Excellence in diabetic foot ulcer management: accelerate healing with topical oxygen therapy

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Oxygen is needed in every phase of wound healing; however, chronic wounds are often hypoxic. Topical oxygen therapy (TOT) is an intervention that can be used to improve oxygen saturation in the wound bed and support healing, especially in the management of hard-to-heal wounds, such as diabetic foot ulcers, venous leg ulcers and pressure ulcers. One approach to providing TOT to wounds is through the application of Granulox®, a topical haemoglobin spray (Mölnlycke, Sweden), as an adjunctive therapy. In numerous clinical studies, it has been demonstrated that the inclusion of Granulox as part of the standard of care for hard-to-heal wounds can accelerate their healing and impart associated economic benefits. A Mölnlycke-sponsored symposium was held at the European Wound Management Association 2022 Conference in Paris, France. The symposium covered three main areas: introduction to the concept of TOT and the use of Granulox, clinical experience in the form of case studies using Granulox as an adjunctive therapy, including those from a revascularisation perspective and, finally, the health economic perspective of using Granulox as an adjunctive therapy.

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Oxygen is needed in every phase of wound healing — haemostasis, inflammation, granulation and epithelialisation; however, chronic wounds are often hypoxic (Dissemond et al, 2018). Oxygen availability is a clear predictor for wound healing outcome (Bishop, 2008). Various technologies are available to deliver oxygen to the wound; Granulox® (Mölnlycke, Sweden), a topical haemoglobin spray, is one product that delivers oxygen to the wound by aiding oxygen diffusion.

This report details the proceedings of the Mölnlycke-sponsored symposium at the European Wound Management Association (EWMA) Conference in Paris, France, in May 2022, chaired by Professor Paul Chadwick from the United Kingdom. He was joined by Nurse Specialist (Wound Care) Sandra Janssen from The Netherlands, Consultant Vascular Surgeon Dr Ivan Cvjetko from Croatia, and Mölnlycke Chief Medical Officer, Executive Vice-President Regulatory Affairs and Quality Assurance Dr Emma Wright. The symposium had the following aims:

- To highlight the importance of oxygen in wound healing and introduce the concept of TOT
- To present clinical experience of the use of Granulox as part of the management regimen of complex, hard-to-heal wounds, including those from a revascularisation perspective
- To explore how Granulox can be used in clinical practice
- To explore the health economic perspective of using Granulox as an adjunctive therapy.

Oxygen is needed at every wound healing phase

Professor Paul Chadwick began by talking about the role of oxygen in wound healing. Oxygen is essential during each phase of wound healing (Bishop, 2008). During the inflammatory phase, oxygen is required for the activation of neutrophils and macrophages and the formation of reactive oxygen species (ROS) that are important in bacterial defence.

In the granulation phase, oxygen is required for the formation of the extracellular matrix (ECM) and for new vessel formation (neoangiogenesis). Oxygen is required for oxidative metabolism derived energy synthesis, protein synthesis and the maturation (hydroxylation) of extracellular matrix proteins, such as collagen. Hypoxic wounds deposit collagen poorly and become infected easily, and angiogenesis is reported to be directly proportional to the partial pressure of

Table 1. Oxygen requirements during wound healing.		
Wound after injury in the inflammatory phase	**Wound in granulation phase**	**Wound in epithelialisation phase**
■ Activation of neutrophils and macrophages ■ Formation of reactive oxygen species (ROS)	■ Formation of the extracellular matrix (ECM) by fibroblasts ■ Collagen building ■ Neoangiogenesis	■ Cell division ■ Tissue remodelling ■ Transformation from collagen 3 to collagen 1

oxygen (pO_2) in injured tissues. When oxygen is missing, tissue in chronic wounds often only build precursors to collagen, rather than complete collagen. This leads to less elastic, less tensile and less resistant tissue.

