An Overview of Advanced Therapies in the Management of Diabetic Neuropathic Foot Ulcers

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The goal of this document is to provide an overview of the existing literature, review expert opinion and establish protocols for the use of advanced therapies in the treatment and management of diabetic foot ulcers.

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INTRODUCTION

Foot complications in persons with diabetes lead to increased morbidity and mortality. For those with peripheral neuropathy and peripheral artery disease the risk of ulceration and lower-extremity amputation is increased.[1] In Canada, the Council of the Federation's Health Care Innovation Working Group identified diabetic foot ulcers (DFUs) as a critical issue requiring immediate attention.[2]

Diabetic neuropathic foot ulcers are costly to the individual, caregivers and the health-care system[3] and continue to constitute a major challenge. If not managed properly they can lead to loss of limb and are associated with a high five-year mortality rate.[4]

Diabetic foot ulcers are classified as neuropathic, neuro-ischemic or ischemic, making their management complex. And yet, through education, monitoring, multidisciplinary teamwork and timely assessment and management,[5] they are one of the most preventable diabetes-related complications. Healing existing DFUs requires a multidisciplinary team,[6] with the causes of the DFU addressed to identify and remove or mitigate the co-factors interfering with healing (see Figure 1).[7,8]

Figure 1: Diabetic Foot Ulcer Management Using a Multidisciplinary Team Approach

- **Vascular**
- **Infection**
- **Pressure & Neuropathy**

→ **Assess**

- **Wound Care**
- **Debridement**
- **Offloading**

→ **Address local factors**

- **Lower Extremity Vascular Status**
- **Glycemic Control**
- **Treat Infection**

→ **Address systemic factors**

→ **Support self management**

→ **Optimize vascular supply & glycemic control**

→ **Ensure early detection and treatment of infection & pressure redistribution**
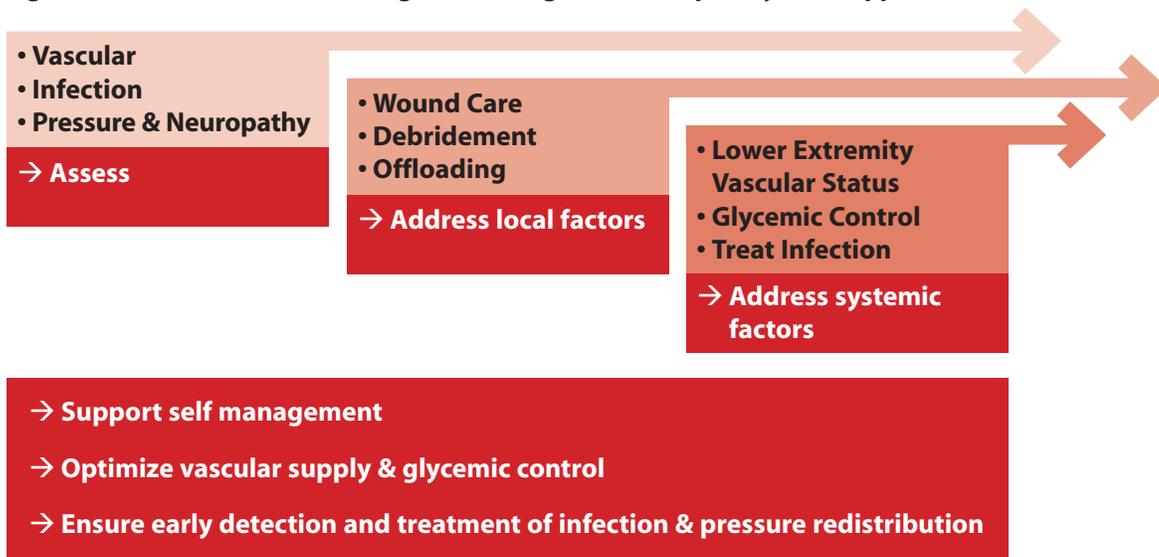
The average costs associated with the healing of a DFU is reported to be as high as $45,000.[9] Research has stated that the global market for advanced wound therapies is expected to grow from $8.6 billion in 2013 to $11.3 billion by 2018. This growth is influenced by the aging and growing global population, as well as by the development of new technologies to address difficult-to-heal wounds.[10] Timely and proper use of advanced therapies can be critical for shortening healing times, which may result in lower overall costs[11,12] when standard wound care options have failed. Therefore, determining the appropriate role of advanced therapies to manage DFUs is essential to ensure cost-effective, patient-focused outcomes.

Unfortunately, the environment in which Canadian health-care professionals practise is variable, depending on location. The different Canadian health-care delivery systems

may or may not have policies and procedures in place to support the clinical use of particular advanced therapies.

As well, a significant consideration for health-care professionals is the differing availability of the therapies in the different jurisdictions. In the U.S. for example, there has been some FDA regulatory approval for the use of some artificial skin grafts with DFUs, while other therapy options have received approval through 510k, meaning they may be covered (paid for) as a dressing.

While major hurdles—including cost and availability—remain, advanced therapies have improved the clinician's toolkit of DFU treatment options. To be successful, these advanced therapies need to be evaluated by policy makers, health-care system providers, interprofessional team members and patients. It is important to note that advanced therapies are not appropriate for every patient. Clinician knowledge, skill and attitude, and client involvement are required to screen, select and prepare appropriate candidates.

While the use of advanced therapies is costly, and at this point the research data to support their use are not strong, studies show that 70% of wounds remain unhealed after 20 weeks of conventional therapy.[13] A study comparing the costs and resource use in persons with DFUs demonstrated that a greater intensity of outpatient visits is associated with a reduction in lower limb amputation, reduction in hospitalizations, inpatient services and overall reduced costs.[12]

Therefore, once usual DFU standard care options are maximized, team consideration of advanced therapies may be a next step. A standard for use of advanced therapies in DFUs has yet to be determined. In the meantime, clinicians need to ensure appropriate patient selection, use of appropriate advanced therapies and the accompanying evidence-based record of outcomes.

To assist the front-line clinician, this document will increase awareness of specific advanced therapies in the management of DFUs and highlight the current evidence on the appropriate use of these modalities.

This DFU advanced therapy discussion includes:

- A review of specific advanced therapies
- A review of randomized controlled trial (RCT) evidence
- A summary of responses from a survey of experts on the use of advance therapies
- A potential advanced therapy framework based on clinical practice guidelines

Methodology

A structured literature search of PubMed and MEDLINE was performed using the keywords *diabetic foot ulcers* and *advanced therapy* alone or in combination with common names of adjunctive therapies (*skin substitutes, negative pressure wound therapy, ultrasound therapy, laser therapy, hyperbaric oxygen therapy, electrical stimulation therapy, advanced dressings* and *growth factors*) for diabetic foot ulcers (see Appendix I for search terms used). Articles were abstracted from January 2000 to May 2014. Additional references were obtained from a search of the Cochrane Library, existing systematic reviews and reference lists of pertinent studies. In searching the Cochrane Library and Embase databases using the same search criteria, no additional relevant articles were retrieved. Abstracts and selected full-article texts were reviewed by an international consultant and a panel of Canadian health-care professionals with clinical and research experience in diabetic foot ulcers.

The evidence-based literature was translated into a structured manuscript composed of evidence tables for each advanced therapy (see Appendix II for the tables). A summary of the evidence was developed and reviewed by the panel.

Clinical practice guidelines that included advanced therapies were also reviewed. This was supplemented by a survey (see Appendix III) sent to 15 wound care clinicians. Eleven replied (see Appendix IV) and identified their actual practices relating to advanced therapies.

Advanced Therapies: Overview and the Evidence
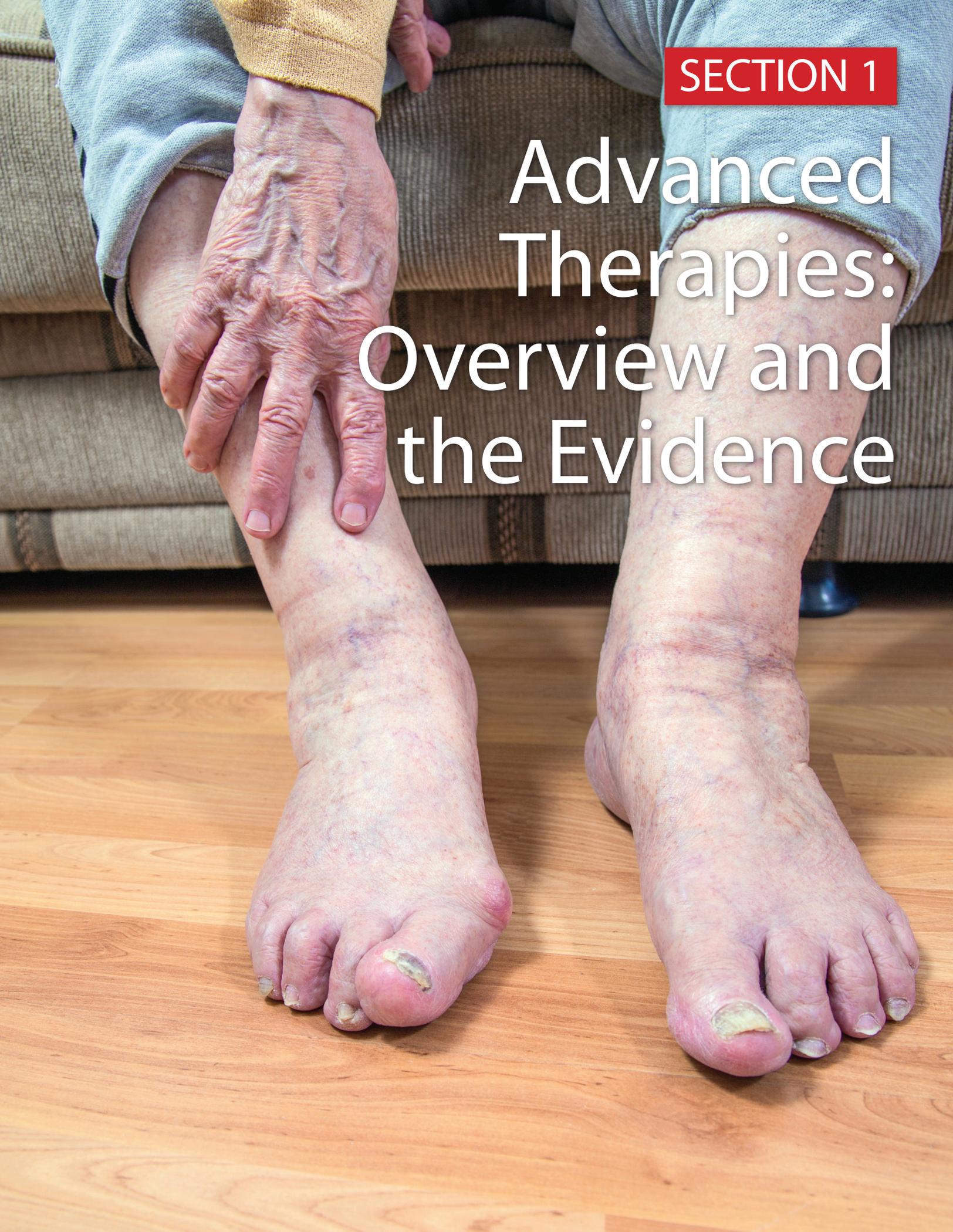
SECTION 1:
ADVANCED THERAPIES: OVERVIEW AND THE EVIDENCE

1. Negative Pressure Wound Therapy (NPWT)

Negative pressure wound therapy (NWPT) has been considered an adjunctive therapy for healable wounds (meaning wounds where the cause has been corrected and there is adequate blood supply) that are stalled and where the exudate is greater than what can be managed with conventional advanced dressing modalities. A review by Ontario Health Technology Advisory Committee suggested the evidence supports this therapy for post-surgical diabetic foot amputations and with the use of split thickness skin grafts.[14]

NPWT delivers sub-atmospheric pressure to a wound bed to promote and accelerate healing. NPWT creates suction that controls undesirable fluid (excess proteases) and promotes healing by influencing the shape and growth of surface tissues.

The removal of excess interstitial fluid using NPWT helps to reduce the intercellular diffusion distance, improving blood flow and augmenting local functional blood perfusion. Removal of excess institial fluid may also reduce the surface bacterial colonization and increase the sequestration of excess MMPs.

RCT Evidence

Fourteen relevant NPWT studies[7,8,12,15–26] were identified for use on DFUs (n = 1346 patients), of which seven were focused on post-amputation wounds (n = 722 patients).

Within the entire study population, nine studies evaluated wound area reduction, seven studied complete wound closure, five evaluated increased healing rates, one evaluated quality of life, four examined amputation rate, one looked at cost and two studied the rate of granulation tissue production.

Of the studies reviewed, four of the eight examined wound area reduction post amputation while the remaining measured other endpoints. Five studies evaluated complete wound closure, three assessed increased healing rates and no study estimated quality of life, two assessed the amputation rate, one analyzed cost and one observed the amount of healthy granulation tissue.

The studies demonstrated that NPWT has been most effective for the immediate post-surgical diabetic foot wound. Use of NPWT on these wounds decreased time to healing and improved rate of complete wound healing. In DFUs in general the cost of NPWT may not compensate for the time saved or rate of complete wound healing. Many of the studies are limited to inpatient care, sponsored by industry, and some have poor methodological quality or study design.

Summary

The majority of NPWT studies with good results were performed on the immediate post-surgical diabetic foot wound. Therefore, it is hard to conclude that the therapy has benefit in all diabetic foot ulcers.

2. Hyperbaric Oxygen Therapy (HBOT)

Adequate tissue oxygen tension is integral to the biologic processes involved in wound healing, and therefore an adequate oxygen supply to wounds may enhance healing. Hyperbaric oxygen therapy (HBOT) involves the administration of 100% oxygen to patients within an airtight vessel at pressures greater than one atmosphere absolute (usually 1.5–3.0 ATA) to promote wound healing and inhibit processes detrimental to wound healing. Typical HBOT sessions involve 45–120 minutes in an oxygen chamber daily for 20–30 sessions. Clinically, HBOT improves transcutaneous pO_2 in certain patients with ischemic ulcers.

Evidence regarding HBOT suggests that increased arterial oxygen tension can up-regulate growth factors and angiogenesis while down-regulating inflammatory cytokines and promoting antibacterial effects. However, a recent systematic review and meta-analysis of the role of HBOT in the management of DFUs concluded that there does not appear to be any benefit from adjunctive HBOT with respect to amputation rates compared with the control for chronic diabetic foot ulcers. This is related to the lack of randomized controlled trials (RCTs) on HBOT.[27,28]

RCT Evidence

Nine studies[29–37] were extracted (n = 616 patients); one study involved a related therapy—ozone therapy—on DFUs (n = 51). Within the entire study population, five studies evaluated decreased wound size, six evaluated complete wound closure, five evaluated increased healing rates, one evaluated quality of life and two focused on amputation rate. None of the studies examined costs or granulation tissue production rate. The ozone therapy study evaluated wound area, wound closure and increased healing rate. Not assessed were quality of life, amputation rate, costs and granulation tissue production rates.

Of the patients identified (n = 616), a general trend of decreased time to healing and increased rate of complete healing were found with the use of HBOT therapy. Based on the available RCTs, HBOT did not decrease the amputation rate or improve long-term health-related quality of life.

Summary

At present, due to limited research, there is insufficient evidence from both systematic reviews and RCTs to determine whether HBOT is effective for the treatment of chronic DFUs.

3. Growth Factors (GFs)

Growth factors (GFs) stimulate the proliferation and growth of cells involved in wound healing and inflammation. They are biologically active peptides acting as cytokines that aid in cell activation during the wound healing process. After binding to specific cell surface receptors that trigger the induction of a complex cascade of signal trans-duction pathways, GFs modulate cellular behaviours. They can act on adjacent cells, on the cell itself or on remote cells.

