Chapter 7
Advanced Wound Healing: Neuropathic Foot

Amber R. Morra, Michael I. Gazes, and Peter A. Blume

7.1 Introduction

Approximately 415 million people worldwide have been diagnosed with diabetes. Twenty-five percent of people within this population will potentially develop diabetic foot ulcerations (DFUs). Diabetic neuropathy is the largest precursor to DFUs and increases risk of amputation fifteenfold; which results in approximately 70,000 annual diabetic amputations in the USA [1]. To minimize the risks associated with diabetes and DFUs, multidisciplinary limb salvage teams are necessary to promptly assess and treat patients to improve overall outcomes. Advanced wound healing is a crucial component of the treatment modality. Numerous advanced wound healing therapies exist, ranging from complex biologic dressings, split thickness skin grafts and flaps, stem cells, laser treatments, hyperbaric oxygen therapies, and negative pressure wound therapies (NPWT) [2, 3].

Wound healing consists of three phases: acute inflammatory, proliferative, and maturation. The acute inflammatory phase includes vasoconstriction of arterioles and capillaries, platelet aggregation, and the inflammatory cell cascade. The proliferative phase comprises fibroblastic activity, extracellular matrix reorganization, and angiogenesis [2–4]. Finally, the maturation phase involves the formation of scar tissue in addition to the synthesis and breakdown of collagen. Diabetic wound healing differs from traditional wound healing as DFUs often linger in the inflammatory phase. This delay, along with neuropathy, vasculopathy, infection, and hyperglycemic states seen in DFUs, leads to basement membrane thickening, endothelial proliferation, decreased vessel permeability, and altered cell migration [5]. This further leads to cellular senescence and induces protease enzymes, leading to an

A. R. Morra · M. I. Gazes · P. A. Blume (✉)
Department of Podiatric Surgery, Yale New Haven Hospital, New Haven, CT, USA
e-mail: peter.b@snet.net

© Springer Nature Switzerland AG 2019

M. E. Edmonds, B. E. Sumpio (eds.), *Limb Salvage of the Diabetic Foot*,
https://doi.org/10.1007/978-3-319-17918-6_7

imbalance of matrix metalloproteinases (MMPs) to tissue inhibitors of metalloproteinases (TIMPs) [6–10]. As a result of this process, DFUs can take significantly longer periods of time to heal and often require specialized treatment options.

7.2 Collagen Modalities

One of the most popular and effective advanced treatment options for DFUs used today are collagen-based modalities. Collagen is the major protein in the extracellular matrix. Sustainable extracellular scaffolds are compromised in DFUs. Treatment with collagen based modalities provide a structural scaffold matrix to support extracellular components, increases fibroblast proliferation, mediates cell migration and organization, and inhibits excessive MMPs [10–12].

Apligraf (Organogenesis), is one of the most popular collagen based products, that is indicated for "care for the treatment of full-thickness neuropathic DFUs of greater than 3 weeks' duration, which have not adequately responded to conventional ulcer therapy and which extend through the dermis but without tendon, muscle, capsule or bone exposure." [13] The bioengineered living bilayer is derived from neonatal foreskin and placed in a type I bovine collagen matrix, composed of both an epidermal keratinocyte layer and a dermal fibroblast layer [3, 10]. The dermoinductive product functions by delivering the growth factors and matrix that are flawed in DFUs. Kirsner et al. evaluated Apligraf on 163 DFUs from 155 patients with an average wound area of 6.0 ± 5.5 cm^2 and wound duration of 4.4 ± 2.6 months. The study reported 70% improvement in wound closure in 12 weeks and found DFUs treated with Apligraf increased the probability of healing by 97% in comparison to dehydrated amniotic membranes [14].

Another bioengineered dermoinductive product for DFUs is Dermagraft (Organogenesis), a cryopreserved human fibroblast-derived dermal substitute. The combination of fibroblasts, extracellular collagen matrix and a bioabsorbable polyglactin mesh scaffold function to stimulate epithelialization. Dermagraft differs from Apligraf in that it is approved for full thickness DFUs present for over 6 weeks, which extend through the dermis but do not involve tendon, muscle, joint capsule or bone [10, 13, 15–17]. Marston et al. examined Dermagraft versus conventional therapy (wet to dry dressing) in 245 patients with chronic DFUs. They concluded that treatment with Dermagraft produced a significantly greater proportion (30%) of fully healed ulcers in comparison to the control group (18%). The Dermagraft group also had median percent wound closure of 91% by week 12 in comparison to 78% in the control group [18].