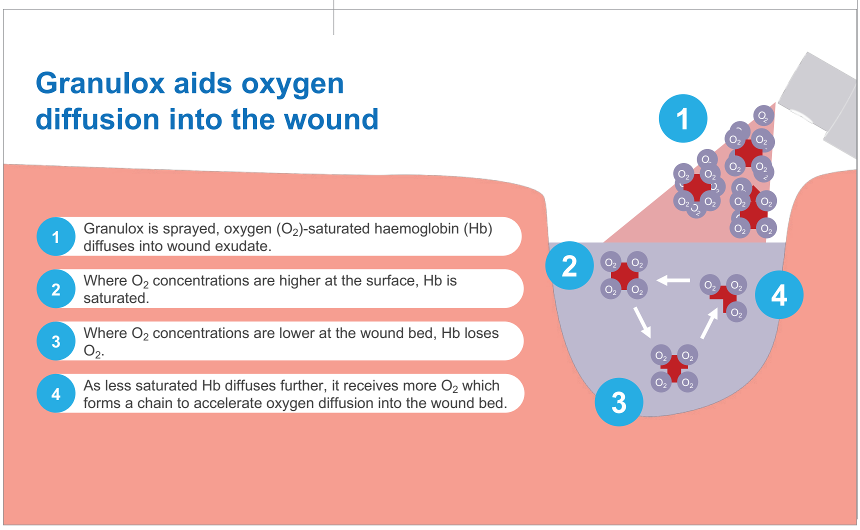
In the epithelialisation phase, an increase in energy demand leads to a hypermetabolic state wherein additional energy is generated from oxidative metabolism, thereby increasing the oxygen demand of the healing tissue. The rate of epithelialisation depends on access to local oxygen. *Table 1* summarises the oxygen requirements during wound healing.

Consequences of hypoxia in wound healing

Hypoxic tissue conditions lead to impaired bacterial defense, resulting in an increased risk of wound infection and chronic inflammation. If there is no oxygen, there is a state of hypoxia, which is a 'common challenge' in wound chronicity. To support wound healing, normal oxygen levels must be restored. If this is not achieved and the wound remains hypoxic, the wound is likely to be stalled in a state of chronicity. Indeed, poor, or inadequate oxygen perfusion to the wounded area is an indicator of slow wound progression (Hauser, 1987; Dissemond et al, 2015).

One of the biggest challenges in delivering oxygen to the wound bed is that wounds cannot access oxygen from the air. Oxygen accounts for 21% of the earth's atmosphere; however, oxygen is poorly soluble in liquids and even a thin layer of exudate will slow its diffusion substantially, as illustrated by Einstein–Smoluchowski's equation of diffusion. In the Einstein-Smoluchowski diffusion model, a liquid film of 0.1 mm reduces the diffusion rate by 99% . Therefore, exudate is a barrier to oxygen diffusion.

Figure 1. Granulox mode of action.



Technologies available for delivering topical oxygen to wounds

There are a range of methods available for the delivery of oxygen to the wound tissues. The EWMA consensus on the 'Use of Oxygen Therapies in Wound Healing' reviewed the available evidence base at the time on methods of oxygen delivery to the wound tissue (Gottrup et al, 2017). The type of oxygen delivery selected is based on the wound characteristics, the patient's needs and the location where care is being provided. The EWMA consensus identified the following methods to deliver oxygen to the wound tissues (Gottrup et al, 2017):

- Oxygen diffusion enhancer (e.g. haemoglobin)
- Oxygen-releasing wound dressing
- Topical oxygen perfusors
- Topical oxygen chambers
- Hyperbaric oxygen therapy chambers.

Granulox Haemoglobin Spray

Granulox is a topical oxygen diffusion enhancer — haemoglobin is applied as a spray to the wound bed and binds to oxygen in the air. Saturated haemoglobin diffuses within the wound bed and releases oxygen to the hypoxic environment *[Figure 1]*.

