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

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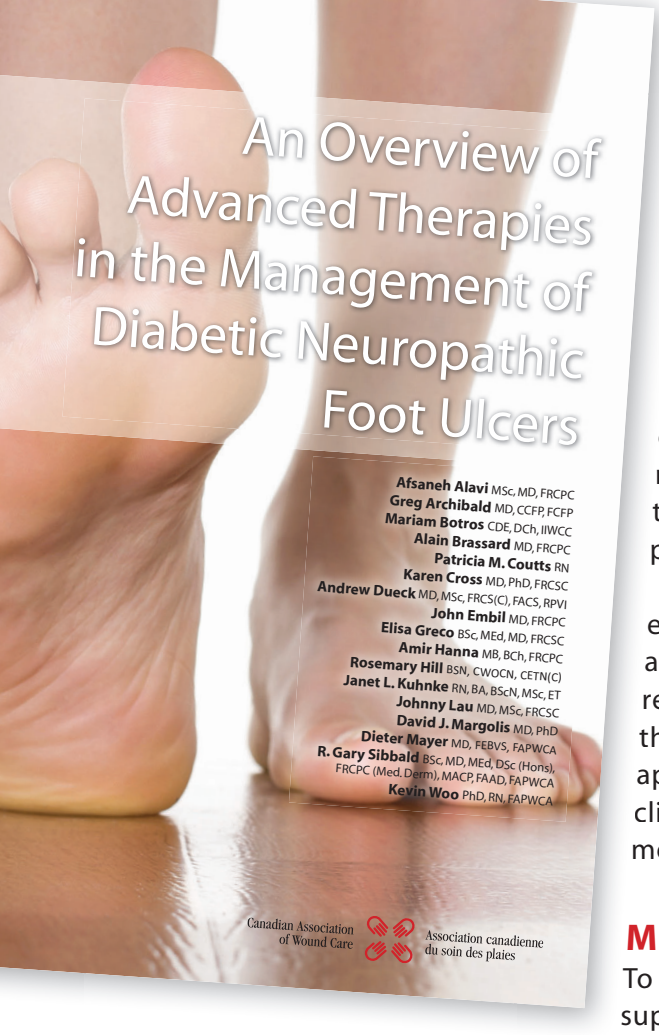
*With the support of an unrestricted educational grant from industry partners* the Canadian Association of Wound Care initiated a review of the literature regarding the use of advanced therapies in the management of diabetic neuropathic ulcers. The goal of the document was to provide an overview of the existing literature, review expert opinion and establish protocols for the use of advanced therapies in the treatment and management of diabetic foot ulcers. The full document has been published as a supplement to* Wound Care Canada *and* Diabetic Foot Canada e-Journal *and is available at www.woundcarecanada.ca/supplements/. A summary of the article is provided here.*

* Acelity Canada, Integra Canada ULC and Smith & Nephew




Foot complications in persons with diabetes are a major challenge, with diabetic neuropathic foot ulcers in particular being costly to the individual, caregivers and the health-care system.[1] If not managed properly they can lead to loss of limb and are associated with a high five-year mortality rate.[2] However, through education, monitoring, multidisciplinary teamwork and timely assessment and management,[3] diabetic foot ulcers (DFUs) are one of the most preventable diabetes-related complications.

The average costs associated with the healing of a DFU is reported to be as high as $45,000.[4] Timely and proper use of advanced therapies can be critical for shortening healing times, which may result in lower overall costs[5,6] 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.

While major hurdles exist—including cost, availability and lack of strong research data to support their use—advanced therapies have improved the clinician's toolkit of DFU treatment options.

## Methodology

To arrive at the evidence to support the full document (of which this article is a summary), a structured literature search on research related to diabetic foot ulcers published since 2000 was performed, with the results reviewed by an international consultant and a panel of Canadian health-care professionals with clinical and research experience in diabetic foot ulcers**.** Clinical practice guidelines that included advanced therapies were also reviewed. This was supplemented by a survey sent to wound care clinicians who identified their actual practices relating to advanced therapies.

## Conclusions from the Evidence

Summaries for each type of therapy examined follow below. For the complete reference list and tables of evidence, please see the full document.

### 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.

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 interstitial fluid may also reduce the surface bacterial colonization and increase the sequestration of excess MMPs.

The studies reviewed 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.

## 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 clinical trials (RCTs) on HBOT.[7,8]

Of the patients identified, 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.

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.