Integra Bilayer Wound Matrix (Integra LifeSciences) is a dermoconductive collagen-based modality for DFU. The epidermal layer is composed of a semipermeable thin silicone layer and the dermal layer is composed of cross-linked bovine type I collagen with glycosaminoglycan and shark chondroitin-6-sulfate. The composition of Integra is unique in that it allows the epidermal layer to

regulate moisture, while maintaining graft flexibility and resisting infection. The dermal layer thus functions to provide a scaffold for cellular invasion and growth [10, 17, 19, 20].

Omnigraft Dermal Regeneration Matrix (Integra LifeSciences), also known as Integra Dermal Regeneration Template, is FDA approved to treat "diabetic foot ulcers that exist for longer than 6 weeks and do not involve exposure of the joint capsule, tendon or bone, when used in conjunction with standard diabetic ulcer care" [21]. Driver et al. evaluated Integra Dermal Regeneration Template for DFUs with a two-phase study consisting of 307 patients with a minimum of one DFU. The first phase of the study was a 14-day period with patients receiving 0.9% sodium chloride gel with a secondary dressing and standard offloading. After the initial 14 days, the patients with less than 30% re-epithelialization entered into the second phase, which was randomized with a control group treated with 0.9% sodium chloride gel and a treatment group treated with Integra bilayer graft. The study concluded that after the 16-week follow-up, patients who received the Integra graft had a significantly greater complete closure rate (51%) versus the control group (32%). The mean time to closure in the treatment group was 43 days versus 78 days for the control group and weekly wound reduction size was 7.2% for the treatment group versus 4.8% for the control group [22].

Graftjacket Regenerative Tissue Matrix (Wright Medical) is another dermoconductive option composed of cadaveric collagen-based fenestrated allograft [3]. The acellular dermal scaffold is comprised of collagen, elastin, hyaluronan, fibronectin and blood vessel channels. Graftjacket Xpress (Wright Medical), functions similarly to Graftjacket Regenerative Tissue Matrix; however, it differs as it is an injectable soft tissue scaffold, suitable for use in wounds that have undermining, tunneling, or irregular shapes [10, 20, 23].

Protease inhibitor dressings are also useful advanced treatment options for DFUs. Promogran (Systagenix) is a hexagonal graft that is 55% collagen and 45% oxidized regenerated cellulose. The product binds and inactivates MMPs and elastases within the wound bed in addition to helping release positive growth factors. Promogran Prisma (Systagenix) is a version of Promogran that reduces bacterial growth with the addition of 1% silver [10, 24, 25]. Lobmann et al. studied the effects of Promogran on 33 patients with DFUs. After an 8-day treatment period, three separate tissue biopsies were obtained to analyze protease levels. The study demonstrated that Promogran treatment provided greater reduction in wound diameter in comparison to the control group (16%) and a significant decrease in the MMP-9/TIMP-2 ratio, likely due to MMPs binding to collagen matrix [26].

In addition to collagen-based dressings, other products add alginate to increase wound healing potential by absorbing excessive wound moisture and exudates. Fibracol Plus (Systagenix) which is composed of 90% collagen and 10% alginate functions as an autolytic debridement to achieve formation of granulation tissue [3, 10]. Donaghue et al. performed a randomized control study comparing Fibracol to saline-moistened gauze in 75 patients with DFUs.

The study concluded that the mean percent reduction in wound area was 80.6% in the Fibracol cohort (48% with complete healing) and 61.1% (36% with complete healing) in the control group [27].

Collagen dressings derived from human amniotic membrane are also effective ways to treat DFUs. PuraPly (Organogenesis) is a purified collagen matrix with a polyhexamethylene biguanide hydrochloride (PHMB) antimicrobial agent. PHMB is an added feature that provides broad antimicrobial coverage and reduction of bacterial loads within the wound with high tissue compatibility [28]. Preclinical studies using Puraply on methicillin- resistant *Staphyloccis aures* (MRSA) inoculated wounds revealed a statistically significant reduction in MRSA levels, 47%, at 72 h when compared to other current wound treatments utilizing silver technology [29].