Platelet-derived Growth Factor (PDGF)

Platelet-derived growth factor (PDGF) is the only growth factor approved by the U.S. Food and Drug Administration (FDA). It is a dimeric protein made of two di-sulfide-linked polypeptide chains. There are three different isoforms of PDGF: heterod-imer PDGF-AB, homodimers PDGF-AA and PDGF-BB (becaplermin). PDGF in a gel form works to stimulate the production of fibronectin and hyaluronic acid and is important to matrix formation as well as the modulation of other growth factor activities in the wound bed.

Platelet Rich Plasma (PRP)

Platelet rich plasma (PRP) is a platelet-enriched blood plasma produced from the patient's own blood. It is therefore a relatively low-risk treatment. PRP can be injected directly into the injured area or as an intramuscular injection. PRP contains growth factors and cytokines that stimulate healing.

Epidermal Growth Factor (EGF)

Epidermal growth factor (EGF) secreted by platelets and macrophages seeks to stim-ulate the proliferation of fibroblasts. When used in a gel-based dressing it may reduce wound healing time when applied topically by directly stimulating the proliferation of epidermal cells.

Basic Fibroblast Growth Factor (bFGF)

Basic fibroblast growth factor (bFGF) is most predominant in early wound repair; bFGF gel dressings can play a role in granulation tissue formation as they increase angio-genesis.

Granulocyte-colony Stimulating Factor (G-CSF)

Granulocyte-colony stimulating factor (G-CSF) gel dressings increase healing by pro-moting proliferation and differentiation of neutrophil progenitors and mature neutro-phils by releasing neutrophils from bone marrow and improving neutrophil functions.

Talactoferrin Alfa

Talactoferrin alfa is a recombinant form of human lactoferrin. As a new immunomodu-latory protein, it plays an important role in the early inflammatory phase of wound re-pair, as it induces IL-18, which attracts both polymorphonuclear cells and macrophag-

es to the wound site. Additionally, when applied topically (as a gel) on the wound, it induces the production of granulocyte-macrophage colony-stimulating factor, playing a role in wound repair.

Thrombin Peptide (TP508)

Thrombin peptide (TP508) is a 23-amino acid peptide that represents the natural sequence of amino acids of thrombin. When TP508 is introduced into a saline dressing, it can increase healing as it imitates part of the thrombin response. However, unlike thrombin, TP508 has no enzymatic activity and does not promote or interfere with blood coagulation. Most studies on TP508 involve animal populations, with the exception of a very few recent studies.

Keratinocyte Growth Factor (KGF)

Topically applied keratinocyte growth factor (KGF) promotes the growth of keratinocytes, which secrete keratin. Keratinocytes are present during the epithelialization phase of wound healing, where they form the epithelium, covering the wound.

RCT Evidence

Fifteen relevant studies[38–52] were found (n = 820 patients); however two studies did not reveal their population size, as they were abstracts only. Of the 15 studies reviewed, specific treatments included PDGF (four studies), PRP (three studies), bFGF (one study), G-CSF (two studies), human EGF (two studies), talactoferin alfa (one study), thrombin peptide (TP508) (one study) and keratinocytes (one study). Outcomes measured included seven studies evaluating wound area, four examining complete wound closure, 10 healing rate, two amputation rate, two costs and one wound granulation rate. None evaluated quality of life.

Summary

With regard to complete healing, studies have revealed that growth factors are only successful in conjunction with adequate wound bed preparation (sufficient blood supply for healing, infection control, pressure offloading and active surgical debride-

ment). Overall, the adjunctive use of growth factors resulted in faster healing rates and a higher proportion of completely closed wounds compared with other treatments. Moreover, cost varies between the products available. PDGF, however, is superior to HBOT in complete healing of DFUs.

It is essential to state that the mean duration of follow-up is limited, and no data exist on the longevity of the healed wound. Note that these studies followed patients for six to 12 weeks only. Longevity of the healed ulcer is essential for the consideration of advanced therapies as part of health-care system cost-effective reimbursement. This same statement also applies to all of the advanced therapies reviewed in this document.

4. Artificial Skin Grafts

Artificial skin grafts are biologic substitutes or synthetic skin equivalents that mimic certain normal skin functions. Ideal functions of biosynthetic skin substitutes include rapid and lasting wound surface adherence, moisture vapour transmission, resistance to friction and shear stresses, prevention of bacterial proliferation, containment of low antigenicity and lack of local and systemic toxicity.

Artificial skin grafts accelerate healing rates by restoring biochemical balance and a moist wound environment as well as acting as structural support for tissue regeneration and the provision of cytokines and growth factors. Autogenous and non-autogenous skin grafts have been used for the healing of DFUs in recent years. There are several types:

- A porcine-derived acellular small intestine submucosa consisting of a collagen-based extra cellular matrix or scaffold that includes glycosaminoglycan, fibronectin and growth factors. It functions to support and accommodate cell proliferation.

- A matrix obtained from human skin, from which the epidermis and dermal cells have been removed and a 3D scaffold has been preserved for tissue regeneration. After application, it is repopulated with the patient's cells and remodeled into functional host tissue, thereby containing natural biological components.

- Cultured neonatal fibroblasts from neonatal foreskin embedded in polyglactin or polyglycolic acid bioabsorbable mesh. The keratinocyte stem cells do not carry the HLA-DR epidermal cells, which results in the reduced potential of allograft rejection due to the lack of surface antigens. As the fibroblasts proliferate, collagen, glycosaminoglycan, fibronectin, ECM proteins and growth factors are produced and play a role in augmenting blood flow by approximately 70%.

- A living-skin construct derived from neonatal foreskin composed of keratinocytes that constitute an epidermis and a lattice of type I bovine collagen containing fibroblasts that constitute a dermal matrix. The epidermal layer creates a natural barrier to protect against mechanical injury while stimulating wound healing.

- An engineered autograft made from epidermal tissue. There is currently very little information on the role of engineered autografts in wound healing.

RCT Evidence

Ten relevant studies[12,53–61] were found (n = 1111 patients). Six studies evaluated wound area reduction, eight observed complete wound closure, eight observed healing rate and no studies evaluated quality of life, amputations, cost or granulation rate. None of these studies included post-amputation DFU wounds.

Summary

Overall, all of the studies revealed a faster healing rate and more completely healed wounds than the control groups. Engineered autografts demonstrated a good prediction of better weekly percentage reduction than the control group. While the study involving a "wound matrix" had a high drop-out rate, it was found to be comparable to PDGF, with no significant differences between time to complete closure or wound healing rate.

5. Collagen-based Dressings

A number of different collagen dressings derived from purified bovine, porcine, equine or avian sources are available. The collagen is purified, making it non-antigenic. It is introduced into a variety of carriers/combining agents such as gels, pastes, polymers, oxidized regenerated cellulose (ORC) and ethylene diamine tetra-acetic acid (EDTA). Collagen-based dressings produce a variety of effects designed to aid in wound healing, particularly in patients with diabetes who have a marked decrease in the ability to synthesize collagen. Collagen-based dressings modulate protease activity, reducing matrix metalloproteinase (MMP) activity.[62]

Some of these dressings have been shown to: produce an increase in fibroblast production; have a hydrophilic property that may be important in encouraging fibroblast permeation; enhance the deposition of oriented, organized collagen fibres by attracting fibroblasts and causing a directed migration of cells; aid in the uptake and bioavailability of fibronectin; help preserve leukocytes, macrophages, fibroblasts and epithelial cells; assist in the maintenance of the chemical and thermostatic microenvironment of the wound.[63]

A combination of collagen and oxidized regenerated cellulose provides another topical wound dressing. This combination has been shown to be effective when EPA is present by enhancing wound healing through the inhibition of proteolytic activity while allowing continued growth factor activity.[64,65,66]

RCT Evidence

Six studies[67–72] were found on collagen-based dressings (n = 566 patients). No studies involved post-amputation DFUs. Overall, three studies reported on wound area reduction, six evaluated complete wound closure and one evaluated healing rate. None examined quality of life, amputations, costs or granulation rate.

Summary

Of the studies reviewed, the collagen studies had mixed outcomes. One of the collagen studies (with a high drop-out rate) reported no significant difference between collagen and control groups in time to closure, while the other had a wound closure reduction in favour of collagen. Two studies revealed more wounds reaching complete closure with collagen, as well as a faster healing time when using collagen. Results of

the two studies on protease modulating matrix indicated it worked best for ulcers of less than six months' duration and for Wagner's grade 1 and 2 ulcers. More complete wound closure and greater ulcer reduction were found with the use of the protease modulating matrix.

6. Physical Therapies

Laser Therapy

The premise behind low-energy light treatments is that light stimulates cell activation, thereby intensifying healing processes. Low-energy laser therapy delivers energy of less than 10 J/cm^2 at powers of 50 mW or less. Various types of lasers exist for treatment, including crystalline, semiconductor, liquid and gas.

It is understood that laser therapy may stimulate protein synthesis as well as fibroblast and macrophage proliferation to aid in wound healing. Furthermore, it generates reactive oxygen species, which help in activating and controlling transcription factors, gene expression, fibroblast proliferation and cell growth.

Electrotherapy (including electrical stimulation)

Electrotherapy is the application of an electrical current that transfers energy directly through a wound or on the skin in close proximity to a wound. Electrotherapy generates an inward trans epithelial potential of sodium ions through the membrane sodium-potassium pump. It maximizes the naturally occurring low-resistance healing pathway flowing laterally to centrally in the wound.

The electrical current generated by electrical stimulation (ES) works to modify cell membrane permeability and transport, thereby stimulating DNA synthesis and enhancing cellular secretion, as well as increasing adenosine triphosphate production

and reorganizing the collagen matrix to attract cells of repair, or galvanotaxis. ES mimics and enhances the natural current of injury to accelerate wound healing. ES is contraindicated in the presence of malignancy, osteomyelitis, implanted electrical devices and topical substances containing metallic ions or in locations over the heart.

ES has been shown to promote fracture healing, enhance migration of fibroblasts, have an antibacterial effect and increase blood flow to the wound area. There is currently very little information to describe the effect of electrical stimulation on wound healing in the diabetic foot.

External Shock Wave Therapy (ESWT)

External shock wave therapy (ESWT) consists of shock waves targeted directly to the wound area to speed healing, with procedures lasting less than 30 minutes. ESWT is contraindicated for patients with pacemakers or with certain medications, for children or pregnant women. Side effects include pain, bruising, reddening and swelling of the area, although these dissipate after a short time.

ESWT promotes the generation of new connective tissue, has an analgesic effect for pain reduction and facilitates blood flow to the area.

Low-frequency Ultrasound through Saline Mist Therapy

This therapy involves the delivery of low-frequency ultrasound to the wound through a saline mist. It works to accelerate the healing process by removing barriers to healing, such as bacteria, inflammation, MMP-9 and by disrupting biofilm. It also causes vasodilation and angiogenesis and promotes growth factor release and collagen accumulation.

RCT Evidence

For all physical therapies, six studies[73–78] were found, with an overall population of 220 patients. Four studies evaluated wound area reduction, four evaluated wound closure and four studied increased healing rate. None of the studies observed quality of life, amputation rate, cost or granulation rate.

Summary

A greater wound area reduction was accomplished with laser therapy. Treatment with ES did not cause a significant difference in wound size and volume compared with local heat therapy alone, but did appear to have a superior effect after one month of treatment. ESWT resulted in faster healing and more completely healed wounds, and while more wounds completely healed with electric stimulation, there was no difference in the rate of healing from placebo groups. Low-frequency ultrasound through saline mist therapy resulted in a significantly higher proportion of healed wounds than placebo. However, the data for most of these therapies are limited and not sufficiently robust to support their routine clinical use.

7. Other Therapies

The De Marco Formula (DMF) is a "procaine chemical combination of Procaine HCI and polyvinylpyrrolidone."[79]

RCT Evidence

Two studies[79,80] (n = 165) evaluated DMF with infected ischemic DFUs (52 days).

Summary

Patients who showed favorable responses to treatment had statistically lower fibrinogen concentrations than those with unfavorable responses within the DMF group. There were fewer amputations with the DMF plus standard treatment groups vs. the standard treatment group alone. Further research is needed for this advanced therapy.

Summary of Expert Panel Opinions

SECTION 2:
SUMMARY OF EXPERT PANEL OPINIONS

In light of the limited RCT evidence available for the advanced therapies listed above, a survey was sent to a group of wound experts (see Appendix IV) to identify what advanced therapies for diabetic foot ulcers they had used or were currently using. Survey questions (see Appendix III) revolved around their belief about the strength of evidence to support this use and the identification of gaps/barriers to care. They were also asked to present any recommendations for the use of advanced therapies. The respondents were an interprofessional group with experience in diabetic foot management ranging from two to 34 years. The manuscript was also circulated to them for further input.

Table 1: Survey Summaries

The table summarizes the opinions of the expert panel about the strength of evidence to support the use of each type of advanced therapy outlined above and their recommendations for use.

Negative Wound Pressure Therapy	Nine panel members stated they had used NPWT in the management of diabetic foot ulcers. Overall, the experts felt that NPWT had the strongest evidence, especially when used in post-surgical wounds.
Hyperbaric Oxygen Therapy	Seven experts acknowledged that they had referred to or used HBOT with their patients.
Growth Factors	Six respondents had experience with growth factors, primarily PDGF.
Artificial Skin Graft	Seven experts had experience with artificial skin.
Collagen-based Dressings	Eight experts had experience with collagen-based dressings.
Physical Therapies	Half of the experts' surveys stated they had used physical therapies or referred patients to physical therapy for specific advanced therapies.

An overwhelming response to the role of advanced therapies in practice was that it is clearly an adjunct to primary strategies such as pressure offloading, infection control and improving vascular status. One expert stated, "no therapy is more effective than optimal pressure offloading." In addition, one stated, "advanced therapy may be considered as an adjunct to pressure relief, and not a replacement for common sense and good care."

The respondents' opinion about the level of evidence of the RCTs reviewed for advanced therapies varied. The comments ranged from: "Evidence is marginal or non-existent" to "evidence is quite extensive."

Regarding the specific evidence currently available, it is summarized by the comment indicating that there is "some decent evidence for HBOT and some good evidence for UV light therapy. NPWT has good evidence for acute wounds."

Some experts identified an issue with the integrity of the available studies. One respondent stated that "the evidence is limited and commonly biased; most of the studies are funded by industry and there is a possibility that negative results are not published." Yet, another that stated, there is "a level of evidence for a lot of the therapies, but cost and availability outside formalized studies are often prohibitive."