How to use Granulox

Granulox is an adjunct to standard of care. Once it has been established that Granulox is suitable for use on a wound, the first step is to conduct appropriate wound bed preparation as per facility protocol (i.e. cleansing and debriding). Granulox should also be used alongside appropriate infection control measures, which will help ensure that Granulox can effectively facilitate enhanced diffusion *[Figure 2]*.

Wound condition	Appropriate wound bed preparation*	Granulox YES / NO
Infection, colonisation	Mandatory	
Slough		
Fibrin		
Biofilm		
Necrosis		
Exudation		
Cavity		
Avital tissue	Reconsider after appropriate surgical treatment	

**appropriate infection control and wound bed preparation including debridement are still important to ensure wound healing and to make sure Granulox can effectively facilitate enhanced diffusion.*

Figure 2. When to use Granulox as an adjunct to wound care therapy based on the wound condition.

Box 1. Evidence supporting the use of Granulox as an adjunct to standard care.

- Time to heal DFUs was 50% shorter with the addition of Granulox than with standard of care alone (Hunt and Elg, 2016)
- Twice as many chronic wounds healed at 8–16 weeks with the addition of Granulox compared to standard of care alone (Hunt and Elg, 2016; 2017; Elg and Hunt, 2018)
- More than 70% lower average pain scores reported at 4 weeks with the addition of Granulox than with standard care alone in chronic wounds (Hunt and Elg, 2017)
- 99% less slough in chronic wounds observed after 4 weeks of Granulox as an adjunctive therapy compared to 33% with standard care alone (Hunt et al, 2018)
- Treatment costs of DFUs was at least 40% lower with the addition of Granulox than with standard care alone (Brüggerjürgen et al, 2017).

In vivo evidence on oxygen transfer

Petri et al (2016) at the University Hospital of Essen, Germany, developed an *in vivo* method to differentiate between haemoglobin that is bound and not bound to oxygen in the tissue below venous leg ulcers. The method uses photo-acoustic imaging, whereby pulsed laser light with a specific wavelength is applied to the tissue. The target molecules — in this case, haemoglobin — absorb the energy from the laser and the short temperature rise leads to a thermo-elastic expansion, which can be detected as an ultrasound wave.

This information is used to create a 3D image of the level of oxygenation of haemoglobin. Petri et al (2016) showed that, at baseline, the leg ulcer showed just 56% oxygen saturation, but 20 minutes after the application of Granulox, oxygen saturation had increased to 79% (P=0.043).

Clinical evidence

Studies have shown that when Granulox was applied to chronic wounds as an adjunct to standard care compared to standard care alone, there were fewer dressing changes and less nursing time was required, reducing total treatment costs (Brüggerjürgen et al, 2017). See *Box 1* for a summary of the evidence supporting the use of Granulox as an adjunct to standard care.

'Seeing is believing': personal experiences of using Granulox on diabetes-related foot ulcers and imaging analysis to measure oxygenation

Nurse Specialist (Wound Care) Sandra Janssen described how the multidisciplinary team (MDT) work together at the Wound Expertise Centre Elkerliek Hospital, The Netherlands, to care for people with diabetes-related foot ulcers using Granulox as an adjunct to standard care. In 2019, a group of specialists from the hospital were invited to test Granulox to assess whether it should be reimbursed. At the same time, the team were also testing TIVITA® (Protex Healthcare) — a camera that uses spectroscopy and tissue oximetry for hyperspectral imaging — so they were able to review the visual effects of using Granulox on the wound. Sandra Janssen presented nine patient cases of how Granulox has been used as an adjunct therapy to standard care. *Cases 1* and *2* are two examples from the presentation.

'Rethinking revascularisation in DFU management'

Dr Ivan Cvjetko, Consultant Vascular Surgeon, Croatia, presented to the audience his clinical experience from a revascularisation perspective. The microcirculation of the human body may seem insignificant, but it is vital for blood flow and wound healing as it contains half of the circulating blood. Dr Cvjetko explained that the number of patients with diabetes in the country has increased year on year — in nearly 20 years the number of patients in Croatia with diabetes has increased from 5,896 in 2000 to 315,298 in 2019. The complications associated with high glycaemia either present as a neuropathy (leading to ulceration) or ischaemia.