Autogenous split thickness skin grafting for wound coverage has been an effective surgical option and treatment modality for decades. Theraskin (Soluble Systems) is an advanced wound care product that is similar to split thickness skin grafts (STSG) without the donor site risks. TheraSkin is a split-thickness human collagen allograft containing both epidermis and dermis, which is harvested within 24 h post-mortem and cryopreserved to sustain living cellular components. The graft contains 12 growth factors, 16 key cytokines, and 14 types of collagen (primarily I, III, IV). A study by DiDomenico et al. compared 12 wounds treated with TheraSkin to 17 wounds treated by Apligraf, resulting in a higher closure rate with the TheraSkin treatment group. The study also concluded that Theraskin had at least twice the amount of type I, III and IV collagen per unit area when compared to Apligraf and Dermagraft [30].

7.3 Hyperbaric Oxygen Therapy

Grafting has proven effective in overall wound treatments. Nonetheless, other treatment styles exist for DFUs. Hyperbaric oxygen therapy (HBOT) is one such therapy utilized for decades and well documented for advanced treatment of DFUs. HBOT works by exposing the patient to 100% oxygen at two to three times the normal atmospheric pressure, which increases the saturation of oxygen in the blood (up to 20 fold) to promote wound healing. More specifically, this process decreases hypoxia and edema to improve tissue perfusion, which promotes fibroblast and collagen proliferation and angiogenesis [31]. These features allow HBOT to promote an "ideal" wound healing environment, even in the uncontrolled diabetic population. Current randomized double blind study by Löndahl et al. revealed 52% (25/48) of diabetics with chronic (>3 months) Wagner grade 2, 3 or 4 ulcers had complete healing at 1 year follow-up when treated with HBOT for 85 min 5 days a week for 8 weeks, when compared to 29% healing in a placebo group [32].

7.4 Low Level Laser Therapy

Low level laser therapy (LLLT) as a therapeutic tool in the medical field has demonstrated numerous benefits, including its treatment with DFUs. While the exact mechanism of how LLLT works is still under investigation, it is widely believed that it functions to stimulate cell activation and enhance wound healing by increasing the proliferation and synthesis of collagen via activation of fibroblasts and keratinocyte motility [33, 34]. Although the power, duration, and frequency of treatment depends on wound characteristics, most DFUs are treated with 2–10 J/cm^2 at 50–60 mW daily, for upwards of 20 weeks. A recent study by Kajagar et al. looked at the use of LLLT for DFU in 68 patients for 15 days at 60 mW, and concluded that the cohort of wounds treated with LLLT contracted significantly more than the wounds in the non-treatment group (40.24% versus 11.87%); concluding that LLLT may be an effective option or adjunct in the treatment of DFU [35].

7.5 Ultrasonic Debridement

Advanced wound debridement techniques are another form of enhancing wound healing. Low frequency ultrasonic debridement instruments can be used in both the clinical and surgical setting. By precisely delivering sterile saline at frequencies between 20 and 40 kHz, these systems, such as MIST Ultrasound Healing Therapy (Alliqua BioMedical), Misonix, and Versajet (Smith & Nephew) all function to help remove necrosis, debris, biofilm, reduce MMPs, and increase angiogenesis while preserving healthy and vital structures [36–38]. More specifically, these devices do so using acoustic streaming, or mechanical force via saline, to revert chronic wounds into acute wounds via the theory of cavitation and dynamic reciprocity [39]. After the enhanced debridement modality is utilized, an advanced collagen based product, STSG, or biological dressing is often applied to the DFU to increase wound healing potential (Fig. 7.1).

7.6 Electrical Stimulation

Another advanced wound healing treatment that accelerates wound healing is electrical stimulation (ES). ES can be delivered to wounds in the form of direct current, alternating current, or pulsed current. ES emulates the natural electrical current that occurs when skin is naturally injured. This process promotes the proliferative stage of wound healing by decreasing the doubling time of fibroblast and endothelial cells, while increasing mitogen-activated protein kinase activation. Clinically, this