"No therapy is more effective than optimal pressure offloading."
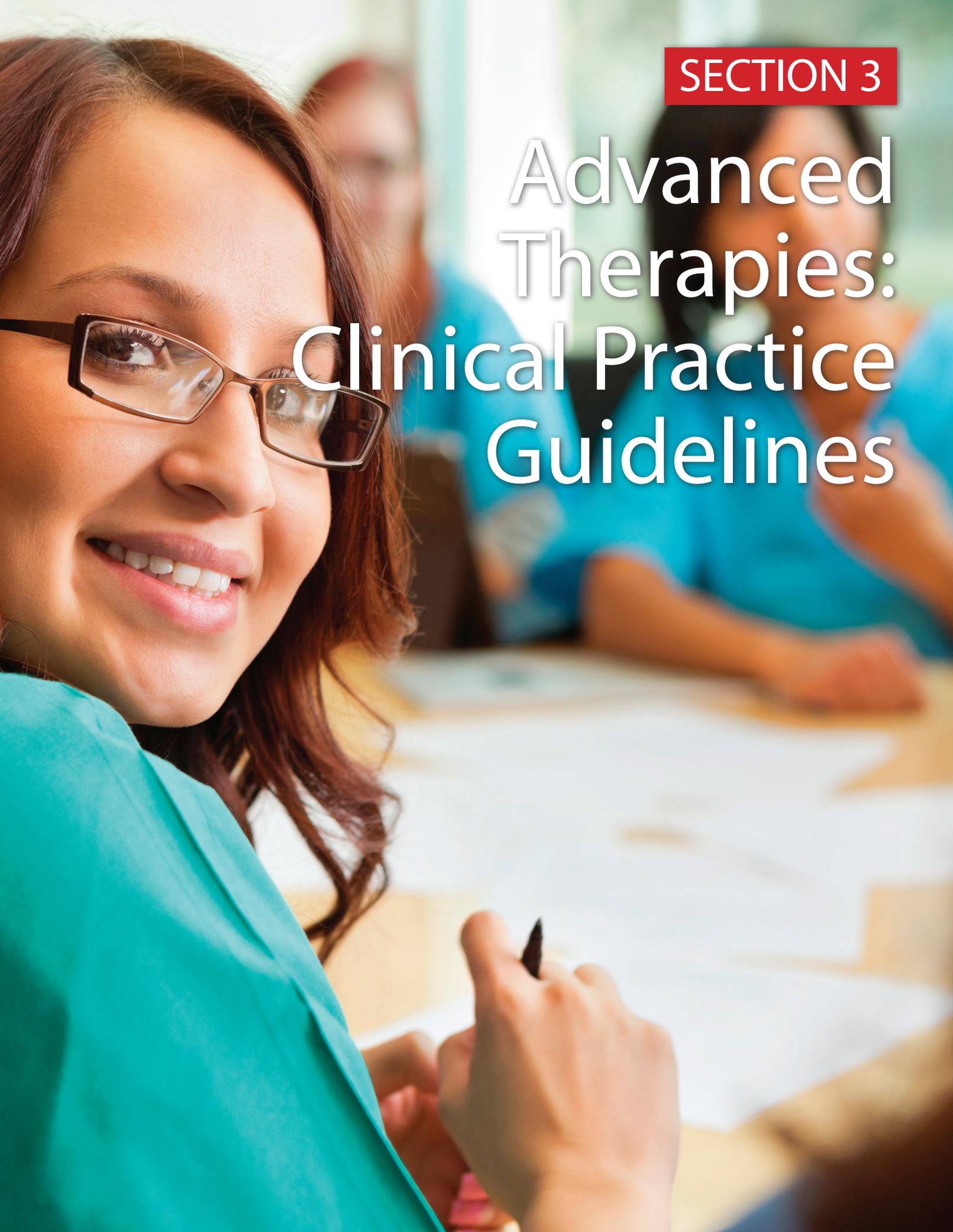
Advanced Therapies: Clinical Practice Guidelines

SECTION 3:
ADVANCED THERAPIES: CLINICAL PRACTICE GUIDELINES

In light of the varied opinions from the experts and limitations of the RCT evidence supporting the use of advanced therapies in the management of diabetic foot ulcers, the clinician may find some assistance from published clinical practice guidelines (CPGs).

Field and Lohr state that CPGs provide "systematically developed statements to assist practitioner and patient decisions about appropriate health care for specific clinical circumstances."[81]

The following CPGs discuss the use of advanced wound therapies specific to diabetic foot ulcer management. Note that the phrase *adjunctive therapies* is sometimes used instead of *advanced therapies.*

Canadian Diabetes Association 2013 Clinical Practice Guidelines for the Prevention and Management of Diabetes in Canada[1] states that evidence is currently lacking to support the routine use of adjunctive wound-healing therapies such as topical growth factors, granulocyte colony-stimulating factors, dermal substitutes or HBOT in diabetic foot ulcers. It further states that they may be considered in healable, non-ischemic stalled wounds when all other options have been exhausted.

The International Working Group on the Diabetic Foot Practical Guidelines on the Management and Prevention of the Diabetic Foot 2011[5] states, under "principles of ulcer treatment," that mechanical offloading is the cornerstone of ulcer management and that optimal diabetes control and local wound care are required. In the section on "local wound care" the document does identify NPWT as a consideration in post-operative wounds. The following treatments are not established as routine management: "biological active products (collagen, growth factors, bio-engineered tissue) in neuropathic ulcers, systematic hyperbaric oxygen treatment, silver or other anti-microbial agents containing dressings."

International Best Practice Guidelines: Wound Management in Diabetic Foot Ulcers[6] identifies that adjunctive treatments such as negative pressure wound therapy (NPWT), biological dressings, bioengineered skin equivalents, hyperbaric oxygen therapy, platelet-rich plasma and growth factors may be considered if appropriate. It goes on to state that these techniques require advanced clinical decision-making skills.

Registered Nurses' Association of Ontario's (RNAO) Assessment and Management of Foot Ulcers for People with Diabetes Clinical Practice Guideline[82] states that, from a wound healing perspective, a secondary analysis of data from a prospective, randomized controlled trial by Marston and the Dermagraft Diabetic Foot Ulcer Study Group (2006) found that people treated with a human fibroblast-derived dermal substitute had better wound healing rates when A1c levels were controlled or reduced over a 12-week period. Similarly, in a retrospective cohort study by Markuson et al. (2009), patients with higher A1c levels did experience wound healing, but over a significantly longer period than those with lower A1c.

> "There is some… evidence for HBOT and some good evidence for UV light therapy. NPWT has good evidence for acute wounds."

Barriers to the Delivery of Advanced Therapies
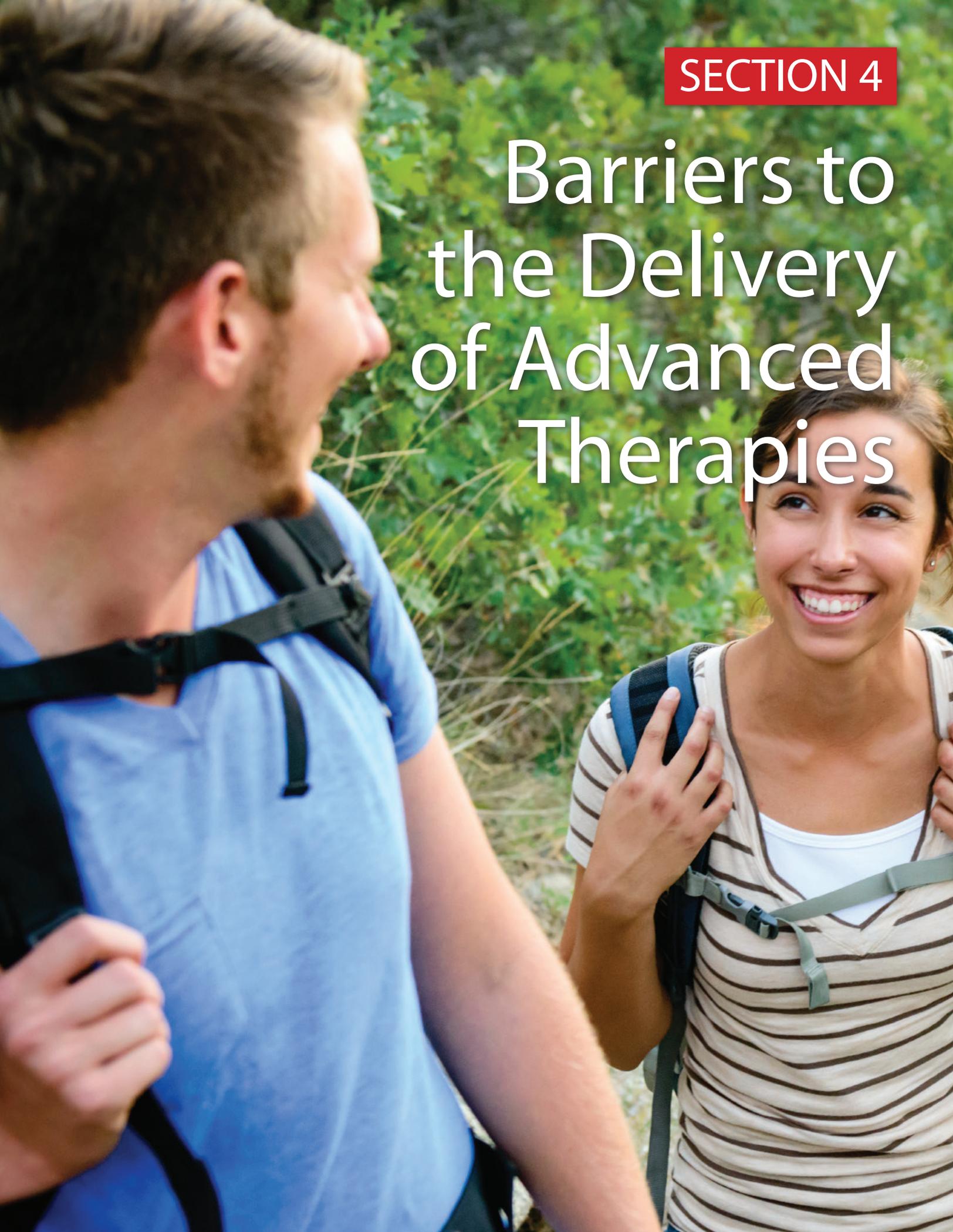
SECTION 4:
BARRIERS TO THE DELIVERY OF ADVANCED THERAPIES

While it may be difficult to translate the existing RCT evidence, expert opinion and clinical practice guidelines relating to advanced therapies into everyday practice, more research may lead to advanced therapies playing a more frequent and appropriate role in clinical practice.[83]

Multidisciplinary teams (clinicians, managers, industry, patients, and researchers) must advocate for more research to address system and clinician factors, patient-centred concerns and technological issues. Barriers to care must be addressed by the health-care professional, depending on the particular context in which they practise.

Listed below are a number of factors to consider and barriers to address, along with recommendations the health-care team can implement now:

Systemic factors:

Barriers

- Research

  - Policies for the funding of therapies often focus mainly on RCTs. It is important to note that other types of wound research is also meaningful and should be considered.

  - Knowledge translation research often identifies gaps in clinician knowledge or the ability of the health-care system to deliver care to the appropriate patient. For example, the existing evidence does not fully explore holistic patient-focused concerns and barriers to care when using advanced therapies.

- Access to care

  - Patient access to advanced therapies varies depending on a number of factors, including:

    - the types of products available in their health jurisdiction

    - the availability of teams or specialists

    - how long patients must wait for an appointment

    - how far they must travel to receive care

    - personal finances and/or coverage by private insurance

- Communication
    - Lack of communication between diabetes education centres and wound care clinicians
    - Lack of interprofessional teams, communication between team members

Recommendations

- Research can be improved by:
    - Additional and varied types of research to help address the factors that currently form the systemic barriers to the use of advanced therapies for DFUs
    - New diagnostic tools to support the indications of advanced therapies
- Care and communication can be improved by:
    - Development of and access to interprofessional teams
    - Organizational policies and procedures that support advanced therapy use
    - Effective education of patients and caregivers
    - Effective education for clinicians related to standard wound prevention and care along with the appropriate use of advanced therapies
    - Widespread availability of preventative footwear and offloading devices with no or low fees
    - Formalized communication between diabetes education centres and wound care teams
    - DFU prevention through education with patients, families, and communities

All clinicians should advocate in their health regions provincially, territorially and nationally for improved support for the prevention and treatment of DFUs.

Patient-centred factors:

Patient-centred concerns are paramount when working collaboratively to fully support patients at risk for diabetic foot complications.

Barriers

- Inadequate focus on prevention of DFUs
- Ineffective patient education
- Lack of care plan adherence
- Lack of awareness regarding the impact of social determinants of health, which may prevent patients from accessing footwear and insulin syringes, medications, healthy foods or achieving appropriate diabetic control with a reasonable A1c

Recommendations

- Focus on prevention. Prevention of the initial DFU is paramount; communities of practice must evaluate their present DFU prevention programs and critically examine if prevention strategies and education are consistently offered to clients and their families.

- Improve patient education and instruction on daily foot care to prevent DFUs and amputation.[3] Individualized foot education should be offered at every opportunity to empower the patient living with a DFU or at risk for a DFU.

- Treat the direct causes of DFUs.[84]

- Treat the underlying disease processes. Ensure adequate blood supply and optimize local wound care, including consistent wound bed preparation, debridement, management of bacterial control and careful moisture balance.[6]

- Create care plans in partnership with the patient, family and caregivers

- Establish multidisciplinary teams to provide comprehensive, holistic assessments to support patients; team members should represent nursing, rehabilitation, social work, medicine, chiropody/podiatry, pedorthy, dietary, education and peer-led education.

- Screen regularly for depression, as depression is linked to the patient's ability to learn new information and participate in care planning and care decisions. Provide access to psychological support.[85]
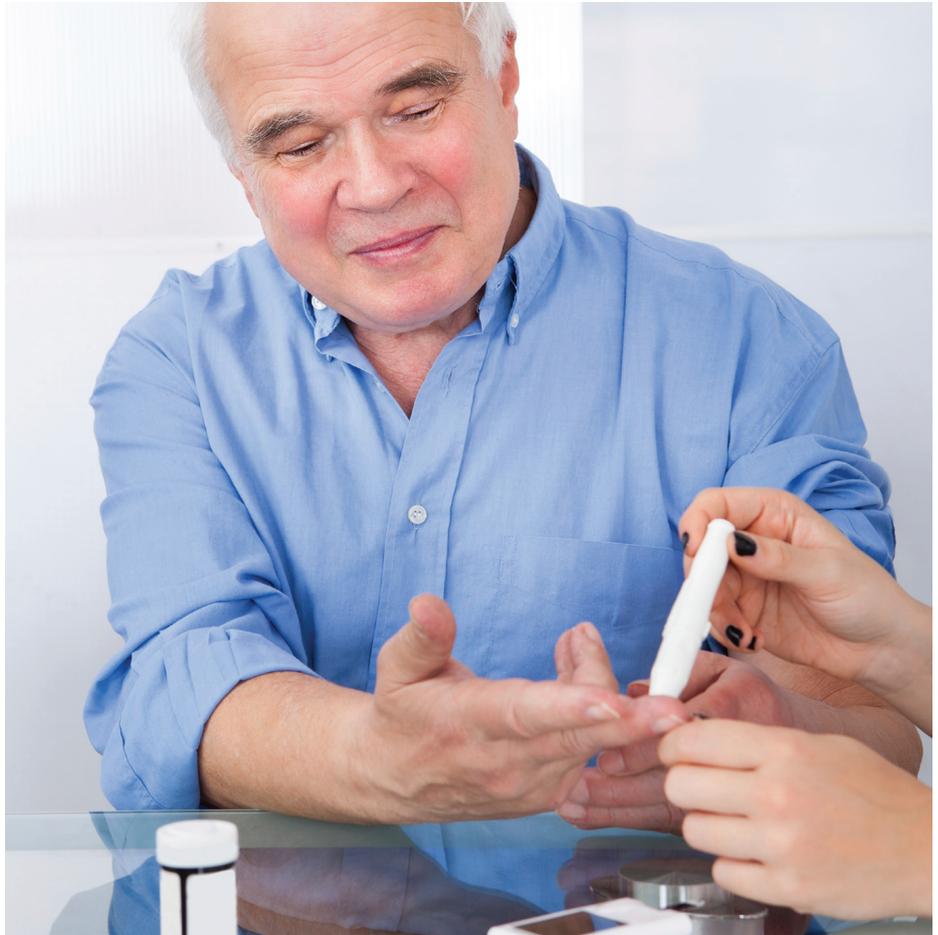
Clinician factors:

Barriers

- Inappropriate patient selection and preparation (removal of risks)

- Inadequate product knowledge by the user, both in how the product works and whether it is available in their health-care jurisdiction

- Lack of interprofessional teams in all settings

The Impact of Social Determinants of Health on DFUs

Food security, housing, income, community and social supports all affect one's risk of experiencing DM or cardiovascular disease[86] and must be addressed. Ross, Gilmour, and Dasgupta, in a 14-year diabetes review,[87] report that prevalence of type 2 diabetes mellitus has been strongly patterned by socioeconomic status, particularly among women. This is partially mediated by overweight/obesity and Aboriginal or South/South East Asian ethno-cultural background.