The 5-year mortality rates associated with diabetes-related foot complications and cancer are comparable, so the rising prevalence of diabetes is a serious health concern. The mortality associated with diabetes-related foot complications is also proportional to the severity of peripheral artery disease (PAD). As part of the holistic diabetic foot assessment, the level of ischaemia should be identified and managed accordingly (*Table 2*; Rutherford, 2009; Gunawansa, 2017).

Management of limb ischaemia is very complex, but the take-away conclusion is that for Class 1 limb ischaemia, there is time to conduct additional tests before treatment, whereas once ischaemia has developed and worsened to class III, it is no longer possible to save the extremity.

Surgery to alleviate the symptoms of ischaemia includes endovascular repair (EVAR) techniques that involve the placement of a stent-graft (fabric-covered tube) into the aneurysm through a small hole in the blood vessels in the groin. The utilisation of EVAR techniques means that open surgery can be avoided. However, there are still challenges and considerations as EVRA techniques do not address the thrombosis or the atherosclerosis (inflammatory process) that is causing PAD, they simply treat the

Case 1. Oxygen requirements in wound healing.

The patient was a 78-year-old male with diabetes and a history of a ruptured aortic aneurysm. Four years prior to the baseline visit, he had abdominal surgery to remove a stomach carcinoma and was told the surgical wound would never heal. When he was reviewed by the wound team at Elkerliek Hospital, this individual had five wounds, which had been present for 1.5 years *[Figure 3a]*. Three wounds were related to the original abdominal surgery that had not healed, and two wounds were in the skin folds of his abdomen. Granulox was initiated as an adjunct to standard care, but as Granulox was not reimbursed by his insurance provider, the patient paid for the product himself. Wound debridement was too painful, even with local anaesthetic. The patient showered every 2 days, and the nurses would apply Granulox, non-adherent gauze and an absorbent dressing to the five wounds. *Figure 3b* shows the wound after 3 weeks of using Granulox as an adjunctive therapy to standard care. After 6 weeks, the wound fully healed.

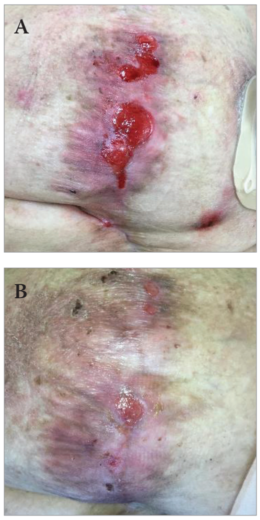


Figure 3. (a) Patient in case 1 at baseline; (b) after 3 weeks of using Granulox as an adjunctive therapy to standard care

Case 2. Oxygen requirements in wound healing.

The patient was a 39-year-old female with diabetes. Over the preceding years, she had struggled to manage her diabetes and had a history of foot complications, including abscesses and amputations. She had no underlying arterial or venous issues. The patient developed a wound from walking; Granulox was added as an adjunct to standard of care *[Figure 4a]*. The patient showered every two days. Granulox was sprayed onto the wound and covered by a capillary action dressing and an absorbent dressing. An elastic, adhesive bandage was applied to hold the dressings in place; the wound fully healed after 3 months *[Figure 4b]*. The TIVITA technology combines imaging with spectrometry and tissue oximetry to give the hyperspectral imaging *[Figure 4c]*. The first row shows a normal coloured image of the wound and the part of the body where it is located. The second row shows the oxygen saturation of the skin at 1mm in depth. The tissue haemoglobin image shows the relative tissue haemoglobin index of the tissue at 1mm in depth, and the fourth row shows the near infrared image: the oxygen saturation of the skin at 3 to 6mm in depth. The final row shows the amount of water, oedema in the superficial skin, and tissue water index. The colours in the images show a relative colour scale — blue means zero percent and red means 100 percent.