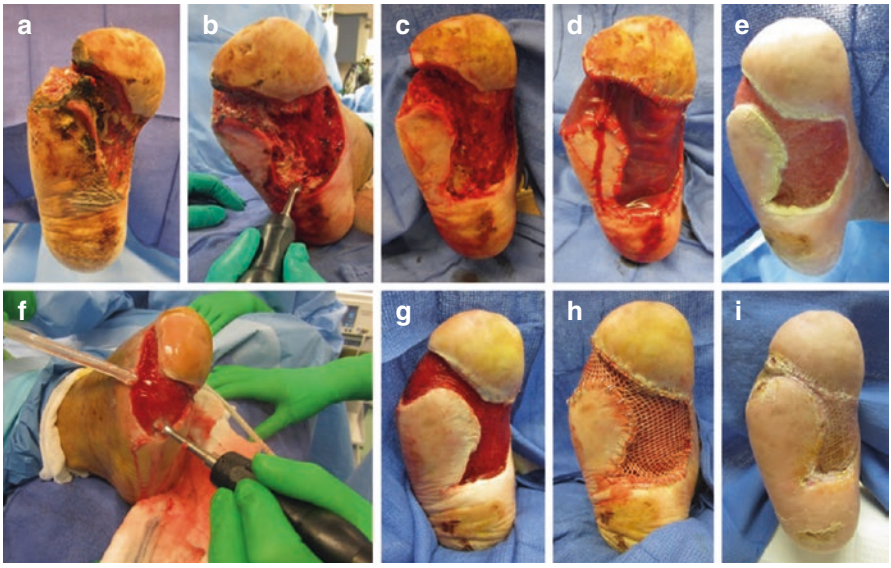

Fig. 7.1 (**a**) Right foot wound post infection debridement, (**b**, **c**) initial ultrasonic debridement staged procedure, (**d**) application of collagen allograft skin substitute, (**e**) appearance of foot after allograft take, pre-ultrasonic debridement in staged procedure for STSG application, (**f**, **g**) ultrasonic debridement and wound appearance, (**h**) application of STSG, (**i**) wound closure

is beneficial as it increases the cascade of neutrophils and macrophages and stimulates fibroblasts [40, 41]. ES has been shown to decrease bacterial load and increase transcutaneous oxygen levels. A randomized double-blinded placebo-controlled study by Peters in 2001 evaluated 40 patients with DFUs treated via ES. The study concluded that ES increased wound healing by 65% and wound area reduction by 86% (as compared to a control group) when treated by ES for 8 h nightly at 50 V for 12 weeks [41].

7.7 Negative Pressure Wound Therapy

Negative pressure wound therapy (NPWT) delivered by vacuum assisted closure (VAC) therapy is a unique treatment system that offers reliable results when used appropriately. The VAC device has been an effective tool in simplifying wound care and creating more manageable wounds. It utilizes a uniform subatmospheric pressure on the wound bed to increase local blood perfusion, stimulate angiogenesis, and increase granulation tissue and cellular proliferation, while decreasing bacterial levels [42–44]. This process then allows the wound to be closed primarily, skin grafted, or to be suitable for advanced biological dressings. The VAC system is beneficial in treating acute, chronic and complex wounds [25, 40]. A multicenter randomized controlled trial for comparison of NPWT utilizing VAC to advanced

moist wound therapy (AMWT) in the treatment of DFUs demonstrated a greater proportion of foot ulcers achieving complete ulcer closure with NPWT (73/169, 43.2%) than AMWT (48/166, 28.9%) within the 112-day active treatment phase ($p = 0.007$). In assessing safety, no significant difference between the treatment and control groups was observed in relation to infection, cellulitis, and osteomyelitis within a 6-month period. NPWT appears to be as safe as, and more efficacious, than AMWT for the treatment of diabetic foot ulcers [44]. Another study analyzing VAC versus bolster dressing for securing skin grafts demonstrated that VAC group had improved wound healing, increased graft survival, required significantly fewer repeated splint thickness skin grafts (3% versus 9%), and decreased hospital stay (Fig. 7.2) [45].