For patients who already have a foot ulcer, the impact low socio-economic status has on their ability to manage the DUF is significant. Not all patients are able to afford nutritious food, appropriate preventative footwear or offloading devices, or pay for medications and diabetes-related wound care supplies not covered by provincial or territorial health-care programs.[88]

Recommendations

For clinicians to successfully follow and adhere to DFU best practices, a number of elements must be in place:

- Timely and relevant DFU education should be offered regularly to team members.

- Interprofessional teams, in which team members collaborate, communicate and co-operate—with the patient and family remaining the focus—should be the standard model. Stressing the importance of a team approach, one panel expert stated that to help reduce the confusion around the use of advanced therapies a "collaborative effort to address wound problems" would be a benefit.

- Equipment, tools and technology need to be readily available to assist with diagnosis, treatment, and care planning.

- Clinician education on equipment, tools, and technologies should be available.

Technological factors:

Barrier

- Emerging bedside diagnostic tools are not yet in widespread use, even though they can help facilitate the appropriate use of technology, thus avoiding inappropriate application of the advanced therapies at a very high cost to the health-care system.

Recommendation

- Technology is a fast-growing area that should be monitored by clinicians interested in adding to their decision-making toolkits.

Next Steps

SECTION 5:
NEXT STEPS

The general consensus among published research is that the decision to use advanced therapies must be guided by experienced wound care clinicians, patients, health-care systems, resource availability and the latest evidence. Yet the survey responses collected from the experts generally expected to guide the use of advanced therapies presented a wide range of opinions in this document. Additionally, a standard has yet to be determined to ensure appropriate patient selection, use of any particular advanced therapy and an evidence-based record of its success.

To address these limitations, we propose the protocol below, which has been based on a review of the RCT evidence, the CPGs and expert recommendations. It is intended to serve as a guide for clinicians on the appropriate use of advanced therapies in practice, as well as for the collection of future evidence toward validating the use of the advanced therapies. A reformatted version of this protocol appears as an enabler in Appendix V.

"There is a level of evidence for a lot of the therapies, but cost and availability outside formalized studies are often prohibitive."

Advanced Therapies Protocol for Diabetic Foot Ulcers

1. Select a patient for advanced therapy only if best practice management (including offloading to reduce plantar pressures, blood glucose management, arterial perfusion and infection control, a mental health and wellness assessment, available family and social supports in place and funding of therapy) has been implemented and wound bed preparation has been addressed to reduce or eliminate impediments to DFU healing.

2. Identify the primary and secondary goals of care (or outcomes) such as wound healing, wound closure, pain management, exudate management, quality of life improvement and/or cost-effectiveness.

3. Plan the length of use (time) of the advanced therapy, and ensure it is part of the assessment, treatment and evaluation processes.

4. Choose an appropriate advanced therapy, based on product description, evidence, availability, funding, available resources, clinician education and patient acceptance.

5. Develop a patient-centred management protocol based on the location and availability of resources and services.

6. Communicate the plan. Communication includes care plan, including the length of time of product use, regular reports, images and photos as needed (evidence).

7. Instruct clinicians, caregivers and patients on the management protocol and provide follow-up information, including written and/or verbal communication to the care team.

8. Initiate the management protocol, ensuring there are built-in standardized assessment parameters to measure progress toward the identified goals of care.

9. Evaluate the impact of the management protocol to identify met and unmet goals of care.

10. Reassess the management plan at least every 2–4 weeks—more often if required—to avoid long-term use of advance therapies with no evidence of improvement.

11. Document results.

12. Publish the findings if possible and applicable.

By following a standardized protocol, variability can be min-imized, allowing treatment outcomes (based on goals of care) to be assessed and compared. This will contribute to the much-needed evidence base required to support the appropri-ate use of advanced therapies.

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APPENDIX I

Internet Search Terms

PubMed was searched with the filters "2000–2014,""RCT,""human" and the following keywords:

- "negative pressure wound therapy" and "diabetic foot ulcer" – found 14 journal articles

- "VAC" and "diabetic foot ulcer" – 5 journal articles retrieved

- "hyperbaric oxygen therapy" and "diabetic foot ulcer" – 19 journal articles

- "ozone oxygen therapy" and "diabetic foot ulcer" – 1 article

- "ozone oxygen" and "diabetic foot ulcer" – 7 articles, 2 of which were related to this study

- "physical therapies" and "diabetic foot ulcer" – 15 articles

- "electric stimulation,""electrical stimulation" and "diabetic foot ulcer" – 3 articles

- "laser" and "diabetic foot ulcer" – 13 articles, 4 were related

- "laser therapy" and "diabetic foot ulcer" – 12 articles, 4 were related

- "low level laser therapy" and "diabetic foot ulcer" or "diabetic foot" – 2 articles

- "electrostimulation" and "diabetic foot" – 3 related articles

- "growth factors" and "diabetic foot ulcer" – 27 articles

- "pdgf" and "diabetic foot ulcer" – 1 article

- "platelet derived growth factor" and "diabetic foot" – 8 articles

- "prp" and "diabetic foot" – 2 articles

- "platelet rich plasma" and "diabetic foot" – 5 articles

- "Regranex" or "becaplermin" and "diabetic foot" – 7 articles

- "Becaplermin gel" and "diabetic foot" – 4 articles

- "basic fibroblast growth factor" and "diabetic foot" – 2 articles, 1 related

- "human epidermal growth factor" and "diabetic foot" – 6 articles

- "granulocyte colony-stimulating factor" and "diabetic foot"

- "artificial skin graft" and "diabetic foot" – 2 articles

- "artificial skin" and "diabetic foot" – 10 articles

- "skin graft" and "diabetic foot" – 9 articles

- "Dermagraft" and "diabetic foot" – 3 articles

- "Apligraf" and "diabetic foot" – 3 articles

- "OASIS" and "diabetic foot" – 2 articles

- "GraftJacket" and "diabetic foot" – 2 articles

- "collagen" and "diabetic foot" – 15 articles
- "Promogran" and "diabetic foot" – 3 articles
- "Ultrasound" and "diabetic foot" – 8 articles, 4 related
- "biobrane" and "diabetic foot" – 1 systematic review on various advanced therapies
- "colactive" and "diabetic foot" – 0 articles
- "stratagraft" and "diabetic foot" – 0 articles
- "ez graft" and "diabetic foot" – 0 articles
- "Orcel" and "diabetic foot" – 0 articles
- "Transyte" and "diabetic foot" – 1 article, not related
- "de marco" and "diabetic foot" – 2 articles

APPENDIX II

Summary of Evidence

Negative Pressure Wound Therapy (NPWT)

Treatment	Study	Year	Sample Size	Wound Type	Control	S1	S2	S3	S4	S5	S6	S7	Comments
NPWT	Etoz, et al.[15] Turkey Funding: None reported	2004	n = 24 Inpatient Study duration: Until nearly total granulation tissue coverage	DFU	Standard medical aspirator system vs. saline moistened gauze dressings	✓						✓	During the first week, an increase in granulation tissue formation and a decrease in nonviable tissue were seen with NPWT. Edema in extremities decreased in all patients, and wound surface area decreased. Mean length of treatment was shorter in NPWT group (p = 0.05). After therapy, wound surface area decreased more in the NPWT group than control group (p = 0.032), with a significant difference in rates of decrease. After NPWT or control therapy, 19/24 patients had split-thickness skin grafting, and 4 needed transposition of regional fasciocutaneous flaps for wound closure. 1 patient required wound closure by distal pedicled fasciocutaneous flap. In the control group, 3 patients had regional distal pedicled fasciocutaneous flaps as 2 sural flaps and one saphenous flap.
VAC with two different foam dressings	Lavery, et al.[16] United States Funding: None reported	2014	n = 40 Outpatient Study duration: 4 weeks	Post-surgical DFU	125 mmHg pressure with polyurethane foam dressing vs. 75 mmHg pressure with a silicone-coated dressing	✓	✓	✓					Wound area reduction was the same in both groups. No differences were observed in: The number of wounds closed surgically (50% in 75 mmHg group, 60% in 125 mmHg group), Wounds that showed 50% wound area reduction (65% in 75 mmHg group, 80% in 125 mmHg group) Wounds that showed 50% wound volume reduction after 4 weeks of therapy (95% of 75 mmHg group vs. 90% 125 mmHg group). VAC with two different foam dressings PU vs. silicone and 2 and different pressures 125 vs. 75 demonstrated no difference in outcomes.
VAC vs. SNaP vs. DFU and VLU	Armstrong, et al.[17] United States Funding: Spiracur, Inc.	2012	n = 132 Outpatient Study duration: 16 weeks	DFU VLU (with or without diabetes)	VAC vs. Smart Negative Pressure Wound Care System (SNaP)	✓	✓						There was no significant difference found in the number of subjects healed over time (p = 0.9620). The decrease in wound area was also the same between both groups (p = 0.004) Side effects were the same in both groups. This suggests that the effect of SNaP was not significantly different than VAC in promoting complete wound closure in the population studied. VAC vs. SNaP vs. DFU and VLU – no difference Patients receiving SNaP device treatment reported fewer interruptions of activities of daily living, less impact on overall activity, less sleep interruption, less noise level and improved wearability, as well as fewer impacts on social situations compared to VAC patients.

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VAC	Karatepe, et al.[18] (Abstract) Istanbul, Turkey Funding: None reported	2011	n = 67 Study duration: Unknown	DFU	VAC vs. standard treatment			✓					VAC was found to be an effective treatment of DFUs. Significant QOL improvement was observed compared to standard treatment. Healing time was significantly reduced in the VAC group (p < 0.05), and all 8 domains of SF-36 questionnaire and Mental Component Summary (MCS) and Physical Component Summary (PCS) had improved remarkably after VAC therapy. Complete healing of DFU was better with VAC vs. standard therapy, with improved quality of life.
VAC	Ulusal, et al.[19] Turkey Funding: None reported	2011	n = 35 Inpatient Study duration:	DFU (Wagner Gr 3 and 4)	VAC vs. standard debridement dressings	✓							VAC dressing was changed every 2 days. Patients had an average of 15 treatment sessions. 20 patients were treated with standard debridement with an average of 59 days of hospitalization length. VAC therapy group had an average stay of 32 days. VAC resulted in more limb salvage. Limb salvage rate with standard debridement was 0%, compared to 63% of wound healing without loss of extremity in VAC group. One patient had an operated calcaneus fracture, and the wound was closed with a free gracilis muscle flap and skin graft. In total, 10 patients (50%) in the standard debridement group received major amputations, and 10 patients (50%) received minor amputations. 2 patients (12%) in the VAC group received major amputations, and 4 (25%) received minor amputations. This study demonstrated fewer amputations and better healing with NPWT.
VAC	Sepulveda, et al.[20] Chile Funding: None reported	2009	n = 24 Inpatient Study duration: Until 90% granulation reached	Post-amputation DFU	VAC vs. gel hydrocolloid, tulle and bandage (if saturation rate < 50%) OR alginate and a bandage (if saturation rate >50%)			✓				✓	NPWT was prepared with a polyurethane ether foam dressing, a Nelaton catheter, transparent adhesive drape and continuous negative pressure of 100 mmHg. The average granulation time was lower in NPWT group. Specifically, NPWT reduces the granulation time of diabetic foot amputation wounds by 40%, compared to standard wound dressings. According to Texas classification, 23 subjects (98%) were classified as grade 2 for depth, and one was grade 3. 50% of patients underwent a transmetatarsal amputation. A statistically significant reduction in healing time was found using NPWT (p = 0.007). Surrogate endpoint of 90% showed statistically faster healing with the VAC.

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VAC	Apelqvist, et al.[21] Sweden Funding: KCI	2008	n = 162 Inpatient Study duration: 16 weeks	Diabetic patients with partial foot amputation wounds up to trans-meta-tarsal level	VAC vs. standard moist wound therapy (MWT)		✓						More wounds healed with VAC than MWT (p = 0.040) Secondary measures: No difference was observed between the two groups for in-patient hospital stay (number of admissions or length of stay) or antibiotic usage. Average number of dressing changes was 118.0 (range 12–226) for MWT vs. 42 (range 6–140) in NPWT group (p = 0.0001). Patients receiving MWT had more dressing changes (average of 118), versus the VAC group (41), as well as more surgical procedures (including debridement) (p < 0.001). All major amputations occurred in the MWT group. More outpatient visits were observed in the MWT group (11, range 0–106) vs. the VAC group (4, range 0–47) p = 0.044). Average cost per patient was higher in the MWT group ($36,096) vs. the VAC group ($27,270), a cost difference of $8826. Average cost to total healing was $38,806 for the MWT group and $25,954 for the VAC group, a cost difference of $12,852. Costs for antibiotics were 30% vs. 15% of total cost in the MWT and VAC patients, respectively. Including all patients in the cost analysis, the incremental cost difference was $9915 (NPWT $26,972 vs. MWT $36,887). Of those patients completing 8 weeks of treatment, the average weekly total cost was $4835 for MWT (range $238–$130,791) vs. $3338 for VAC patients (range $480–$36,673). Treatment with VAC resulted in lower resource utilization and greater wound healing at a lower cost than standard care. Although the cost for the VAC vs. standard treatment on a weekly basis was lower for NPWT, both treatments were very costly for inpatient use. Suggest outpatient care would be less costly with both treatments

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VAC	Lavery, et al.[22] United States Funding: Costs of publication were defrayed in part by the payment of page charges	2008	n = 162 Outpatient Study duration: 16 weeks	Diabetic partial foot amputees	VAC vs. standard moist wound therapy (MWT)	✓	✓						Study observed wound healing based on percentage of wound area reduction (PWAR). PWAR at 4 weeks was predictive of complete wound healing at 16 weeks. Wounds treated with VAC needed to achieve a 7% reduction in wound area at 1 week to achieve a 50% probability of healing by 16 weeks. Comparatively, patients treated with MWT needed to achieve a 37.5% reduction in wound area at 1 week to achieve the same 50% probability of healing at 16 weeks. The observed mean 1-week PWAR change in the VAC group was 18.9%, which was associated with a 60% probability of healing. Comparatively, the observed mean 1-week PWAR in the MWT group was only 9.9%, which was associated with a much lower (39%) probability of healing by 16 weeks. Observed mean 4-week PWAR change in the VAC group was 46%, which was associated with a lower probability of healing (34%) by 16 weeks. VAC-treated patients were about 2.5 times more likely to have a PWAR of 15% at 1 week, compared to those receiving standard MWT. MWT patients who experienced a 15% reduction in wound area at 1 week had a 41% probability of healing. Results showed that patients, who achieved a 60% reduction at 4 weeks had a 71% probability of healing compared to MWT patients who had the same wound area reduction at 4 weeks, but only had a 51% probability of healing. Patients receiving VAC were 2.5 times more likely to have both a 15% PWAR at 1 week and a 60% area reduction at 1 month compared to patients receiving standard moist wound therapy.
VAC	Blume, et al.[7] United States Funding: KCI, U.S.	2008	n = 342 Outpatient Study duration: 9 months	DFU (Gr 2 or 3 – Wagner's) cacaneal, dorsal or plantar DFU ≥2 cm² after debridement	VAC vs. Advanced moist wound therapy (AMWT)		✓	✓					Trial evaluated treatment until day 112 or ulcer closure. Those whose wounds had ulcer closure were followed at 3 and 9 months. VAC had a statistically significant complete ulcer closure (p = 0.007) vs. AMWT. For patients completing the ATP (active treatment phase), more VAC-treated patients achieved ulcer closure (60.8% vs. 40%). Kaplan-Meier median time to complete ulcer closure was 96 days for NPWT (p = 0.001) vs. AMPT patients whose median time could not be estimated. Duration of therapy for NPWT was 63.6 +/− 36.57 days vs. 78.1 +/− 39.29 days for AMWT. Kaplan-Meier median estimates for 75% ulcer closure were 58 days for NPWT and 84 days for AMWT. Estimates for 76–100% granulation tissue formation were 56 days for NPWT vs. 114 days for AMWT (p = 0.022). Time to closure was better in NPWT group (p = 0.001). NPWT was associated with significantly fewer amputations (p = 0.035) vs. AMWT patients. No significant differences were observed in all other categories.
VAC	Akbari et al.[8] Zahedan, Iran Funding: Unfunded at the time of manuscript preparation	2007	n = 18 Outpatient Study duration: 3 weeks (12 sessions)	DFU (Gr 2 – Texas)	VAC + standard treatment vs. standard treatment	✓							Mean foot ulcer surface area decreased from 46.88 +/− 9.28 mm² to 35.09 +/− 4.09 mm² in the treatment group vs. 46.62 +/− 10.03 mm² to 42.89 +/− 8.1 mm in the control group. The mean foot ulcer area decreased further in the experimental group than in the control group (p = 0.03). Authors concluded that VAC enhances diabetic foot ulcer healing when used in conjunction with standard treatment (p = 0.024). Standard treatment = debridement, blood glucose control agents, systemic antibiotics, wound cleaning with normal saline, offloading, daily wound dressings VAC improved 3-week healing, but is this cost effective?

