The role of topical oxygen therapy in the management of diabetic foot ulcer wounds in Scotland: round table recommendations

Duncan Stang, Matthew Young, Debbie Wilson, Sandie Montgomery, Drew Davidson

Citation: Stang D, Young M, Wilson D et al (2018) The role of topical oxygen therapy in the management of diabetic foot ulcer wounds in Scotland: round table recommendations. *The Diabetic Foot Journal* 21(1): 56–61

Article points

1. The evidence base on topical haemoglobin is growing and findings to date have been positive; Granulox®, a topical haemoglobin spray, is an adjunct therapy to best practice wound management.
2. The group designed a best practice pathway to provide guidance on assessment and management, with practical tips for application and review for using Granulox within good wound care practice.
3. Granulox therapy can be used on ulcer grades I–III after 4 weeks of standard care.

Key words

- Diabetic foot ulcer
- Oxygen therapy
- Texas Ulcer Classification
- Topical haemoglobin

Authors

Duncan Stang is Podiatrist and National Diabetes Foot Co-ordinator, Lanarkshire; Debbie Wilson is Diabetes Specialist Podiatrist, Lanarkshire; Sandie Montgomery is Vascular Consultant, Lanarkshire; Drew Davidson is Vascular Nurse Specialist, Greater Glasgow and Clyde; Matthew Young is Diabetologist, Edinburgh Royal Infirmary, Edinburgh, Scotland

Wounds require oxygen to heal to generate energy required for cellular functions necessary for healing and resistance against infection (Sen, 2009). Expert clinicians from across Scotland met in Edinburgh in October 2017 to consider the type of patient and non-healing diabetic foot ulcers suitable for topical haemoglobin and to develop an algorithm for using Granulox® for multidisciplinary teams in Scotland. The group's recommendations are presented here.

Oxygen is required for normal cellular processes, and it has been accepted wisdom for some time that oxygen is vital to wound healing. Mild hypoxia (low oxygen) is a normal biological response following an injury, and 97% of chronic, non-healing wounds have been shown to have low oxygen levels (Wounds UK, 2017).

Oxygen therapy was first used in the wound care field in the 1960s, following the discovery that the burns of those receiving treatment in hyperbaric chambers for carbon monoxide poisoning healed more quickly than those who did not receive hyperbaric oxygen treatment (Wada et al, 1965). More recently, the role of topical oxygen therapy, without the need for full-body hyperbaric chambers, has come to the fore (Tawfick and Sultan, 2009).

Granulox® (infirst Healthcare, London, UK) is a topical haemoglobin spray produced from sterile porcine products, which is an adjunct therapy to best practice wound management. As Granulox is sprayed on the non-healing or slow-healing wound (following appropriate debridement), the haemoglobin binds with atmospheric oxygen and carries it to the wound bed where it diffuses into the tissue. The published research on topical haemoglobin is growing and findings to date have been positive: a European Wound Management Association (EWMA) evaluation of the currently available oxygen therapies in wound care awarded Granulox a Grade 1B, indicating a positive benefit risk value with moderate quality of evidence (randomised controlled trials with limitations and very strong observational studies) (Gottrup et al, 2017).

With this in mind, clinicians for the multidisciplinary foot care team met in Edinburgh in October 2017 with the following objectives:

- To create guidelines for the use of Granulox therapy for people with diabetic foot ulcers, with the overall objective of improving patient care
- To consider where 'oxygen' treatment fits alongside other good wound care practice
- To consider for which patients Granulox therapy is most appropriate
- To develop recommendations for the use of Granulox therapy within hospital-based multi-disciplinary teams or foot clinics across Scotland. The group worked through questions to complete these objectives.

Which wound types are currently responding best to Granulox treatment?

Short-term (≤7 months) case and pilot studies in the UK have demonstrated an elimination of slough (Hunt, 2015), pain and wound area (Wounds UK, 2017), as well as increase granulation of epithelial tissue and improvement in patient quality of life following treatment with Granulox in non-healing