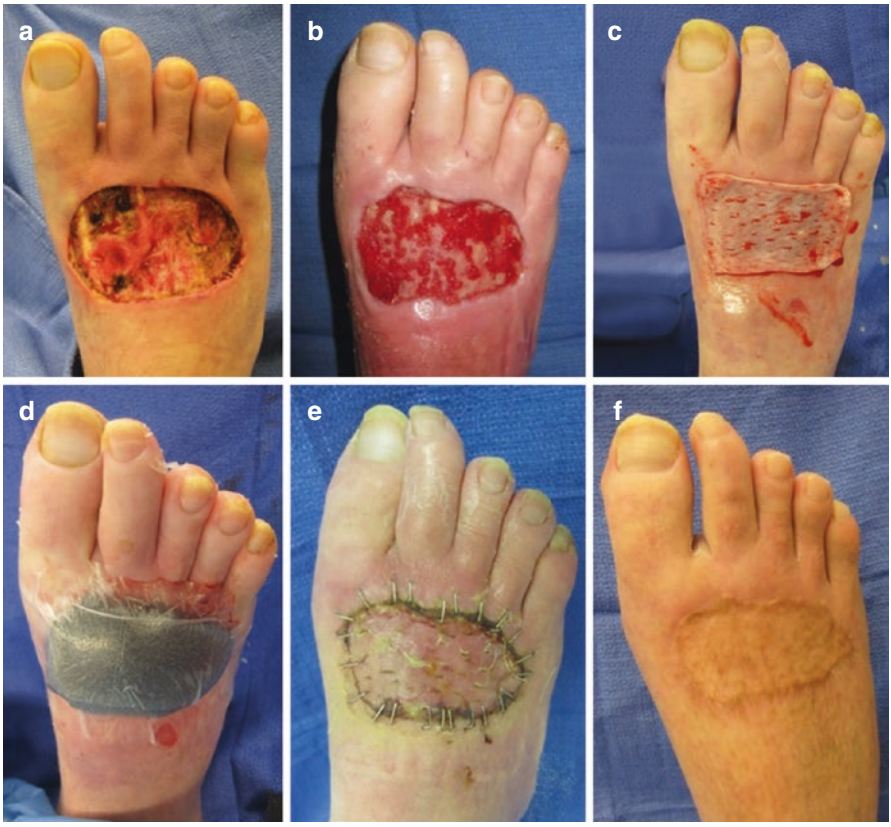

Fig. 7.2 Dorsal right foot wound treated with debridement, STSG application, and wound VAC therapy. (**a**) Dorsal right foot wound, (**b**) post debridement, (**c**) application of autologous STSG, (**d**) wound VAC application to site, (**e**) healing period, (**f**) completion of wound closure

7.8 Stem Cell Therapy

A newer treatment modality being utilized for the treatment of DFUs is stem cell therapy. Stem cells offer an alternative treatment aimed at increasing revascularization to reduce limb ischemia and promote wound healing. Generally, there are two types of stem cells: embryonic and adult. Embryonic stem cell have proliferative capacity and low differentiation maturity; while adult stem cells vary in the ability to differentiate based on tissue origin [46]. Current use of stem cells for DFUs include intramuscular and intraarterial injections, topical application, and grafts. While the use the stem cells is a fairly new concept, preliminary results appear promising [47]. Albehairy and colleagues demonstrated that patients with diabetes receiving autologous mesenchymal stem cell (MSC) injections around DFU borders had a significantly higher reduction in ulcer size at both 6 and 12 week follow-ups when compared to a control group. The results were 49.9% versus 7.67% at 6 weeks and 68.24% versus 5.27% at 12 weeks. The initial ulcer size for the MSC group in this study was larger than the ulcer size of the control group. This study shows that stem cells are a promising option for healing DFUs where standard treatments had limited effect [48].

7.9 Conclusion

In situations with recalcitrant wounds, advanced wound healing options are available and have demonstrated effective results. The associated morbidity and mortality in patients with these wounds are staggering; however, with appropriate treatment, wound healing and limb salvage can potentially be achieved. In this population, various comorbities, especially in deformities, vascular status, and neuropathy cause increasingly difficult wounds, leading to the need for initiation of advanced wound healing treatment plans. Without these treatment modalities, the risk of infection, complications, and potential loss of limb or life quickly escalates. Advanced wound healing options for DFUs are emerging and evolving regularly. However, while the array of advanced wound healing options for DFUs is plentiful, patient specific needs can always guide therapy. It is important to utilize evidence based medicine and effective treatment algorithms for the most predictable results. While all advanced wound healing modalities are unique and have individual guidelines, risks, and benefits, the underlying goal consistently remains to heal the wounds, prevent new ulcerations, reduce amputations, decrease mortality, and preserve both limb and quality of life.

References

1. International Diabetes Foundation Diabetes Atlas, Sixth Edition. https://www.idf.org/sites/default/files/EN_6E_Atlas_Full_0.pdf.
2. Snyder RJ, Kirsner RS, Warriner RA 3rd, Lavery LA, Hanft JR, Sheehan P. Consensus recommendations on advancing the standard of care for treating neuropathic foot ulcers in patients with diabetes. Ostomy Wound Manage. 2010;56(4 Suppl):S1–S24.