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VAC	Armstrong, et al.[23] United States Funding: None reported	2007	n = 162 Outpatient Study duration: 16 weeks	Post amputation of acute and chronic DFU	VAC vs. standard treatment		✓	✓					Increased healing rates were observed in acute (p = 0.030) and chronic (p = 0.033) wounds. No significant difference in achieving complete wound closure was observed between the groups, however VAC treatment resulted in faster healing rates in acute and chronic wounds. Superior results were observed overall with VAC treatment (although statistically insignificant).
VAC	Armstrong, et al.[24] United States Funding: KCI, U.S.	2005	n = 162 Outpatient Study duration: 16 weeks	Post-amputation DFU (Gr 2, 3 – University of Texas) to trans meta-tarsal level	VAC vs. standard treatment	✓	✓					✓	VAC therapy resulted in better outcomes in all areas. An increased healing rate in favour of VAC was found (p = 0.005), as well as an increased rate of granulation tissue formation, also in favour of VAC (p = 0.002). All patients in the trial received offloading therapy. There were a significantly higher amount of acute wounds (75.3%) than chronic wounds (24.7%) evaluated (p < 0.001). No significant difference was found: For those patients achieving complete wound closure, between proportion of acute and chronic (p = 0.716) In time to complete closure between acute and chronic wounds (p = 0.979) Between the proportion of acute and chronic wounds achieving complete closure between VAC and SWT groups (acute p = 0.072, chronic p = 0.320) In proportion of patients who achieved 76–100% wound granulation in patients with acute vs. chronic wounds (60% with acute vs. 100% of chronic). Curves based on time to 76–100% granulation showed a significant difference in acute and chronic wounds (p > 0.001) The number of acute wounds in patients who had 76–100% granulation between NPWT and control (p > 0.264). The outcome was similar for chronic wounds, as all of these wounds were able to reach 76–100% granulation, and proportions were the same for VAC and SWT groups. Time to granulation profiles was significantly in favour of NPWT (p < 0.001) in acute wounds. The log-rank test comparing time-to-event profiles for chronic wounds showed no significance but did seem to be trending in the direction of VAC group (p = 0.090). Chronic wounds were the same between two groups. Log-rank test comparing time-to event profiles was significantly in favour of VAC group in acute and chronic wounds (p = 0.030, p = 0.033 respectively). VAC seems to be a safe and effective treatment for complex diabetic foot wounds and could lead to a higher proportion of healed wounds, faster healing rates and potentially fewer re-amputations than standard care. The rate of healing was the same but time to closure was better in negative pressure (acute – p = 0.030, chronic p = 0.033).

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VAC	Eginton, et al.[25] United States Funding: None provided	2003	n = 6 Inpatient Study duration: 4 weeks	Large DFU	VAC vs. moist gauze dressings	✓							Study started with 10 patients and ended with 6 due to large drop-out rate. 14 dressing changes were analyzed for each dressing type. 12 of these (86%) resulted in a decrease in wound depth, while 11 (78%) resulted in a decrease in wound volume. Moist dressing changes were associated with a decrease in wound depth and volume in 71% and 57% of changes, respectively. Moist dressings were associated with an increase in wound length and width in 57% and 43% respectively, while VAC changes showed an increase in wound length and width in 28% and 21%, respectively. VAC dressings decreased wound volume (59% vs. 0% in moist gauze dressing group) and depth (49% vs. 8%) more effectively than moist gauze dressings. VAC may accelerate closure of DFUs. Wound volume was significantly less in VAC ($p < 0.005$). Wound depth was significantly less in VAC ($p < 0.05$).
VAC	McCallon, et al.[26] (abstract) United States Funding: None reported	2000	n = 10 Study duration: Unknown	Post-operative DFU	VAC vs. saline-moistened gauze	✓		✓					Study observed whether VAC resulted in quicker wound resolution compared to saline-moistened gauze in treating post-operative diabetic foot wounds. Measurements and photos were used to document wound progress. VAC facilitated faster healing rates compared to saline-moistened gauze (22.8 days vs. 42.8 days), as well as decreased wound surface area (28.4% decrease vs. 9.5% were measured).

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Hyperbaric Oxygen Therapy

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HBOT	Ma, et al.[29] China Funding: Subei People's Hospital of Yangzhou University	2013	n = 36 Inpatient Study duration: 2 weeks or 20 sessions	DFU (Wagner Gr 3 or less, > 3 months)	HBOT + standard treatment vs. standard treatment (offloading, wound de-bridement, glucose control)	✓							On day 7, average ulcer size reduction was 12.3% in the control and 15% in the HBOT group. On day 14, average reduction in ulcer area was significantly greater in the HBOT vs. control group (42.4 vs. 18.1%) (p < 0.05). Malondialdehyde (MDA), superoxide dismutase (SOD) and catalase (CAT) all increased in favour of HBOT (P < 0.05). MDA levels were not significantly different between the two groups on day 7 (29.9 pmol/L in HBOT group vs. 34.1 pmol/L in control group). At day 14, there was a statistically significant difference in MDA with 92.6 pmol/mg in HBOT cs. 29.0 pmol/mg in control group (p < 0.05). Western-blot analysis results showed similar expression between HBOT and control group on both day 7 and day 14. On day 7, protein levels of SOD-1 and CAT were not significantly different, but on day 14 HBOT group had an average 16.2 to SOD and 11.9 to CAT vs. 11.9 to SOD and 12.2 to CAT, in the control group (p < 0.05). GPc-1 gene was 0.71 vs. 0.66 at day 7, and 0.98 vs. 1.14 at day 14 (p < 0.05). Authors suggested HBOT treatment for 2 weeks starts a healing response in chronic DFUs, but the observed oxidative stress in local ulcer tissue may offset this effect long term, since it was significantly increased in the HBOT group.
HBOT	Londahl, et al.[30] Sweden Funding: 1. Mrs. Thelma Zoegas Foundation 2. Region Skane Foundation 3. Medical Faculty of Lund University	2011	n = 75 Outpatient Study duration: 8 weeks/40 treatments	DFU	HBOT vs. placebo (hyperbaric air)			✓	✓				Comparing health-related quality of life in healers vs. non-healers, post treatment levels of social functioning and role limitations due to physical and emotional health were significantly higher in the HBOT group. Health-related quality of life at the 12-month follow-up visit was significantly higher than pre-treatment for SF-36 domains role limitations for physical and emotional health and mental health summary scores. This was consistent when comparing baseline and 12-month follow-up in healers of the hyperbaric oxygen group, but not for non-healing patients.
HBOT	Wang, et al.[31] Taiwan Funding: Chang Gung Research Fund (CMRPG880221)	2011	n = 77 (39 ESWT, 38 HBOT) Outpatient Study duration: 6 treatments (ESWT), 20 treatments (HBOT)	DFU	HBOT vs. ex-tracorporeal shock wave therapy (ESWT)	✓	✓						Completely healed ulcers were seen in 57% vs. 25% (p = 0.003), ≤ 50% improved ulcers in 32% and 15% (p = 0.071), and unchanged ulcers in 11% and 60% (p < 0.001), all in favour of ESWT. 27 patients received a second course of treatment due to improved but incomplete healing. Results: • Completely healed ulcers (p = 0.005) • ≤ 50% improved ulcers (p = 0.815) • Unchanged ulcers (p = 0.015)

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HBOT	Londahl, et al.[32] Sweden Funding: 1. Thelma Zoegas Foundation 2. Region Skane Foundation 3. Medical faculty of Lund university	2010	n = 94 Outpatient Study duration: 1 year	DFU (Wagner Gr 2–4, present for > 3 months)	HBOT vs. placebo (hyperbaric air)		✓	✓		✓			All patients received 95-minute sessions (in a multi-place hyperbaric chamber for 85 minutes), 5 days/week for 8 weeks (40 treatments). 57% of patients completed all 40 treatments. Early treatment termination was due to claustrophobia (2 patients) and worsening medical conditions (2 deaths, 2 amputations, 5 hospitalizations). During first-year follow-up, new ulcers developed in 9 patients in the HBOT group and 8 in the control group. In the intention-to-treat analysis, complete healing seen at 1-year follow-up was in favour of the HBOT group (p = 0.03). In the per protocol analysis, complete healing was in favour of the HBOT group (p = 0.009). In a sub analysis of patients completing >35 HBOT sessions, ulcer healing occurred in 23/38 (61%) in the HBOT group, compared to 10/37 (27%) in the placebo group (p value = 0.009). 4 patients (1 in HBOT, 3 in placebo) died during the study. 3 major amputations were done in the HBOT group vs. 1 in the placebo group. Four minor amputations were performed in each group.
* Follow-up from the previous Londahl study	Londahl, et al.[33] Sweden Funding: 1. Mrs. Thelma Zoegas Foundation 2. Faculty of Medicine, Lund University	2011	n = 75 Outpatient Study duration: 9 months	DFU (Wagner Gr 2–4)	TBP (toe blood pressure) vs. ABI (ankle-brachial index) vs. $TcPO_2$ (baseline oximetry) in predicting effect of HBOT		✓						Patients who completed therapy (received at least 36/40 scheduled HBOT/placebo sessions) were included in the study. A statistically significant correlation was seen between TBP and ABI (p = 0.0003), and between basal and stimulated $TcPO_2$ (p < 0.000001), but no significant correlation between TBP or ABI and $TcPO_2$. In HBOT group, basal and stimulated $TcPO_2$ were significantly lower for patients whose ulcer didn't heal vs. those whose ulcers did heal. A statistically significant increased healing frequency was seen at higher $TcPO_2$ levels. No statistically significant relation between the level of TBP or ABI and healing frequency was observed. Basal $TcPO_2$ was significantly related to ulcer healing. Authors suggested HBOT as a feasible adjunctive treatment modality in diabetic patients with chronic non-healing foot ulcers when basal $TcPO_2$ at the dorsum of the foot is above 25 mmHg.
HBOT	Wang, et al.[34] Taiwan Funding: 1. National Science Council (95-2314-B-182A-081) 2. Tissue Regeneration Technologies 3. National Health Research Institute (NHRI-EX96-9423EP)	2009	n = 70 (72 ulcers) Outpatient Study duration: 6 weeks (ESWT), 20 treatments (HBOT)	Chronic DFU	HBOT vs. ESWT (300 + 100/cm² impulses of shockwave at 0.11 mJ/cm²) vs. HBOT	✓							ESWT was evenly applied to ulcer surface once every 2 weeks for a total of 3 treatments in 6 weeks. HBOT involved the administration of 100% oxygen for 25 minutes with a 5-minute break in between for a total of 90 minutes per treatment. Afterward, air pressure was decompressed from 2.5 ATA to 1 ATA within 15 minutes to complete treatment. HBO was performed once a day, 5 times a week for a total of 20 treatments. Both groups showed a bacteriostatic effect, but with insignificant differences between groups. Differences in increases of eNOS, VEGF and PCNA expressions, and decreases of TUNEL expression were statistically significant after treatment (p < 0.05) with ESWT showing significant increases, and decrease of TUNEL vs. insignificant changes in HBOT group (p > 0.05). Significant improvement in local blood flow perfusion scan was seen after ESWT (p = 0.04), but not after HBOT (p = 0.140), a statistically significant difference (p = 0.043). ESWT group: results showed 31% completely healed, 58% improved and 11% unchanged ulcers (p < 0.001). HBOT group: 22% completely healed, 50% improved and 28% unchanged ulcers (p < 0.001).

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HBOT	Duzgun, et al.[35] Turkey Funding: None reported	2008	n = 100 Outpatient Study duration: 92 weeks	Infected DFU	HBOT + standard treatment (ST) vs. standard treatment alone		✓			✓			Statistically significant findings: 0% of patients in the ST group healed without surgery vs. 66% of patients in the HBOT. 100% of those in the ST group needed operative debridement, an amputation or a flap or skin graft vs. 16% of those in the HBOT group who required those treatments. 48% of patients in the ST group had distal amputation (p < 0.05) vs. 34% requiring proximal amputation (p < 0.05). Comparatively, of those in the HBOT group, 8% required distal amputation and 0% required proximal amputation. 0% of patients in the ST group vs. 18% in HBOT group showed no change in wound healing (p < 0.05). Authors suggest HBOT may be useful in healing when other modalities fail. Additionally, it seems to reduce the need for costly and more involved surgical interventions.
HBOT	Kessler, et al.[36] France Funding: Le Centre européen d'étude du Diabète	2003	n = 28 Outpatient Study duration: 2 months	Nonischemic chronic DFU (Wagner Gr 1–3)	HBOT + standard treatment vs. standard treatment	✓	✓						HBOT was applied twice daily, 5 days/week for 2 weeks. Sessions lasted 90 minutes at 2.5 ATA. After 2 weeks, there was more ulcer surface area reduction in HBOT patients (p = 0.037). Two weeks later, it was comparable between the groups. After 4 weeks, there was no difference in reduction between the groups. TcPO$_2$ significantly increased during the 1st and 20th HBOT sessions (p < 0.001). These values were significantly increased when it was measured in the 2nd intercostal space (p < 0.001). At day 15, ulcer size had decreased significantly in the HBOT group (41.8 mmHg) compared to the control group (21.7 mmHg), observing fewer differences at day 30 (48.1 vs. 41.7). After 4 weeks, complete healing was observed in two patients who underwent HBOT and none in the control group.
Ozone Oxygen Therapy	Wainstein, et al.[37] Israel Funding: None reported.	2011	n = 61 (34 completed treatment) Outpatient Study duration: 24 weeks	DFU (Wagner Gr 2, 3, post debridement Gr 4)	Ozone oxygen therapy + standard treatment vs. placebo (standard treatment + sham treatment)	✓	✓	✓					Ozone treatment used Ozoter 101 device, with control group receiving sham treatments with the same device on inactive mode. Patients had treatment 4 times/week, for a maximum of 4 weeks or until 50% granulation was achieved. The second treatment period involved treatment twice/week to complete 12 treatment weeks. A significant difference between groups for full wound closure was not found (p = 0.34). An increase in healed wound area was seen in the ozone group vs. placebo group (p = 0.23), an insignificant difference. Of 34 patients in the PP cohort, the ozone group had more complete wound closure than controls (p = 0.03). Of PP patients with wound size of ≤ 5cm^2, the rate of total wound closure was in favour of the ozone group (p = 0.006).