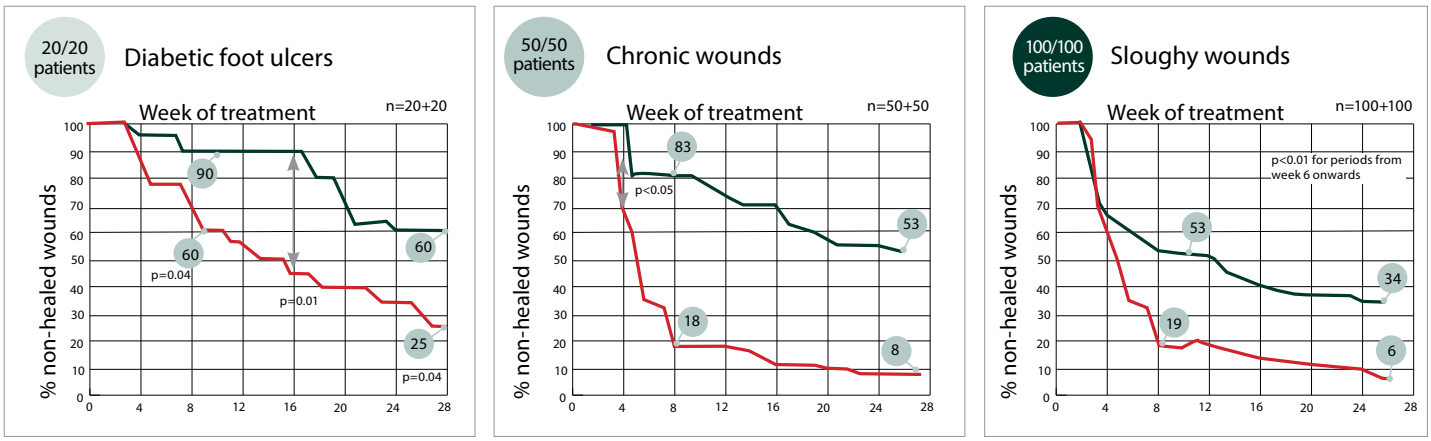

Figure 1. Percentage of wounds not closed by week in three studies comparing Granulox therapy (red) to standard care (blue).

and slow-healing ulcers (Green et al, 2014; Green and Mohamud, 2014; Norris, 2014; Tickle, 2015). Based on their own clinical observations and published research, the panel agreed that wounds that were slow-healing, painful and sloughy were responding best to Granulox treatment, especially in the initial 4–8 weeks of Granulox use (Arenbergova et al, 2015; Hunt and Elg, 2016; Hunt and Elg, 2017; *Figure 1*).

How should oxygen therapy fit into current management of diabetic foot ulcers (DFUs)?

Oxygen therapy should be an adjunct to good wound care practice and run alongside standard wound bed preparation (after cleansing and debridement) for the management of DFUs as per *Best Practice Guidelines for Wound Management of Diabetic Foot Ulcers* (Wounds International, 2013).

The results from the 2014–2016 National Diabetic Foot Audit for England and Wales (NHS Digital, 2017) indicate that immediate referral to a multidisciplinary foot care team when a DFU is suspected offers the best clinical outcomes at 12 weeks for patients. Quick referral and patient education are vital for good wound care practice. All new DFUs should be seen by a multidisciplinary foot care team and at this time, the specialist team can make an informed decision regarding the initiation of oxygen therapy, which should be alongside current standard practice for debridement, cleansing and offloading.

The panel designed a best practice pathway to provide guidance on DFU assessment, management and Granulox therapy within good wound care practice (*Figure 2*). Full holistic assessment of both the patient and wound is essential. Once Granulox is initiated, the wound and patient should be assessed every 4 weeks, using clinical judgement to determine whether wound progression is occurring. Expected markers of healing would be reduction in wound size and/or improvements to the wound bed, tissue, range of movement or exudate volume.

Which patient or wound characteristics suggest high-risk of microvascular complications, and thus may benefit from early topical oxygen therapy?

Patients with diabetes are at increased risk of microvascular complications (e.g. retinopathy, nephropathy and neuropathy). Patients with neuropathy have impaired cutaneous blood flow and can also have ischaemia, which can affect DFU healing (NICE, 2016). The group agreed that if an individual has a DFU and nephropathy, then topical oxygen therapy could be considered appropriate (Ndip et al, 2010). Measuring ischemia in people with neuropathy can be difficult, for example, the skin can continue to feel warm and other complications, such as renal calcinosis, can increase the risk of slow healing. There are a number of diagnostic tests and indicators that can be implemented to detect blood flow and peripheral arterial disease (see *Figure 3*).

Poorly oxygenated wounds can be suggestive of a microvascular complications, and thus may benefit from early topical oxygen therapy.