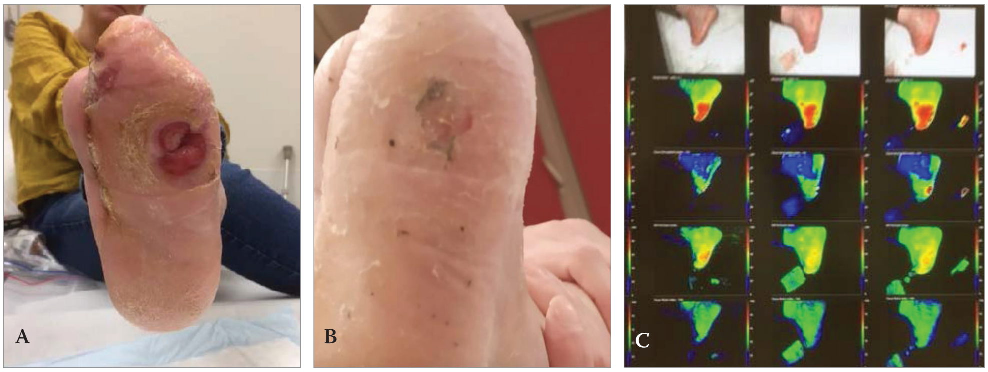


Figure 4. (a) Patient in case 2 prior to Granulox; (b) Wound is fully healed after 3 months; (c) TIVITA image showing oxygen saturation before Granulox application, immediately after and 3 minutes after.

consequences of the atherosclerosis. Additionally, revascularisation can sometimes fail due to inadequate blood flow, endothelial injury and/or hypercoagulability.

Diabetes-related foot ulceration is a potentially lethal condition, but surgery and stenting are not the answer for every patient. Neither is it possible or realistic to perform endovascular surgical treatment on every artery in all patients, and even if this was possible, it would not stop amputations from happening.

Ideal diabetic foot ulcer (DFU) treatment involves the MDT and management of the underlying causes of the wound

The treatment of a person with a DFU should be under the care of the MDT. The specialist MDTs are supported by and centred around the patient

Table 2. Classification of acute limb ischaemia (adapted from Rutherford, 2009; Gunawanza, 2017).

Arterial Category	Sensory impairment	Motor impairment	Doppler signal Category	Venous Doppler signal	Management options	Associated risk
Class I Viable – No immediate threat	No	No	Audible	Audible	Observation, diagnostics and treatment	
Class IIa Marginally threatened	Minimal in the toes or none	No	Often inaudible impairment	Audible	Immediate attempt to revascularise	Increasing risk of irreversible ischaemia and damage
Class IIb Immediately threatened	Involves forefoot ± Rest pain	Mild to moderate	Usually inaudible	Audible	Immediate attempt to revascularise	Increasing risk of amputation
Class III Irreversible	Anaesthetic	Paralytic/rigor	Inaudible	Inaudible	Amputation	

Box 2. What is health economics?

Health economics is the study of how society uses its limited resources to produce, distribute and consume healthcare goods and services with the aim of putting society on the path towards a state of complete physical, mental, and social wellbeing. Based on this definition, health economics relates not only to saving money, but also about people and their beliefs and values.