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Growth Factors

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PDGF	Bhansali, et al.[38] India Funding: None reported	2009	n = 20 Outpatient Study duration: Complete wound closure or 20 weeks	Neuropathic plantar ulcers (Wagner ≥ Gr 2)	0.01% rh-PDGF-BB vs. standard treatment			✓					Duration of healing was 50 days for rh-PDGF-BB and 86 days for standard treatment, a 41.8% reduction in time to healing in the rh-PDGF-BB group, compared to standard treatment (p = 0.02). Ulcers In the rh-PDGF-BB group had a 58.4% reduction in mean baseline area within the first month vs. 57.8% reduction at the end of the second month. There was a fast decline in mean ulcer area in the rh-PDGF-BB group in the first 2 months vs. standard treatment. Complete ulcer healing was observed by 90 days in the rh-PDGF-BB group vs. 120 days by the SWC group. Baseline ulcer size did not influence healing rate (p > 0.05). Incidence of healing was equal in both groups, since all ulcers healed by the end of the study period.
PDGF	Landsman, et al.[39] (Abstract) United States Funding: None reported	2010	n/a Study duration: Unknown	DFU	Becaplermin gel + TheraGauze vs. TheraGauze			✓					Becaplermin gel did not play a significant role in healing. TheraGauze-treated wounds showed faster changes in wound area and a higher percentage of closed wounds at 12 and 20 weeks, regardless of whether becaplermin gel was used. Higher closure rates were observed in both TheraGauze and Theragauze + becaplermin gel groups at 12 weeks (46.2% in both groups) and 20 weeks (61.5% and 69.2%). Wound closure rates were faster with TheraGauze + becaplermin (p = 0.034)
PDGF	Park and Hay[40] (Abstract) United States Funding: None reported	2003	n/a	DFU	Becaplermin gel + standard foot care vs. Apligraf + standard foot care vs. standard foot care alone						✓		Apligraf + standard care > becaplermin + standard care > standard care alone, in treating DFUs (evaluated by QALYs and cost). Apligraf group had higher QALYs (quality-adjusted-life years) and was more cost-effective compared to both standard care and becaplermin groups. Patients in the Apligraf group gained $2202 and $179 in savings compared to standard care and becaplermin group. While standard care costs less at the initial state, patients receiving standard care alone are more likely to have costly outcomes compared to patients receiving Apligraf or becaplermin, therefore translating to higher expected costs overall.
PDGF	Khandelwal, et al.[41] India Funding: Dr. Ram Manohar Lohia Hospital, New Delhi	2013	n = 60 Inpatient, followed by outpatient Study duration: 10 weeks or complete ulcer healing	DFU (Gr 3 and 4 – International Association of Enterostomal Therapy classification)	HBOT vs. PDGF vs. antiseptics (debridement + EUSOL) Group I = PDGF Group 2 = HBOT Group 3 = antiseptics		✓	✓		✓	✓		60 patients were randomized into 1 of 3 treatment groups in a 1:1:1 ratio. Significant findings: Complete wound contraction (p = 0.0348) Insignificant findings: Healing time (p = 0.6534) Ulcer size (p = 0.0593) Complete healing of rhPDGF patients was 80% vs. 70% of HBOT vs. 40% in antiseptic dressings. Authors found that between HBOT and PDGF, healing time wasn't significant, but the percentage of patients with complete wound contraction was significantly higher in the PDGF group. Cost of treatment is lower in HBOT and PDGF than other therapies. PDGF was associated with more wound contraction than other two groups. PDGF should be recommended for all Gr 3 and 4 DFUs at least 8 weeks old. HBOT is an equal option, but has limitations and side effects. Further studies must be done to prove the superiority of PDGF over HBOT or vice versa.

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Treatment	Study	Year	Sample Size	Wound Type	Control	S1	S2	S3	S4	S5	S6	S7	Comments
PRP	He, et al.[42] (Abstract) China Funding: None reported	2012	n = 86 Outpatient Study duration: 15 days	Diabetic dermal ulcer	PRP + standard treatment vs. standard treatment	✓							Ulcer areas of patients in APG group decreased significantly (p < 0.05), and concentrations of MMP-1 in the granulation tissues of these patients reached lowest levels at day 15 (p < 0.05). MMP-9 concentrations of these patients decreased without statistical significance (p > 0.05). Ratio of MMP-9/TIMP-1 at day 6 and 15 decreased significantly vs. day 0 (p < 0.05). MMP-1 concentrations reached a peak at day 6 and decreased in patients with standard care, but was still higher than the patients treated with APG (p < 0.05). MMP-9 concentrations significantly decreased at day 15 compared to day 0 in patients treated with standard care (p < 0.05), but change in TIMP-1 was not significant. Ratio of MP-9/TIMP01 in patients treated with standard care decreased at day 15 vs. day 0 (p < 0.05). Ratio of MMP-9/TIMP-1 was positively correlated with ulcer area (p < 0.05). MMP-9/TIMP-1 ratio is a predictor of poor healing of refractory diabetic dermal ulcers. Topical application with PRP decreases MMPs and increases TIMPs in granulation tissues. Standard care results yielded a decrease in MMPs (still higher than patients treated with PRP) and a statistically insignificant change in TIMP-1.
PRP	Saad Setta, et al.[43] Egypt Funding: None reported	2011	n = 24 Outpatient Study duration: Until complete ulcer healing or 20 weeks	DFU	Platelet-rich plasma vs. platelet-poor plasma (PPP)	✓		✓					PRP group had dressing changes twice/week with an interval of 3–4 days between dressings. For the PPP group, after applying PPP, Vaseline gauze was applied, with dressing changes twice/week. Mean healing time for PRP was 11.5 weeks (8–18 weeks) and the mean healing time for PPP was 17 weeks (14–20 weeks); a statistically significant difference (P < 0.005). Healing in the PRP group was significantly faster (p < 0.005) than the PPP group. PRP enhances healing of chronic diabetic foot ulcers.
PRP	Driver, et al.[44] United States Funding: None reported	2006	n = 40 Outpatient Study duration: 24 weeks or complete ulcer healing	DFU	PRP vs. saline gel dressing	✓	✓	✓					Duration of the study was 12 weeks, with patients coming into clinic at 3- or 4-day intervals. More patients in the PRP groups had complete healing (p = 0.125). Kaplan-Meier median time to complete closure was faster for the PRP group as well (p = 0.126). When standardized for wound size, PRP treatment had more completely healed wounds (p = 0.036). PRP group had a faster average wound area closure rate per day (0.051cm^2 vs. 0.054cm^2). The difference in the rate of healing was not statistically significant between the two groups. Of the patients (40) in the PP dataset, 22 with healed wounds took part in a 12-week follow-up phase, and one patient in the PRP gel group had a wound that reopened vs. none of the control patient wounds that reopened, a statistically insignificant finding. PRP-gel-treated wounds were significantly more likely to heal than control-treated wounds, even though healing rates in control group were higher after 12 weeks (42%) than most control groups in other studies. In the most common size of DFU (≤ 7 cm^2 in area and ≤ 2 cm^3 in volume), PRP-gel-treated wounds are more likely to heal than control-treated wounds. PRP or saline gel treatment resulted in healing in about 6 weeks, but in the most common wound sizes, almost twice as many PRP treated wounds healed in the same time. Significantly more wounds healed with PRP gel (81.3%) than with control gel (42.1%). Kaplan-Meier time-to-healing was also significantly different between the 2 groups.

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Treatment	Study	Year	Sample Size	Wound Type	Control	S1	S2	S3	S4	S5	S6	S7	Comments
bFGF	Uchi, et al.[45] (Abstract) Japan Funding: None reported	2009	n = 148 Study duration: 8 weeks	Non-ischemic diabetic ulcers	0.001% bFGF group vs. 0.01% bFGF group vs. placebo group	✓		✓					0.01% bFGF had the highest closure rate and wound-area reduction of all 3 groups. A significant difference between placebo group and 0.01% bFGF was seen in reduction of ulcer size (p = 0.025). Area of ulcer decreased by 82.2% (37/45) in the 0.01% bFGF group vs. 72.3% (34/47) in the 0.001% bFGF group vs. 57.5% (27/47) in the placebo group. Closure rate was 66.7% (30/45) in the 0.01% bFGF group vs. 57.4% (27/47) in the 0.001% bFGF group vs. 46.8% (22/47) in the placebo group. Authors concluded that bFGF accelerates wound healing on diabetic ulcers.
G-CSF	Kastenbauer, et al.[46] Austria Funding: Amgen Austria	2003	n = 37 Inpatient Study duration: 10 days	Infected DFU	G-CSF vs. placebo (0.9% sterile saline solution)	✓							This study was conducted during a 10-day hospital stay. Patients were on bed rest and treated with IV antibiotics until inflammation had improved. Patients received an initial dose of either 5 µg/kg body weight G-CSF or placebo. No differences were observed in Wagner's grade of foot ulcers at baseline (p = 0.59) or at the end of the study (p = 0.54). Ulcer volume was not larger in placebo patients (p = 0.20), but did decrease in placebo by 35% (p = 0.03), and in G-CSF treated patients, by 59% (p = 0.0005). An earlier resolution of clinically defined cellulitis was not found in G-CSF compared to placebo patients (p = 0.57). At day 10, local, forefoot and lower leg erythema were absent in more than 80% of patients in G-CSF or placebo groups. Authors concluded that treatment of G-CSF with standard wound care had no additional beneficial effect. Patients who received G-CSF did not have earlier resolution of clinically defined cellulitis. Ulcer volume (which was not greater among placebo patients) was reduced by 59% in G-CSF vs. 35% in placebo patients.
G-CSF	Yonem, et al.[47] Turkey Funding: None reported	2001	n = 30 Inpatient Study duration: Until complete healing	DFU (Wagner ≥ Gr 2 or pedal cellulitis)	G-CSF + standard treatment vs. standard treatment (local wound care and antibiotics)			✓		✓			G-CSF was given subcutaneously, once a day. G-CSF treatment led to significantly higher neutrophil counts at the 5th (p < 0.001) and 10th days (p < 0.001) and at the end of treatment (p < 0.001), compared to the standard group. Post-treatment phagocytosis test and respiratory burst of neutrophils were similar between the two groups, increasing significantly in both groups (p = 0.001 for C-GSF and p = 0.02 for standard group). Phagocytosis of neutrophils increased significantly in G-CSF group (p = 0.004), but not in the standard group (p = 0.3). The following were similar between G-CSF and standard groups: Hospital stay (26.9 days vs. 28.3 days, p < 0.05) Duration of parenteral antibiotic administration (22.9 vs. 23.3 days; p < 0.05) Time to infection resolution (23.6 vs. 22.3 days, p < 0.05). Two patients in G-CSF group and 3 patients in the standard group required amputation, a statistically insignificant difference (p > 0.05) Study found that while G-CSF improves neutrophil function and absolute numbers, the improvement is not associated with shortening of duration of antibiotic administration, duration of hospital stay or need for amputation in DFU. Duration of parenteral antibiotic administration, time to resolution of infection and need for amputation were similar between the G-CSF and control groups.

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Treatment	Study	Year	Sample Size	Wound Type	Control	S1	S2	S3	S4	S5	S6	S7	Comments
hEGF	Fernandez-Montequin, et al.[48] Cuba Funding: Ministry of Public Health of Cuba	2009	n = 149 Outpatient Study duration: 8 weeks	DFU (Wagner Gr 3 and 4)	EGF (75 υg)+ standard treatment vs. EGF (25 υg) + standard treatment vs. placebo + standard treatment			✓				✓	Endpoint of study was granulation tissue covering more than 50% of the ulcer at 2 weeks. 44/53 75 µg EGF-treated patients vs. 34/48 25 µg group vs. 19/48 of controls reached the endpoint. End of treatment granulation response was 46/53 in 75 µg vs. 34/48 with 25 µg EGF vs. 24/48 controls. Time to complete response was 3 weeks for both EGF groups and 5 weeks for controls. Wound closure after follow-up was 40/53 with 75 µg EGF vs. 25/48 with 25 µg EGF vs. 25/48 controls. Closure was significantly favoured by neuropathic versus ischemic ulcer; smaller wound area and treatment with 75 µg EGF. All amputations in the EGF treated groups were ischemic patients vs. 5 neuropathic patients with placebo. Both 2 weeks > 50% granulation and end of treatment complete granulation predicted final wound closure very well. Recombinant human EGF local injections offer a favourable risk-benefit balance in patients with advanced DFU.
hEGF	Tsang, et al.[49] China Funding: None reported	2003	n = 61 Outpatient Study duration: 24 weeks	DFU (Wagner Gr 2 or 3)	Actovegin + 0.02% hEGF vs. Actovegin + 0.04% hEGF vs. Actovegin 5% cream (control)			✓					Endpoint of treatment was defined as complete closure of the wound (failure to heal was incomplete closure after 12 weeks of treatment). Application of hEGF-containing cream, in addition to good foot care, significantly enhances diabetic foot ulcer wound healing and reduces healing time. After 12 weeks, the control group had 8 patients with complete healing, 2 toe amputations and 7 non-healing ulcers. 20/21 patients in Actovegin + 0.04% hEGF showed complete wound healing. Healing rates were 95% for the 0.04% hEGF group, 57.14% for the 0.02% hEGF group and 42.10% for the control group. Application of cream with 0.04% hEGF caused more ulcers to heal by 12 weeks and increased the rate of healing compared to the other treatments. Kaplan-Meier survival analysis suggested that 0.04% hEGF caused more healed ulcers by 12 weeks and increased the rate of healing compared to other treatments.
Talactofer-rin alfa	Lyons, et al.[50] United States Funding: 1. Agennix, Inc. 2. National Institute of Arthritis and Musculoskeletal and Skin Diseases of the National Institutes of Health	2007	n = 46 Outpatient Study duration: 12 weeks	Neuropathic DFU	8.5% Talacto-ferrin alfa vs. 2.5% Talac-toferrin alfa vs. standard treatment	✓							2 phases to this study: Phase 1 was an open-label, sequential, dose-escalation design; Phase 2 was a single-blind RCT. Phase 1 was evaluating different doses of Talactoferrin alfa. More patients achieved ≥ 75% reduction in ulcer size with 8.5% and 2.5% talactoferrin alfa than with placebo (p = 0.091). Both talactoferrin alfa groups had more wound size reductions at 30 and 90 days post treatment than placebo, although statistically insignificant. Complete healing at 30 days post treatment was higher in both treatment groups vs. placebo, and still remained high at 90 days, although statistically insignificant. The 8.5% talactoferrin gel had a consistently higher rate of overall healing vs. placebo, starting as early as week 3.