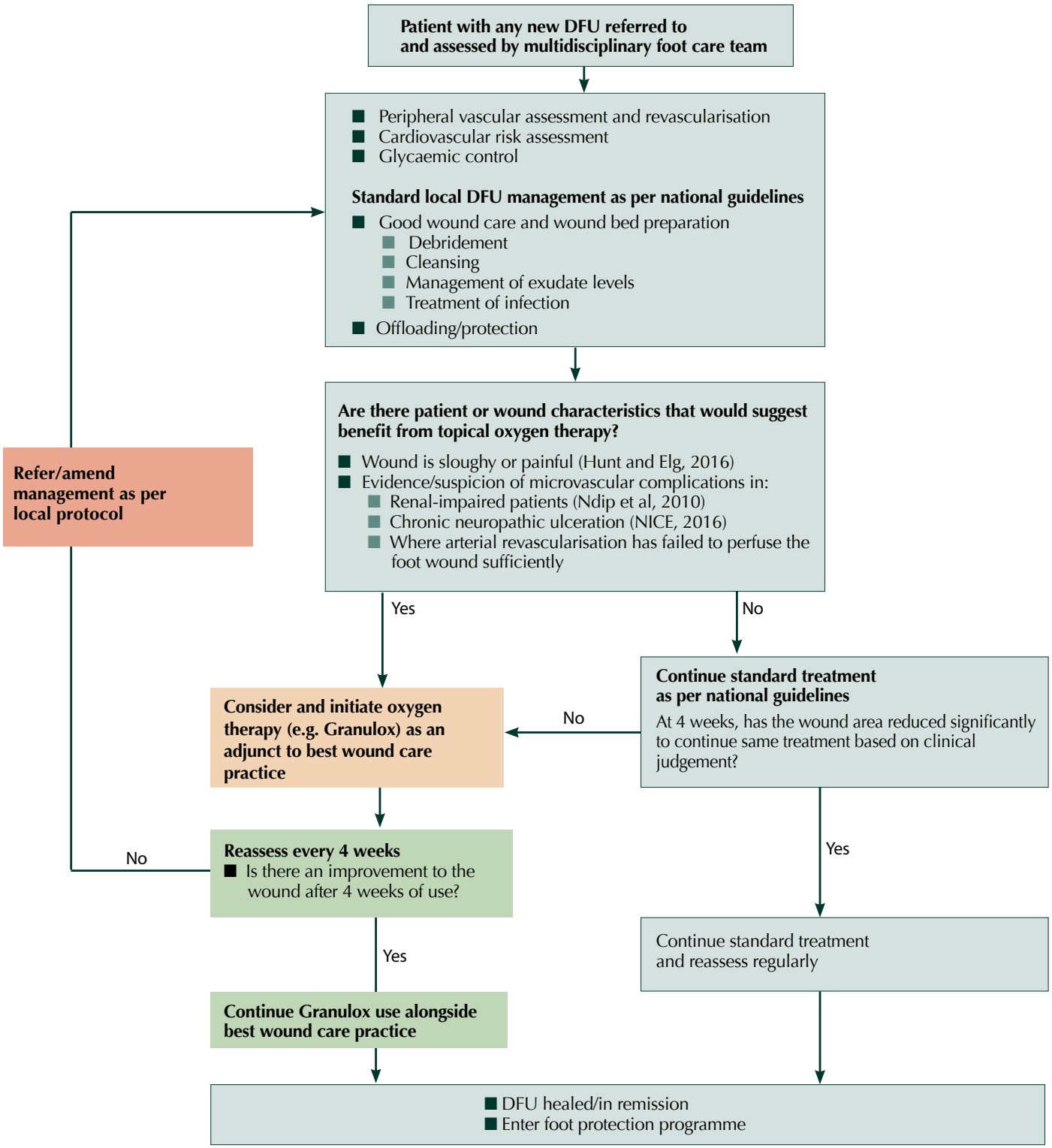

Figure 2. Principles of management of DFUs with Granulox (adapted and simplified from Frykberg and Banks, 2016; World Union of Wound Healing Societies, 2016).

Box 1. The Texas Classification system (Laverty et al, 1996; Oyibo et al, 2001).

