ulcers. A phase III randomized placebo-controlled double-blind study. *Diabetes Care* 1998; 21: 822-7
62. Robson MC, Payne WG, Garner WL, et al. Integrating the results of phase IV (post-marketing) clinical trial with four previous trials reinforces the position that Regranex (becaplermin) gel 0.01% is an effective adjunct to the treatment of diabetic foot ulcers. *J Appl Res* 2005; 5: 35-45
63. Khandelwal S, Chaudhary, P Poddar DD, Saxena, N, Singh RAK, Biswal UC. Comparative study of different treatment options of grade III and IV diabetic foot ulcers to reduce the incidence of amputations. *Clinics and Practice* 2013; 3:e9 20-4
64. Landsman A, Agnew P, Parish L, Joseph R, Galiano RD. Diabetic foot ulcers treated with becaplermin and TheraGauze, a moisture-controlling smart dressing: a randomized, multicenter, prospective analysis. *J Am Podiatr Med Assoc* 2010, 100: 155-60

65. Richard JL, Parer-Richard C, Daures JP, et al. Effect of topical basic fibroblast growth factor on the healing of chronic diabetic neuropathic ulcer of the foot. A pilot, randomized, double-blind, placebo-controlled study. *Diabetes Care* 1995; 18: 64-9
66. Uchi H, Igarashi A, Urabe K, et al. Clinical efficacy of basic fibroblast growth factor (bFGF) for diabetic ulcer. *Eur J Dermatol* 2009; 19: 461-8
67. Tsang MW, Wong WK, Hung CS, et al. Human epidermal growth factor enhances healing of diabetic foot ulcers. *Diabetes Care* 2003; 26: 1856–1861.
68. Viswanathan V, Pendsey S, Sekar N, Murthy GSR. A phase II study to evaluate the safety and efficacy of recombinant human epidermal growth factor (REGEN-D™ 150) in healing diabetic foot ulcers. *Wounds* 2006; 18: 186-96
69. Fernandez-Montequin JI, Valenzuela- Silva CM, Diaz OG, et al. Intra-lesional injections of recombinant human epidermal growth factor promote granulation and healing in advanced diabetic foot ulcers: multicenter, randomised, placebo-controlled, double-blind study. *Int Wound J* 2009; 6: 432-43
70. Kusumanto YH, Van Weel V, Mulder NH, et al. Treatment with intramuscular vascular endothelial growth factor gene compared with placebo for patients with diabetes mellitus and critical limb ischaemia: a double-blind randomized trial. *Human Gene Ther* 2006; 17: 683-91
71. Gentzkow GD, Iwasaki SD, Hershon KS, et al. Use of Dermagraft, a cultured human dermis, to treat diabetic foot ulcers. *Diabetes Care* 1996; 19: 350-4
72. Naughton G, Mansbridge J, Gentzkow G. A metabolically active human dermal replacement for the treatment of diabetic foot ulcers. *Artif Organs* 1997; 21: 1203-10
73. Marston WA, Hanft J, Norwood P, Pollak R, Dermagraft Diabetic Foot Ulcer Study Group. The efficacy and safety of Dermagraft in improving the healing of chronic diabetic foot ulcers: results of a prospective randomized trial. *Diabetes Care* 2003; 26: 1701-5
74. Bayram Y, Deveci M, Imirzalioglu N, Soysal Y, Sengezer M. The cell based dressing with living allogenic keratinocytes in the treatment of foot ulcers: a case study. *Br J Plast Surg* 2005; 58: 988-96
75. Veves A, Falanga V, Armstrong DG, Sabolinski ML, Apligraf Diabetic Foot Ulcer Study. Graftskin, a human skin equivalent, is effective in the management of noninfected neuropathic diabetic foot ulcers: a prospective randomized multicenter clinical trial. *Diabetes Care* 2001; 24: 290-5