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Treatment	Study	Year	Sample Size	Wound Type	Control	S1	S2	S3	S4	S5	S6	S7	Comments
TP508	Fife, et al.[51] United States Funding: Chrysalis BioTechnology, Inc.	2007	n = 60 Outpatient Study duration: 20 weeks or complete wound closure	Below-the-knee ulcers, with a subset of DFU	1 µg Chrysalin vs. 10 µg Chrysalin vs. saline		✓						Chrysalin more than doubled the incidence of complete healing (p < 0.05), increased mean closure rate (p < 0.05) and decreased median time to complete closure (p < 0.05). Treatment of heel ulcers with Chrysalin resulted in mean closure rates higher than placebos (p < 0.02) and higher incidence of complete healing (p < 0.03). Foot ulcers closed with 1 and 10 µg Chrysalin closed completely after 7 and 13 weeks, respectively vs. placebo ulcer, which did not completely close by 20 weeks. (1µg Chrysalin vs. placebo p < 0.05, both treatment groups vs. placebo, p < 0.05) Kaplan-Meier analysis predicted that twice as many ulcers treated with 10 µg Chrysalin would be completely healed by 60 days, compared to the placebo group. Median time to closure was faster with the 10 µg Chrysalin group compared to placebo (p < 0.05), as well as the 1 µg Chrysalin group (p < 0.05). Linear rate of wound closure/day was greatest for 10 µg (p < 0.05), representing an 80% increase over placebo. A further subset of heel ulcers was performed: Ulcers treated with either Chrysalin showed early improvement in wound bed granulation within 5 weeks, where 1 µg Chrysalin reached closure in 8 weeks and 10 µg Chrysalin in 16 weeks, while placebo ulcers did not heal within 20 weeks. Wound healing rates more than doubled in the 10 µg group compared to placebo (p < 0.02). More ulcers completely healed with 1 or 10 µg than placebo (p < 0.03). The one patient who did not heal in the Chrysalin population was removed from treatment due to an unrelated infection, and thus Chrysalin treatment was 100% effective in the treatment of diabetic heel ulcers.
Keratino-cytes	You, et al.[52] Korea Funding: Tego Science (TG-KDM-07-201)	2012	n = 59 Outpatient Study duration: 21 weeks	DFU	Allogenic keratinocyte sheets vs. Vaseline gauze	✓	✓	✓					The control group excluded 8 patients without complete healing. Complete wound healing was achieved in 100% of the keratinocyte group vs. 69% of the control group (p < 0.05). Mean percentage of wound area reduction was in favour of the keratinocyte group (p < 0.05). Time to complete healing was faster in the keratinocyte group (p = 0.90). Kaplan-Meier median times to complete closure were 35 and 57 days for the keratinocyte and control groups, respectively.

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Artificial Skin Graft

Treatment	Study	Year	Sample Size	Wound Type	Control	Study Parameter							Comments
						S1	S2	S3	S4	S5	S6	S7	
Artificial Skin Graft	Marston, et al.[53] United States Funding: 1. Advanced Tissue Sciences Inc. 2. Smith and Nephew, Inc.	2003	n = 314 Outpatient Study duration: 12 weeks	DFU of > 6 weeks duration	Dermagraft vs. standard treatment	✓	✓	✓					Prior to randomization, patients received sharp debridement and saline-moistened gauze dressings, as well as off-weight bearing instructions. Dermagraft group received their first application at day 0 and up to 7 applications once a week over the study. More Dermagraft patients had complete wound closure than control patients (p = 0.023), as well as for forefoot/toe ulcers (p = 0.065), and heel ulcers (p = 0.10). Faster time to ulcer healing was found with the Dermagraft group (p = 0.04), and by week 12, the median percent wound closure was greater for the Dermagraft group (p = 0.044). More patients underwent surgery in the control group (p = 0.07). After controlling for ulcer area and sex, Dermagraft patients were 1.7 and/or 1.6 times more likely to have complete wound closure at any time than the control patients, respectively.
Artificial Skin Graft	Hanft, et al.[54] United States Funding: 1. Advanced Tissue Sciences, Inc. 2. Smith and Nephew	2002	n = 28 Outpatient Study duration: 12 weeks	DFU (plantar foot ulcer on the heel or forefoot, including toes)	Dermagraft + saline moistened gauze vs. saline moistened gauze alone	✓	✓	✓					Patients achieving wound closure was greater with Dermagraft (p = 0.003). 70% of Dermagraft patients with a forefoot or toe ulcer had complete wound closure vs. 15% in the control group. 75% of heel ulcers in the Dermagraft group completely healed vs. none in the control group. Dermagraft resulted in significantly faster complete wound closure (p = 0.004), and the percent wound closure was significantly higher in the Dermagraft group as well (p = 0.002). The percent of patients who experienced an infection was less in the Dermagraft group than the control group.
Artificial Skin Graft	Edmonds, et al.[55] UK Funding: Organogenesis Inc.	2009	n = 82 Outpatient Study duration: 24 weeks	Neuropathic DFU	Apligraf + standard treatment vs. standard treatment alone		✓	✓					106 were eligible for study treatment; 82 were randomized to treatment, 24 were not. Of the 82 patients, 72 were treated in the clinical study. While this study ended prematurely, it suggested that the use of Apligraf resulted in a higher incidence of wound closure by 12 weeks. There was a trend to shorter time to reach complete healing in the Apligraf group (p = 0.059). There were more subjects in the Apligraf group who did not have debridement at the weekly visit after the first application (p = 0.001) or at week 4 (p = 0.0273). More subjects completely healed with Apligraf compared to standard therapy (p = 0.049). There was no difference in the amount of healed patients with ulcer recurrence in both treatment groups during the follow-up period (p = 1.000).
Artificial Skin Graft	Veves, et al.[11] United States Funding: Organogenesis	2001	n = 208 Outpatient Study duration: 24 weeks	Nonischemic plantar DFU	Graftskin vs. saline moistened gauze	✓	✓	✓					More patients completely healed with Apligraf (p = 0.0042). The Kaplan-Meier median time to complete closure was significantly lower than the control group (p = 0.0026, 65 days vs. 90 days, respectively). After adjusting for all factors found in the final model, Apligraf was found to have a statistically significant effect on time to closure (p = 0.0001). Statistically significant differences appeared between the 2 groups for maceration, exudate and eschar (p < 0.05). Rate of adverse reactions was similar between the 2 groups, with the exception of osteomyelitis and lower limb amputations, which were less frequent in the Apligraf group. By week 5, unhealed ulcers were covered with saline-moistened gauze and a layer of petrolatum gauze and wrapped with a layer of Kling for the duration of the study.

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Treatment	Study	Year	Sample Size	Wound Type	Control	S1	S2	S3	S4	S5	S6	S7	Comments
Artificial Skin Graft	Niezgoda, et al.[56] United States Funding: Cook Biotech Incorporated	2005	n = 98 (73 completed treatment) Outpatient Study duration: 6 months	DFU (unhealed for ≥ 1 month)	OASIS vs. Regranex Gel + secondary dressing		✓	✓					Amount of OASIS applied depended on the amount of matrix on the wound surface and extent of epithelialization at the change of each secondary dressing. Study size was too small to find statistical significance, but OASIS is as effective as Regranex in healing full-thickness DFUs. More patients healed with OASIS than Regranex Gel at 12 weeks (p = 0.055). This trend followed for plantar ulcers (p = 0.014). No significant difference was found in mean time to healing between groups (p = 0.245). A Cox proportional hazards regression showed no significant difference between survival curves in the 2 groups (p = 0.087), but it did predict an improved trend of healing for the OASIS group. At 7 weeks, it predicts that patients in the OASIS group are about twice as likely to heal as those in the Regranex group. After adjusting for baseline measures, it was found that the proportion of patients completely healed was not significantly different between the two groups (p = 0.089). A noninferiority test revealed noninferiority of the healing proportion for the OASIS group vs. Regranex Gel group (p = 0.01)
Artificial Skin Graft	Uccioli, et al.[57] Italy Funding: Anika Therapeutics srl	2011	n = 160 Outpatient Study duration: 18 months	DFU (unhealed for ≥ 1 month) (Wagner Gr 1–2)	HYAFF autograft + LaserSkin therapy (after 2 weeks) vs. nonadherent paraffin gauze	✓	✓						At baseline, 2 groups were similar except for ulcer area (p = 0.016). Complete ulcer healing was found in favour of LaserSkin treatment at 12 weeks (p = 0.850) and 20 weeks (0.344). In a dorsal ulcer subgroup, treatment had a statistically significant effect on the probability of wound healing (p = 0.047), after adjusting for ulcer area and duration. Mean time to complete ulcer healing was faster for the LaserSkin treatment group (p = 0.253). A 50% reduction was found significantly faster in the LaserSkin group (p = 0.018), as well as the weekly percentage reduction (p = 0.023). In a subgroup of non-healing ulcers (84 ulcers), treatment with autologous skin substitutes was beneficial on the probability of healing (p = 0.035), as well as a better chance of wound healing/unit time in dorsal ulcers (p = 0.047).
Artificial Skin Graft	Caravaggi, et al.[58] Italy Funding: Fidia Advanced Biopolymers	2003	n = 79 Outpatient Study duration: 32 weeks	DFU (Wagner Gr 1–2)	Hyalograft3D (Autologous fibroblasts) vs. nonadherent paraffin gauze (control)		✓	✓					Both groups received weekly assessment, aggressive debridement, wound infection control and pressure relief. Treatment group achieved 65.3% complete ulcer healing vs. 49.6% in the control group (p = 0.191). Mean time to closure was 57 days in treatment group vs. 77 days in control group. Complete healing in dorsal foot ulcers was significantly in favour of the treatment group (p = 0.049), and the odds ratio for complete dorsal ulcer healing was p = 0.037. For plantar ulcers, more ulcers healed with the treatment group (p = 1.00). In the per protocol analysis, complete wound healing was higher in the treatment group (0.332). At the end of the study, the treatment group showed more improvement in exudate presence than the control group at visit 7 (p = 0.036) and 12 (p = 0.013). For plantar ulcers, mean reduction was greater in the control group (p = 0.823), while it was greater in the treatment group for dorsal ulcers (p = 0.072).

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Treatment	Study	Year	Sample Size	Wound Type	Control	S1	S2	S3	S4	S5	S6	S7	Comments
Artificial Skin Graft	Reyzelman, et al.[59] United States Funding: Wright Medical Technology, Inc.	2009	n = 86 Outpatient Study duration: 12 weeks	DFU – Gr 1 or 2 (Texas)	GraftJacket vs. standard treatment		✓	✓					Of patients completing the trial, a higher incidence of complete healing was observed in the GraftJacket group (p = 0.0289). The odds ratio suggested the GraftJacket group was 2.7 times more likely to heal than the control group. Complete healing didn't occur in 30.4% of the GraftJacket patients, and 53.8% of the placebo patients. Of these patients, no statistically significant differences were seen in final ulcer size, percent of ulcer area healed or change from ulcer size at presentation. However, 12 GraftJacket patients had decreased ulcer size and 2 did not change. 15 placebo patients had a decrease and 5 did not change in size. Furthermore, 21.4% of patients in the GraftJacket group had at least 90% healing vs. 28.6% in the placebo group. A significant difference in non-healing rates was found between groups (Kaplain-Meier, p = 0.0075), with a higher healing rate in the GraftJacket group. The proportion of healed ulcers was still greater in the study group at the 3-week follow-up.
Artificial Skin Graft	Brigido, S.A[60] United States Funding: None reported	2006	n = 28 Outpatient Study duration: 16 weeks	DFU (Wagner Gr 2)	GraftJacket + sharp debridement vs. sharp debridement	✓		✓					More patients experienced wound closure with GraftJacket. By week 16, 12/14 patients treated with GraftJacket tissue matrix demonstrated complete wound closure vs. 4/14 patients in the control group. GraftJacket patients healed faster than control patients (11 vs. 13 weeks). Patients treated with GraftJacket also showed a statistically significant higher percentage of wound healing with respect to wound area, depth and volume (p ≤ 0.001).
Artificial Skin Graft	Van Schie, et al.[61] UK Funding: None reported	2000	n = 28 Outpatient Study duration: 1 year	DFU	Liquid silicone vs. placebo (saline)	✓							Liquid Silicone included 6 injections of 0.2ml liquid silicone in the plantar surface of the foot. Placebo had an equal volume of saline injected. The silicone-treated group had a more significant increase in tissue thickness from baseline than did the control group at 3, 6 and 12 months (p < 0.005). A further decrease in peak plantar pressure was measured in the silicone-treated group at 3 months (p < 0.05), with similar results at 6 and 12 months. There was a significant correlation between percentage change in peak plantar pressure and plantar tissue thickness after injection with silicone (p < 0.05). The median score for callus build-up change was greater in the silicone-treated group (p = 0.3).

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Collagen-based Dressings

Treatment	Study	Year	Sample Size	Wound Type	Control	S1	S2	S3	S4	S5	S6	S7	Comments
Collagen	Lipsky, et al.[67] United States Funding: Innocoll Technologies Ltd.	2012	n = 56 Outpatient Study duration: 42 days	DFU	Gentami-cin-collagen sponge + standard treatment vs. standard treatment alone		✓						23 patients discontinued the study early, leaving 33 to completely finish. Topical application of the gentamicin-collagen sponge seems safe and may improve clinical and microbiological outcomes of diabetic foot infections of moderate severity when combined with standard therapy. Clinical cure was defined as resolution of all baseline signs and symptoms of infection. On day 7, there was clinical cure found in 0 collagen patients and 3 control patients (p = 0.017). At the test-of-cure visit (day 42), more patients in the treatment group had clinical cure (p = 0.024). On days 10, 14 and 21, the control group had a non-significantly higher cumulative percentage of patients with clinical cure, compared to the treatment group. At the test-of-cure visit, the evaluable patients in the treatment group had more patients with clinical cure (p = 0.024). The treatment group also had a higher cumulative percentage of patients with clinical cure at the end of treatment visit (p = 0.119). Kaplan-Meier estimates of time to clinical cure indicated 75% of patients achieved clinical cure after 28 days in the treatment group vs. 40 days in the control group. The treatment group had fewer baseline pathogens at all visits (p ≤ 0.038) and a reduced time to pathogen eradication (p < 0.001). Log-rank test comparing the likelihood of baseline pathogen eradication by treatment group was significantly in favour of the treatment group (p < 0.001). The difference in reduction of the Lipsky wound score at the final visit was in favour of the treatment group (p = 0.042), while the difference in percentage reduction wasn't significant (p = 0.376). There was no significant difference in the percentage of patients achieving complete wound closure at the end of treatment.
Collagen	Motzkau, et al.[68] Germany Funding: Ethicon GmbH Johnson & Johnson	2011	n = 19 Inpatient Study duration: Average of 26 treatment days	Chronic DFU (Wagner/ Armstrong Gr 2A)	Protease-inhibitor-modulating-matrix (ORC/ collagen matrix) vs. standard treatment	✓	✓						Local treatment with a protease-inhibitor has a beneficial effect on wound healing. Expression of MMP (1,2,9,13,14), TIMP (1,2) and TNF-α mRNA was not significantly different between groups at the 2 time points (day 1 and 5). Cytokine Il-1β-mRNA expression was increased in in the treatment group on day 1 and 5 (p = 0.038). Protein levels of MMP (2,8,9) and TIMP-2 were not significantly different between the 2 groups. ORC/Collagen group had a reduction of MMP-2 active on day 5, (p = 0.043) vs. day 1, but this was not seen with the control group. There was no difference in protease MMP-2 between groups. Levels of MMP-2 pro increased in the control group, and decreased in the treatment group, but not to statistical significance. A reduction in wound size was in favour of the treatment group (p = 0.003), and 8 patients in the treatment group achieved wound closure.