3. Garwood C, Steinberg J, Kim P. Bioengineered alternative tissues in diabetic wound healing. Clin Podiatr Med Surg. 2015;32(1):121–33.
4. Ennis WJ, Lee C, Gellada K, Corbiere TF, Koh TJ. Advanced technologies to improve wound healing. Plast Reconstr Surg. 2016;138:94–104.
5. Albanna M, Holmes J. Skin tissue engineering and regenerative medicine. N.P: Academic; 2016.
6. Brett D. A review of collagen and collagen-based wound dressings. Wounds. 2008;20(12):347–56.
7. Gould LJ. Topical collagen-based biomaterials for chronic wounds: rationale and clinical application. Adv Wound Care. 2016;5(1):19–31.
8. Braun L, Fisk W, Lev-Tov H, Kirsner R, Isseroff R. Diabetic foot ulcer: an evidence-based treatment update. Am J Clin Dermatol. 2014;15(3):267–81.
9. Margolis DJ, Kantor J, Berlin JA. Healing of diabetic neuropathic foot ulcers receiving standard treatment: a meta-analysis. Diabetes Care. 1999;22(5):692–5.
10. Gazes M, Morra A, Blume P. Assessing collagen-based modalities for diabetic foot ulcerations. Podiatry Today. 2016;29:50–6.
11. Bakker K, Apelqvist J, Lipsky B, Van Netten J. The 2015 IWGDF guidance documents on prevention and management of foot problems in diabetes: development of an evidence-based global consensus. Diabetes Metab Res Rev. 2016;32(Suppl 1):2–6.
12. Lipsky BA, Berendt AR, Cornia PB, et al. 2012 Infectious Diseases Society of America Clinical Practice Guideline for the Diagnosis and Treatment of Diabetic Foot Infections. Clin Infect Dis. 2012;54(12):132–73.
13. 2015 Biologic Device Application Approvals. http://www.fda.gov/biologicsbloodvaccines/developmentapprovalprocess/bio. Accessed 27 Sept 2016.
14. Kirsner RS, Sabolinski ML, Parsons NB, Skornicki M, Marston WA. Comparative effectiveness of a bioengineered living cellular construct vs. a dehydrated human amniotic membrane allograft for the treatment of diabetic foot ulcers in a real world setting. Wound Repair Regen. 2015;23(5):737–44.
15. Wu L, Norman G, Dumville JC, O'Meara S, Bell-Syer SEM. Dressings for treating foot ulcers in people with diabetes: an overview of systematic reviews. Cochrane Database Syst Rev. 2015;7:CD010741.
16. Reyzelman AM, Bazarov I. Human acellular dermal wound matrix for treatment of DFU: literature review and analysis. J Wound Care. 2015;24(3):128;129–34.
17. Dermagraft®—P000036. http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/DeviceApp. Accessed 14 Feb 2016.
18. Marston W, Hanft J, Norwood P, Pollak R. The efficacy and safety of Dermagraft in improving the healing of chronic diabetic foot ulcers. Results of a prospective randomized trial. Diabetes Care. 2013;26(6):1701–5.
19. Holmes C, Wrobel J, MacEachern M, Boles B. Collagen-based wound dressings for the treatment of diabetes-related foot ulcers: a systematic review. Diabetes Metab Syndr Obes. 2013;6:17–29.
20. Helary C, Abed A, Mosser G, Louedec L, et al. Evaluation of dense collagen matrices as medicated wound dressing for the treatment of cutaneous chronic wounds. Biomater Sci. 2015;3(2):373–82.
21. FDA approves Integra Omnigraft Dermal Regeneration Matrix to treat diabetic foot ulcers. http://www.fda.gov/newsevents/newsroom/pressannouncements/ucm480564.htm. Accessed 27 Sept 2016.
22. Driver V, Lavery L, Reyzelman A, Dutra T. A clinical trial of Integra Template for diabetic foot ulcer treatment. Wound Repair Regen. 2015;23(6):891–900.
23. Cereceres S, Touchet T, Browning M, Smith C, Rivera J, et al. Advances Wound Care. 2015;4(8):444–56.
24. Cullen B, Ivins N. Promogran & promogran prisma made easy. Wounds Int. 2010;1(3):1–6.
25. Schultz GS, Sibbald RG, Falanga V, et al. Wound bed preparation: a systematic approach to wound management. Wound Repair Regen. 2003;11(Suppl 1):1–28.
26. Lobmann R, Zemlin C, Motzkau M, et al. Expression of metalloproteinases and growth factors in diabetic wounds treated with a protease absorbent dressing. J Diabetes Complicat. 2006;20(5):329–35.