76. Edmonds M. Apligraf in the treatment of neuropathic diabetic foot ulcers. *Int J Low Extrem Wounds* 2009; 8: 11-8
77. Uccioli L, Giurato L, Ruotolo V, Ciavarella A, Grimaldi MS, Piaggese A, Teobaldi I, Ricci L, Scionti L, Vermigli C, Seguro R, Mancini L, Ghirlanda G. Two-step autologous grafting using HYAFF scaffolds in treating difficult diabetic foot ulcers: results of a multicenter, randomized controlled clinical trial with long-term follow-up. *Int J Low Extrem Wounds* 2011; 10: 80-5
78. Puttirutvong P. Meshed skin graft versus split thickness skin graft in diabetic ulcer coverage. *J Med Assoc Thai* 2004; 87: 66–72
79. Baker LL, Chambers R, DeMuth SK, Villar F. Effects of electrical stimulation on wound healing in patients with diabetic ulcers. *Diabetes Care* 1997; 20: 405-12
80. Peters EJ, Lavery LA, Armstrong DG, Fleischli JG. Electric stimulation as an adjunct to heal diabetic foot ulcers: a randomized clinical trial. *Arch Phys Med Rehabil* 2001; 82: 721-5
81. Petrofsky JS, Lawson D, Berk L, Suh H. Enhanced healing of diabetic foot ulcers using local heat and electrical stimulation for 30min three times a week. *J Diabetes* 2010; 2: 41-6
82. Ennis WJ, Foremann P, Mozen N, Massey J, Conner-Kerr T, Meneses P. Ultrasound therapy for recalcitrant diabetic foot ulcers: results of a randomized, double-blind, controlled, multicenter study. *Ostomy Wound Manage* 2005; 51: 24-39
83. Alvarez OM, Rogers RS, Booker JG, Patel M. Effect of noncontact normothermic wound therapy on the healing of neuropathic (diabetic) foot ulcers: an interim analysis of 20 patients. *J Foot Ankle Surg* 2003; 42: 30-5
84. Szor J, Holewinski P. Lessons learned in research: an attempt to study the effects of magnetic therapy. *Ostomy Wound Manage* 2002; 48: 24-9
85. Chiglashvili DS, Istomin DA. Complex treatment of patients with the diabetic foot. *Klin Med (Mosk)*. 2004; 82: 66-9
86. Wang CJ, Kuo YR, Wu RW, et al. Extra- corporeal shockwave treatment for chronic diabetic foot ulcers. *J Surg Res* 2009; 152: 96-103
87. Wang CJ, Wu RW, Yang YJ Treatment of diabetic foot ulcers: a comparative study of extracorporeal shockwave therapy and hyperbaric oxygen therapy. *Diabetes Res Clin Pract* 2011; 92:187-93

88. Rullan M, Cerdà L, Frontera G, Masmi- quel L, Llobera J. Treatment of chronic diabetic foot ulcers with bemiparin: a randomized, triple blind, placebo-controlled, clinical trial. *Diabet Med* 2008; 25: 1090-5
89. Sert M, Soydas B, Aikimbaev T, Tetiker T. Effects of iloprost (a prostacyclin analogue) on the endothelial function and foot ulcers in diabetic patients with peripheral arterial disease. *Int J Diabetes Metab* 2008; 16: 7–11
90. Leung PC, Wong MV, Wong WC. Limb salvage in extensive diabetic foot ulceration: an extended study using a herbal supplement. *Hnk Kng Med J* 2008; 14: 29–33
91. Bahrami A, Kamali K, Ali-Asgharzadeh A, et al. Clinical applications of oral form of ANGIPARS TM and in combination with topical form as a new treatment for diabetic foot ulcers: a randomized controlled trial. *DARU* 2008; 16(Suppl 1): S41–48
92. Larijani B, Heshmat R, Bahrami A, et al. Effects of intravenous Semelil (ANGI-PARSTM) on diabetic foot ulcers healing: a multicenter clinical trial. *DARU* 2008; 16(Suppl 1): S35–40
93. Marfella R, Sasso FC, Rizzo MR, Paolisso P, Barbieri M, Padovano V, Carbonara O, GualdieroP, Petronella P, Ferraraccio F, Petrella A, Canonico R, Campitiello F, Della Corte A, Paolisso G, Canonico S. Dipeptidyl peptidase 4 inhibition may facilitate healing of chronic foot ulcers in patients with type 2 diabetes. *Experimental Diabetes Research* 2012, Article ID 892706, doi:10.1155/2012/892706
94. Lavery LA, Barnes SA, Keith MS, Seaman JW Jr, Armstrong DG. Prediction of healing for postoperative diabetic foot wounds based on early wound area progression. *Diabetes Care* 31: 26–29, 2008