S1 = Wound Area Reduction   S2 = 100% Wound Closure   S3 = ♠ Healing Rates   S4 = ♠ Quality of Life   S5 = Amputations   S6 = Cost   S7 = Granulation Rate

Treatment	Study	Year	Sample Size	Wound Type	Control	S1	S2	S3	S4	S5	S6	S7	Comments
Collagen	Blume, et al.[69] United States Funding: None reported	2011	n = 124 (ITT) Outpatient Study duration: 20 weeks	DFU (Wagner Gr 1)	Formulated collagen gel (FCG) vs. FCG + GAM501 vs. standard treatment (daily wound control, de-bridement, callus and necrotic tissue removal, wounds covered with soft silicone wound contact layer)	✓	✓						8 patients withdrew from the study. GAM501 + FCG patients had 41% wound closure, compared to FCG alone (45%) and standard of care (31%). Ulcer closure was greatest in the FCG group (45%) vs. GAM501 (41%) and SOC (31%). No significant differences in healing rates were found from day 1 to week 4 between groups. Photographic data evidence suggests standard therapy had no significant effect on wound radius change, but both FCG and GAM501 significantly increased healing rates that gradually declined over subsequent weeks. 12-week complete closure incidence in SAP2 was greatest in GAM501 (41%) vs. SOC (31%) and FCG (35%). Cumulative wound healing had a significant difference between FCG and SOC groups for day 1 to week 1 and day 1 to week 2. Authors concluded that a single application of GAM501 or FCG increases the healing rate of neuropathic DFUs for the first 2 weeks after treatment, while weekly visits with SOC has a much smaller and delayed effect on healing rate. This finding suggests that more frequent applications of GAM501 or FCG may significantly improve overall incidence of complete wound closure. Further testing is required to determine whether one or more administrations of GAM501 has advantages over FCG alone in certain circumstances (i.e., treating larger or more difficult to treat wounds)
Collagen	Lazaro-Martinez, et al.[70] (Abstract) Spain Funding: None reported	2007	n = 40 -- Study duration: 6 weeks	DFU (≥ 6 weeks)	Protease-modulating dressing vs. standard treatment		✓	✓					After 6 weeks, healing was achieved in 63% of patients in the collagen group vs. 15% in the control group (p < 0.03). Collagen group had a faster mean time to healing (p < 0.03). The use of protease-modulating dressings in patients with neuropathic DFUs leads to better tissue regeneration than good wound care alone.
Collagen Dressing	Veves, et al.[71] United States Funding: Johnson & Johnson Wound Management	2002	n = 276 (180 completing) Outpatient Study duration: 12 weeks	DFU ≥ 30 days (Wagner Gr 1 or 2)	Promogran vs. moistened gauze + secondary dressing		✓						Promogran resulted in more complete wound closure (p = 0.12). In a subgroup of ulcers of < 6 months, 45% of Promogran-treated patients healed vs. 33% of controls (p = 0.056); and of ulcers ≥ 6 months, 20% of Promogran patients healed vs. 19% of controls (p = 0.83). The proportion of healed wounds of < 6 months duration varied across centres (p = 0.07). Wagner Gr 1 and 2 ulcers healed more in the Promogran group (p = 0.15 and p = 0.30). Average number of dressing changes was similar between groups (p = 0.03). Mean percentage reduction was similar between groups. Mean time to healing for complete healing was faster in the control group (5.8 weeks vs. 7.0 in treatment group). There were fewer suspected infections in the Promogran group at any time (p = 0.14). Dressings were rated higher in the Promogran group according to patients (p = 0.01), as well as clinicians (p < 0.05). Promogran was comparable to moistened gauze in promoting wound healing in diabetic foot ulcers. It showed an additional efficacy for ulcers <6 months duration; this was of marginal statistical significance. Promogran had a safety profile similar to that of moistened gauze, with greater user satisfaction. Thus, it may be a useful adjunct in managing DFUs, especially in ulcers of less than 6 months' duration.

S1 = Wound Area Reduction   S2 = 100% Wound Closure   S3 = ↑ Healing Rates   S4 = ↑ Quality of Life   S5 = Amputations   S6 = Cost   S7 = Granulation Rate

Treatment	Study	Year	Sample Size	Wound Type	Control	Study Parameter							Comments
						S1	S2	S3	S4	S5	S6	S7	
Collagen Dressing	Kakagia, et al.[72] Greece Funding: None reported	2007	n = 51 Outpatient Study duration: 16 weeks	DFU	Promogran vs. autologous growth factors by Gravitational Platelet Separation System (GPS) vs. combination of both treatments	✓	✓						The study found there was significantly greater reduction of all 3 dimensions of the ulcers in the combination treatment, compared to Promogran or GPS alone (p < 0.001). Promogran insignificantly decreased ulcer length, width and depth further than GPS (length: p = 0.507, width: p = 0.194, depth: p = 0.979). 2 patients in each group reached complete healing. Protease modulating dressings work with autologous growth factors to enhance their efficacy in DFUs.

S1 = Wound Area Reduction   S2 = 100% Wound Closure   S3 = ↟ Healing Rates   S4 = ↟ Quality of Life   S5 = Amputations   S6 = Cost   S7 = Granulation Rate

Physical Therapies

Treatment	Study	Year	Sample Size	Wound Type	Control	Study Parameter							Comments
						S1	S2	S3	S4	S5	S6	S7	
Laser Therapy: Broadband light source (400–800nm)	Landau, et al.[73] Israel Funding: Qray LTD	2011	n = 10 (19 ulcers) Outpatient Study duration: 16 weeks	DFU (n = 8) or VLU (n = 2), (Wagner Gr 1 or 2)	Vireo (phototherapy device) vs. placebo (non-healing light fluency projections)	✓	✓	✓					A broadband light source in the visible and near IR range (400–800 nm) operating at 180 mW/cm^2 was used. More wounds were fully closed with laser therapy (p = 0.0357). Laser therapy also further reduced ulcer size (89% vs. 54%). Mean time to wound closure was shorter in the laser therapy group (7.14 weeks vs. 11.16 weeks in control group). Patients were instructed to treat their wound twice a day using the Vireo, over the entire wound from 2 cm distance, for 4 min/treatment. Following treatment, wounds were dressed with a saline solution and sterile gauze. If a patient had a closed wound that stayed closed for >1 month, no further treatment or follow up was done. Average area of remaining open ulcers was 0.12 cm^2 (treatment) vs. 0.21 cm^2 (placebo).
Laser Therapy: Low-level laser therapy (LLLT)	Kaviani, et al.[74] Iran Funding: 1. Endocrinology & Metabolism Research Center (EMRC) 2. Tehran University of Medical Sciences	2011	n = 23 Outpatient Study duration: 20 weeks	DFU (Wagner Gr 1, 2)	LLLT + standard treatment vs. placebo (standard treatment)	✓	✓	✓					Ulcer size was bigger in the LLLT group at the beginning of the study (p = 0.799). Ulcer size reduction was higher in the LLLT group (p = 0.125). After 2 weeks, compared to baseline, ulcer size reduction was still greater in the LLLT group (p = 0.046). Four weeks later, LLLT group was still greater in wound reduction (p = 0.03). More ulcers in the LLLT group achieved complete healing (p = 0.470). Mean time of complete healing in LLLT patients was less than placebo (although not a statistically significant difference). 2 patients from the placebo group were hospitalized and had amputations due to gangrene. One patient in LLLT group was hospitalized for infection. One patient from each group died from a myocardial infarction. LLLT can accelerate the healing process of chronic diabetic foot ulcers and may shorten the time needed to achieve complete healing.
Electro-stimulation Therapy	Petrofsky, et al.[75] United States Funding: None reported	2010	n = 20 Outpatient Study duration: 1 month	DFU (Wagner Gr 2)	Electrostimulation (EST) via biphasic sine wave stimulation + local heat vs. local heat only Standard care provided to all patients (debridement, cleaning, dressing)	✓							Local heat was provided by an infrared lamp positioned 35 cm above the wound. A thermocouple was used to measure and regulate skin temperature outside the wound, and a computerized controller adjusted the lamp intensity to keep skin temperature at 37C. In the local heat-only group, wounds that had not healed for at least 2 months showed significant healing, but ultimately less than that observed in the ES + heat group. Average wound area and volume decrease did not significantly differ between EST + heat group and heat-only group (p > 0.05). In the EST+ heat group, wound area and volume decreased significantly after 1 month of treatment (p < 0.05), compared to baseline. In the local heat-only group, wounds that didn't heal for +2 months showed 30.1% and 22.3% healing (p < 0.05). Blood flow increased more from rest with EST + heat. For the whole group, blood flow increased on the 1st day, decreased by the last day on outside, edge and centre of the wound (most around edge and centre). Local dry heat and ES work well together to heal chronic diabetic foot wounds; however local heat appears to be a relevant part of this therapy, as previous studies indicate that ES alone has produced little healing.

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Treatment	Study	Year	Sample Size	Wound Type	Control	S1	S2	S3	S4	S5	S6	S7	Comments
Electric Stimulation	Peters, et al.[76] United States Funding: None reported	2001	n = 40 Outpatient Study duration: 12 weeks, or until complete healing	DFU (Gr 1A-2A, University of Texas Diabetic Wound Classification System)	Electric stimulation vs. placebo (identical electric stimulation units that deliver no currents)	✓		✓					5 patients dropped out due to severe infection (2 treatment, 3 placebo). Among those who healed, average healing times were 6.8 weeks (electric stimulation) vs. 6.9 weeks (placebo). More patients completely healed with the electric stimulation therapy (p = 0.058). After stratifying for compliance, a significant difference was seen between groups (p = 0.037). There was no significant difference in the rate of wound healing or the average time until wounds healed among treatment and placebo groups. Total change in ulcer cross-sectional area was 86.2% vs. 71.4% in treatment and control groups.
External Shock Wave Therapy	Moretti, et al.[77] (Abstract) Italy Funding: None reported	2009	n = 30 Outpatient? Study duration: 20 weeks	Neuropathic DFU	Shockwave therapy + standard treatment vs. standard treatment		✓	✓					Complete wound healing rate was significantly increased in ESWT-treated patients vs. standard therapy (p < 0.001). Proportion of healed ulcers was 53.33% and 33.33% in the ESWT treated patients and control patients, respectively (p < 0.001). Significant differences in the index of the re-epithelialization were seen between groups (2.97 mm^2/die in ESWT group and 1.30 mm^2/die in control group, p < 0.001).
Low-frequency Ultrasound through Saline Mist	Ennis, et al.[78] United States Funding: None reported	2005	n = 97 Outpatient and inpatient Study duration: 12 weeks	DFU (Wagner Gr 1 or 2)	40 KHz ultrasound delivery by a saline mist + standard care vs. "sham device" (saline mist without the use of ultrasound) + standard care		✓						Treatment included visits 3x/week with 4-minute treatment intervals. Patients were allowed up to 7 missed visits. 24 patients were lost to follow-up before completing 10 weeks of therapy. 5 centres were found to be using the placebo incorrectly, resulting in 55 patients eligible for the study. Proportion of healed wounds was significantly higher than that in the sham control group (40.7% vs. 14.3% respectively). No difference between the two devices (p = 0.69). Standard care in this study was defined as: moist environment, offloading diabetic shoes and socks, debridement, wound evaluation and wound measurement.

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Other Therapies

Treatment	Study	Year	Sample Size	Wound Type	Control	S1	S2	S3	S4	S5	S6	S7	Comments

Treatment	Study	Year	Sample Size	Wound Type	Control	Study Parameter S1	S2	S3	S4	S5	S6	S7	Comments
DeMarco Formula	Mesa, et al.[79] Cuba Funding: None reported	2011	n = 47 Outpatient Study duration: 52 days	Ischemic DFU post amputation of toe(s), transmeta-tarsal or partial amputation or a surgical debridement with or with-out previous procedures	DMF + standard treatment vs. standard treatment alone					✓			DMF used with standard treatment for infected ischemic DFUs was associated with plasma fibrinogen decreases. Patients treated with DMF had significantly lower amputation rates (p = 0.011). No minor amputations were performed during follow-up. Standard treatment was not associated with a significant change of the fibrinogen concentration mean. Decreased fibrinogen was greater with DMF (p = 0.0016) than with conventional therapy (p = 0.11). 50% of patients receiving standard treatment and 21.7% of patients receiving DMF showed unfavorable responses (unfavorable responses were major amputation rates). Patients who showed favorable responses to treatment had statistically lower fibrinogen concentrations than those with unfavorable responses within the DMF group.
DeMarco Formula	Duarte, et al.[80] Cuba Funding: None reported	2009	n = 118 Study duration: 52 days or complete ulcer healing	Ischemic diabetic foot, amputation of 1 or more toes, history of trans-metatarsal amputation	DMF + standard treatment vs. standard treatment alone					✓			There were fewer amputations with the DMF + standard treatment groups vs. the standard treatment group alone (p = 0.02). Four slight adverse reactions were associated with DMF: vertigo and nausea at 7th dose (one patient), headache and tachycardia at 12th dose (one patient), with a 44% reduction in wound size. Difference in amputation prevention between groups (p = 0.5225). There was no difference in glycemic control between groups Effect on DMF on: • Blood hemoglobin (g/L) • Day 0–10 (p = 0.0638) • Day 11–24 (p = 0.2550) • Day 25–52 (p = 0.2302) • Blood leukocyte count • Day 0–10 (p = 0.0960) • Day 11–24 (p = 0.0766) • Day 25–52 (p = 0.1692) • Serum alanine transaminase activity (IU/L) • Day 0–10 (p = 0.7238) • Day 11–24 (p = 0.8801) • Day 25–52 (p = 0.8313)

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APPENDIX III

Survey Questions

DFU Advanced Therapy Consensus Document: Interview Questions

1. What do you think the evidence is to support this therapy?

2. What is your experience with this treatment, and what are the barriers to implementing it?

3. What are the changes you would like to make to the health system to improve the use of this therapy?

4. What can help to integrate this therapy into your routine therapy?

5. What are the indications of this treatment?

6. What are the key priorities you'd like to implement in your practice?

APPENDIX IV

Survey Respondents

Afsaneh Alavi – dermatologist

Mariam Botros – chiropodist

Alain Brassard – dermatologist

Pat Coutts – nurse

Andrew Dueck – vascular surgeon

John Embil – infectious disease/internist

Elisa Greco – vascular surgeon

Rosemary Hill – nurse

Johnny Lau – foot and ankle surgeon (orthopedic)

R. Gary Sibbald – dermatologist/internist

Kevin Woo – nurse

Advanced Therapies Protocol for Diabetic Foot Ulcers

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Protocol
1. Select a patient for advanced therapy only if best practice management (including offloading to reduce plantar pressures, blood glucose management, arterial perfusion and infection control, a mental health and wellness assessment, family and social supports and funding) has been implemented and wound bed preparation has been addressed to reduce or eliminate impediments to DFU healing.
2. Identify the primary and secondary goals of care (or outcomes) such as wound healing, wound closure, pain management, exudate management, quality of life improvement and/or cost-effectiveness.
3. Plan the length of use (time) of the advanced therapy and ensure it is part of the assessment, treatment and evaluation processes.
4. Choose an appropriate advanced therapy, based on product description, evidence, availability, funding, available resources, clinician education and patient acceptance.
5. Develop a patient-centred management protocol based on the location and availability of resources and services.
6. Communicate the plan. Communication includes care plan, including the length of time of product use, regular reports, images and photos as needed (evidence).
7. Instruct clinicians, caregivers and patients on the management protocol and provide follow-up information, including written and/or verbal communication to the care team.
8. Initiate the management protocol, ensuring there are built-in standardized assessment parameters to measure progress toward the identified goals of care.
9. Evaluate the impact of the management protocol to identify met and unmet goals of care.
10. Reassess the management plan at least every 2–4 weeks—more often if required—to avoid long-term use of advance therapies with no evidence of improvement.
11. Document results.
12. Publish the findings if possible and applicable.

By following a standardized protocol, variability can be minimized, allowing treatment outcomes (based on goals of care) to be assessed and compared. This will contribute to the much-needed evidence base required to support the appropriate use of advanced therapies.

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