27. Donaghue VM, Chrzan JS, Rosenblum BI, Giurini JM, Habershaw GM, Veves A. Evaluation of a collagen-alginate wound dressing in the management of diabetic foot ulcers. Advances Wound Care. 1998;11(3):114–9.
28. Hübner N, Kramer A. Review of the efficacy, safety and clinical applications of polihexanide, a modern wound antiseptic. Skin Pharmacol Physiol. 2010;23(Suppl):17–27.
29. "Scientific data from partial-thickness wound model (Porcine)." *PuraPly Antimicrobial*. Organogenesis, 2016.
30. DiDomenico L, Emch K, Landsman AR, Landsman A. A prospective comparison of diabetic foot ulcers treated with either cryopreserved skin allograft or bioengineered skin substitute. Wounds. 2011;23(7):184–9.
31. Lipsky B, Berendt R. Hyperbaric oxygen therapy for diabetic foot wounds. Diabetes Care. 2010;33(5):1143–5.
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(5):998–1003.
33. Forney R, Mauro T. Using lasers in diabetic wound healing. Diabetes Technol Ther. 1999;1(2):189–92.
34. Hopkins JT, McLoda TA, Seegmiller JG, David Baxter G. Low-level laser therapy facilitates superficial wound healing in humans: a triple-blind, sham-controlled study. J Athl Train. 2004;39(3):223–9.
35. Kajagar BM, Godhi AS, Pandit A, Khatri S. Efficacy of low level laser therapy on wound healing in patients with chronic diabetic foot ulcers—a randomised control trial. Ind J Surg. 2012;74(5):359–63.
36. Kim PJ, Steinberg JS. Wound care: biofilm and its impact on the latest treatment modalities for ulcerations of the diabetic foot. Semin Vasc Surg. 2012;25(2):70–4.
37. Voigt J, Wendelken M, Driver V, Alvarez O. Low frequency ultrasound (20–40kHz) as an adjunctive therapy for chronic wound healing: a systematic review of the literature and meta-analysis of eight randomized control trials. Int J Lower Ext Wounds. 2011;10(4):190–9.
38. Al-Mahfoudh R, Qattan E, Ellenbogen JR, Wilby M, Barrett C, Pigott T. Applications of the ultrasonic bone cutter in spinal surgery—our preliminary experience. Br J Neurosurg. 2014;28(1):56–60.
39. Blume P, Schmidt B. Ultrasonic debridement for wounds: where are we now? Podiatry Today. 2015;28:7.
40. Millington JT, Norris TW. Effective treatment strategies for diabetic foot wounds. J Fam Pract. 2000;49(11):S40–8.
41. 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.
42. Meloni M, Izzo V, Vainieri E, Giurato L, Ruotolo V, Uccioli L. Management of negative pressure wound therapy in the treatment of diabetic foot ulcers. World J Orthop. 2015;6(4):387–93.
43. Kim PJ, Attinger CE, Steinberg JS, Evans KK. Negative pressure wound therapy with instillation: past, present, and future. Surg Technol Int. 2015;26:51–6.
44. Blume PA, Walters J, Payne W, Avala J, Lantis J. Comparison of negative pressure wound therapy utilizing vacuum-assisted closure to advanced moist wound therapy in the treatment of diabetic foot ulcers: a multicenter randomized controlled trial. Diabetes Care. 2008;31:631–6.
45. Scherer LA, Shiver S, Chang M. The vacuum assisted closure device: a method of securing skin grafts and improving graft survival. Arch Surg. 2002;137(8):930–3.
46. Jiang X-Y, Lu D-B, Chen B. Progress in stem cell therapy for the diabetic foot. Diabetes Res Clin Pract. 2012;97(1):43–50.
47. Blumberg SN, Berger A, Hwang L, Pastar I, Warren SM, Chen W. The role of stem cells in the treatment of diabetic foot ulcers. Diabetes Res Clin Pract. 2012;96(1):1–9.
48. Albehairy A, Kyrillos F, Gawish H, State O, Abdelghaffar H, Elbaz O, et al. Autologous mononuclear versus mesenchymal stem cells in healing of recalcitrant neuropathic diabetic foot ulcers. Diabetologia. 2016;59(Suppl 1):S19. Poster 34.