The Texas Classification system assesses ulcer depth, the presence of wound infection, and the presence of clinical signs of lower-extremity ischaemia. The grades of the UT system are as follows: grade 0 (pre- or postulcerative site that has healed), grade 1 (superficial wound not involving tendon, capsule, or bone), grade 2 (wound penetrating to tendon or capsule), and grade 3 (wound penetrating bone or joint).

Within each wound grade there are four stages: clean wounds (stage A), non-ischaemic, infected wounds (stage B), ischaemic, non-infected wounds (stage C), and ischaemic, infected wounds (stage D).

		Ulcer grade (depth)				Consideration for early use of Granulox therapy
		0	I	II	III	
Ulcer stage	A	Pre/post ulcerative lesion completely epithelialised	Superficial lesion, not involving tendon, capsule or bone	Wound penetrating to tendon or capsule	Wound penetrating to bone or joint	Post-surgical amputation wounds
	B	Non-ischaemic, infected wound	Non-ischaemic, infected wound	Non-ischaemic, infected wound	Non-ischaemic, infected wound	Sloughy wounds
	C	Ischaemia, non-infected wound	Ischaemia, non-infected wound	Ischaemia, non-infected wound	Ischaemia, non-infected wound	Not suitable for vascular intervention
	D	Ischaemic and infected wound	Ischaemic and infected wound	Ischaemic and infected wound	Ischaemic and infected wound	Severe PAD* Ulcer pain
People with CKD		Granulox therapy not required	For people with stage >3 CKD, consider for earlier use due to increased risk of delayed wound healing			
Necrotic tissue		Do not use directly on necrotic tissue. Debride first if appropriate.				

Key

- Consider Granulox therapy for early use
- Consider Granulox therapy if <40% wound size reduction after 4 weeks of standard care
- Granulox therapy is not required for ulcer grade 0

***Indicators of severe PAD**

Toe pressure	<50mmHg
$TcPO_2$	<30mmHg
ABPI	<0.6
Pulse oxymetry	<60mmHg

Figure 3. 'Traffic light' system for the initiation of Granulox therapy based on the Texas Ulcer Classification (adapted from Laverty et al, 1996). CKD=chronic kidney disease; PAD=peripheral arterial disease.
Note: Granulox can be used on infected wounds.

Evidence shows that poorly oxygenated wounds almost never heal, while oxygenated wounds do – in one study, 97% of non-healing wounds were found to have low oxygen levels (Hauser, 1987). Non-healing wounds due to a lack of oxygen may signal underlying macrovascular problems (Sen, 2009); therefore, it is important to check for macrovascular complications, while initiating early Granulox therapy. However, wound ischaemia can often go unnoticed and this may be due to difficulty in measuring tissue oxygenation ($TcPO_2$), absence of cardinal signs and symptoms, or lack of nursing/podiatry time and resources. The panel recommended that clinicians recognise the role of hypoxia in non-healing wounds, and that further work be done to raise awareness of the role of oxygen in non-healing wounds and the potential for interventions that can aid healing.

The panel also agreed that topical oxygen therapy wound be appropriate for individuals where arterial revascularisation had failed to perfuse the DFU sufficiently.

DFU classification system

The Texas Ulcer Classification (Laverty et al, 1996) is a tool used in Scotland and parts of England to classify all new DFUs (*Box 1*). Based on the Texas Ulcer Classification, the panel developed a "traffic light" system for determining when Granulox therapy is appropriate to initiate or for early use (*Figure 3*).

After 4 weeks of standard care, Granulox therapy can be used on ulcer grades I–III, and is indicated for use on sloughy or infected wounds. The panel also identified patient groups and wound types that may benefit for early oxygen therapy intervention: those not suitable for vascular intervention, those with severe peripheral arterial disease, ulcer pain

or chronic kidney disease; and post-surgical amputation wounds or sloughy wounds.

Summary

Haemoglobin therapy should be considered after 4 weeks of standard care in patients with a non-healing wound, and could be considered earlier for patients at high risk of delayed wound healing. Full holistic assessment of both the patient and wound is vital, and any underlying causes for non-healing wounds should be treated as priority before initiation of an adjunct therapy.