## 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 transduction pathways, GFs modulate cellular behaviours. They can act on adjacent cells, on the cell itself or on remote cells. Many different types of growth factors were investigated, including: platelet-derived growth factor (PDGF), platelet-rich plasma (PRP), epidermal growth factor (EGF), basic fibroblast growth factor (bFGF), granulocyte-colony stimulating factor (G-CSF), talactoferrin alfa, thrombin peptide (TP508) and keratinocyte growth factor (KGF).

In terms of 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 debridement). Overall, the adjunctive use of growth factors resulted in faster healing rates and a higher proportion of completely closed wounds compared with other treatments. PDGF is superior to HBOT in complete healing of DFUs.

## 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.

Overall, all 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, the grafts were found to be comparable to PDGF, with no significant differences between time to complete closure or wound healing rate.

### 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, and 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.

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.

### Physical Therapies

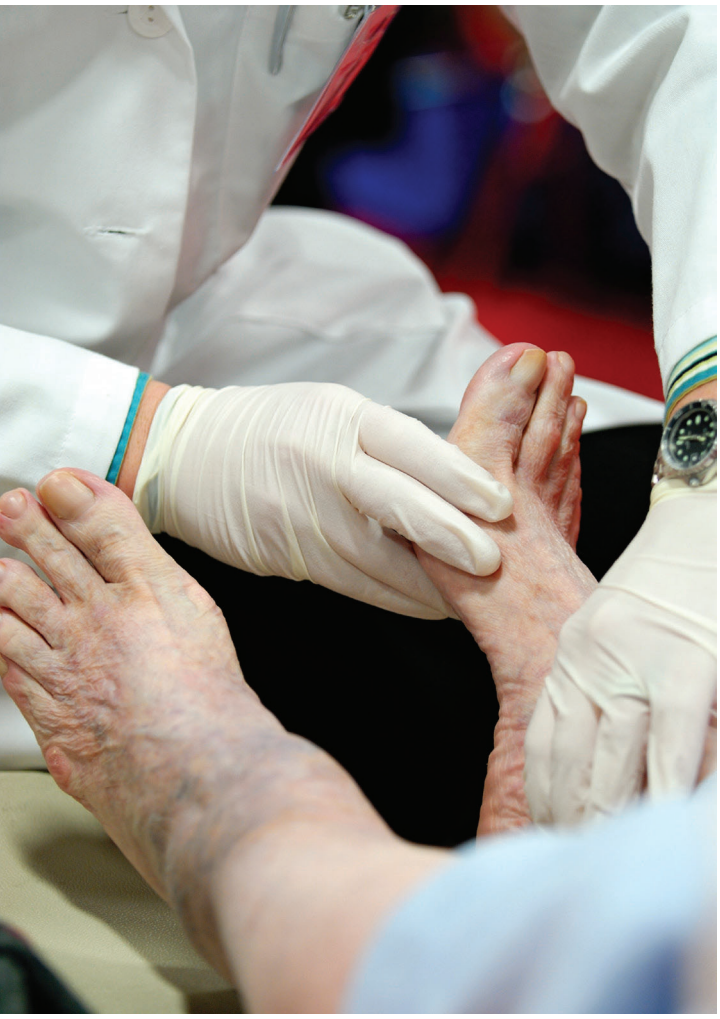
A number of physical therapies were reviewed, including:

**Laser therapy:** 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.

**Electrotherapy (including electrical stimulation – ES):** 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 transepithelial 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.



**External shock wave therapy (ESWT):** Shock waves targeted directly to the wound area to speed healing. 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:** Use of saline mist to deliver low frequency ultrasound to the wound. 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.

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.

### Other Therapies

De Marco Formula (DMF, a "procaine chemical combination of Procaine HCI and polyvinylpyrrolidone."[9]): 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.

## Summary of Expert Panel Opinions

Table 1 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.

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" and another said, "advanced therapy may be considered as an adjunct to pressure relief, and not a replacement for common sense and good care."

**Table 1.** Survey Summaries

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|---|---|
| **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. |

Some experts identified an issue with the integrity of the available studies, referring to bias and limited evidence.

## 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).

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**[10] 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, but also 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**[3] 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**[11] 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**[12] states that a 2006 study 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 2009 study, patients with higher A1c levels did experience wound healing, but over a significantly longer period than those with lower A1c.

## Next Steps

The general consensus among published research is that the decision to use advanced therapies must be guided by a combination of 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 on page 17, 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.

**In the next issue of *Wound Care Canada* we will look at the barriers to the delivery of advanced therapies as well as recommendations for overcoming them.**

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# Advanced Therapies Protocol for Diabetic Foot Ulcers

Canadian Association of Wound Care / Association canadienne du soin des plaies
www.cawc.net

| 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.