The 'traffic light' system for the initiation of Granulox therapy based on the Texas Ulcer Classification and best practice algorithm developed by the panel provide simple tools for clinicans in day-to-day practice to know when and how to initiate Granulox. ■

Arenbergerova M, Engels P, Gkalpakiotis S et al (2013) Effect of topical haemoglobin on venous leg ulcer healing. *EWMA J* 13(2): 25–30

Frykberg RG, Banks J (2016) Management of diabetic foot ulcers: a review. *Federal Practitioner* 33(2): 16–23

Green M, Parmer R, Padhiar M (2014) *Granulox in practice for 4 patient case studies*. Poster presented at Wounds UK, November 10, 2014

Green M, Mohamud L (2014) Use of Granulox haemoglobin spray in clinical practice: case report series. J *Community Nursing* suppl: S1–S8

Gottrup F, Dissemond J, Baines et al (2017) Use of oxygen therapies in wound healing, with special focus on topical and hyperbaric oxygen treatment. *J Wound Care* 26(5): Suppl S1–S42

Hauser CJ (1987) Tissue salvage by mapping of skin surface transcutaneous oxygen tension index. *Arch Surg* 122(10): 1128–30

Hunt SD (2015) Topical oxygen-haemoglobin use on sloughy wounds: positive patient outcomes and the promotion of self-care. *Wounds UK* 11(4): 90

Hunt S, Elg F (2016) Clinical effectiveness of hemoglobin spray (Granulox†) as adjunctive therapy in the treatment of chronic diabetic foot ulcers. *Diabetic Foot Ankle* 7: 33101

Hunt S, Elg F (2017) The clinical effectiveness of haemoglobin spray as adjunctive therapy in the treatment of chronic wounds. *J Wound Care* 26(9):1–8

Lavery LA, Armstrong DG, Harkless LB (1996) Classification of diabetic foot wounds. *J Foot Ankle Surg* 35(6):528–31

Margolis DJ, Allen-Taylor L, Hoffstad O et al (2004) The accuracy of venous leg ulcer prognostic models in a wound care system. *Wound Repair Regen* 12(2): 163–8

Ndip A, Rutter MK, Vileikyte L et al (2010) Dialysis treatment is an independent risk factor for foot ulceration in patients with diabetes and stage 4 or 5 chronic kidney disease. *Diabetes Care* 33(8):1811–6

NICE (2016) *Diabetic foot problems: prevention and management (NG19)*. NICE, London

NHS Digital (2017) *National Diabetes Foot Care Audit Report 2014-2016*. NHS Digital, London

Norris R (2014) A topical haemoglobin spray for oxygenating chronic venous leg ulcers. *Br J Nurs* 23(20): S48–S53

Oyibo SO, Jude EB, Tarawneh I (2001) A comparison of two diabetic foot ulcer classification systems: the Wagner and the University of Texas wound classification systems. *Diabetes Care* 24(1): 84–8

Sen CK (2009) Wound healing essentials: let there be oxygen. *Wound Repair Regen* 17(1):1–18

SIGN (2017) *Management of Diabetes. A National Clinical guideline*. Scottish Intercollegiate Guidelines Network, Edinburgh

Tawfick WA, Sultan S (2009) Does topical wound oxygen (TWO2) offer an improved outcome over conventional compression dressings (CCD) in the management of refractory venous ulcers (RVU)? A parallel observational comparative study. *Eur J Endovasc Surg* 38(1): 125–32

Tickle J (2015) A topical haemoglobin spray for oxygenating pressure ulcers: a pilot study. *Br J Community Nurs* Suppl S14–S8

Wada J, Ikeda T, Kamata K (1965) Oxygen hyperbaric treatment for carbon monoxide poisoning and severe burns in coal mine gas explosion. *Igakunoayumi* (Japan) 54: 68

Wounds UK (2017) O*xygen Wound Therapy: The Clinical and Cost Impact of Using Topical Haemoglobin Spray (Granulox®)*. London: Wounds UK, 2017. Available to download from: www.wounds-uk.com (accessed 26.03.2018)

World Union of Wound Healing Societies (2016) *Position Document: Local Management of Diabetic Foot Ulcers*. Wounds International, London. Available at: http://www.woundsinternational.com/wuwhs/view/position-document-local-management-of-diabetic-foot-ulcers (accessed 26.03.2018)

Wounds International (2013) *Best Practice Guidelines: Wound Management in Diabetic Foot Ulcers*. Wounds International, London. Available at: https://bit.ly/2fV6oGT (accessed 26.03.2018)

Wounds UK (2017) Oxygen wound therapy: The clinical and cost impact of using topical haemoglobin spray (Granulox®). Wounds UK, London. Available to download from: www.wounds-uk.com (accessed 26.03.2018)