The potential value of a technology is determined by multiple considerations (Lakdawalla et al, 2018), and the value is always compared to another technology on a range of considerations:

- Safety: Is it safe?
- Efficacy: Does it work under ideal conditions? (e.g. evidenced by randomised controlled trials)
- Effectiveness: Does it work in real life? (e.g. evidenced by case studies and registry data)
- Cost-effectiveness: Is it value for money?
- Budget impact: Is it affordable?
- Moral, cultural and legal impact: Are there other considerations?

and their family. The patient can be supported in following a treatment plan that includes pharmacological interventions and lifestyle changes that will improve the likelihood of healing and reduce the risk of recurrence (i.e. smoking cessation, reduction of calorie intake, exercise to support metabolic and glycaemic control). Local care of the wound begins with a thorough wound assessment to determine the DFU classification. Local wound care should involve thorough and regular cleansing (for example with Granudacyn Wound Irrigation Solution (hypochlorous acid; Mölnlycke) and debridement, appropriate dressing selection, infection management and offloading of the DFU or weight-bearing surfaces. Granulox can be added as an adjunct to standard of care as part of the DFU treatment and management regimen.

Dr Cvjetko described how positive clinical and patient experiences using Granulox has led to its integration into clinical protocol for chronic wounds in the facility where he is based. If a wound has not healed within 21 days, the patient is referred to a wound specialist who will ensure that all the underlying causes or comorbidities can be addressed accordingly (e.g. infection control, revascularisation, compression, offloading and metabolic control). If the wound still does not improve, Granulox is added as an adjunct to standard care.

A cost-effective approach to wound healing

Dr Emma Wright, Chief Medical Officer, Executive Vice-President Regulatory Affairs and Quality Assurance, Mölnlycke, closed the symposium with an introduction to health economics *[Box 2]*, followed by the health economic perspective of Granulox as an adjunct to standard care. When reviewing the cost-effectiveness of Granulox, there are a range of questions to consider:

- Does it increase the healing rate in stagnant, non-healing wounds?
- Does it increase the healing rate in chronic wounds that are on a healing trajectory?
- How easy is it to use and implement?
- Is patient selection required?

In an ideal world, we are looking for a new product that is more clinically effective and less costly than the current standard of care. When comparing a new technology to standard care, the first element to assess is the budget impact. The budget impact is the costs involved in bringing the product to the clinic. To calculate the budget impact, first the patient population is reviewed to estimate the current costs associated with consumption of healthcare resources (e.g. dressings and other consumables used during dressing changes, caregiver time, hospital beds, drugs, diagnostic tests). The cost of making the new technology available is also determined by reviewing the unit cost of the new technology, plus any other changes to practice that may be required to use the technology safely and effectively. The break-even point is the point in time when the cost of the current technology is the same as the new technology (Choudhary et al, 2013).

A challenge in measuring cost-effectiveness in wound care is that wounds heal at different rates; while the average wound is estimated to heal in an average of 6–8 weeks, we know that this isn't always the outcome and wounds can often take much longer to heal. New technologies need to reduce healing time to be cost-effective.

The clinical effectiveness and healing rates of Granulox as an adjunctive to standard of care for chronic wounds has previously been reported in a range of studies *[Box 1]*. In a 26-week study undertaken in the community setting in the United

Kingdom, more wounds healed and the wounds healed quicker in the cohort where Granulox was added to standard care (90%; *n*=45/50) than in the group that received standard care alone (38%; *n*=19/50; Hunt and Elg, 2017). Over the 26-week evaluation period for all patients involved in the study, this equated to 874 weeks healed in the Granulox cohort and only 278 weeks healed in the standard care group (Hunt and Elg, 2017). As there were more weeks healed in the Granulox cohort, less dressings were required so the cumulative cost of dressings was £6,953 compared to £9,547 in the standard care group (Elg and Bothma, 2019).

Cost-effectiveness analysis has shown that Granulox can accumulate more weeks healed by healing more wounds and healing wounds quicker, thereby consuming fewer wound care resources than standard care alone, rendering the Granulox regimen both cost-effective and dominant over standard care alone (Elg and Bothma, 2019).

The break-even analyses for the community setting in the UK support that savings in other healthcare settings are probable (Elg and Bothma, 2019). The healing rate required for the use of Granulox to break-even with standard care is 70% (Elg and Bothma, 2019); however, the analysis in the community showed that 90% of patients in the Granulox cohort healed (Hunt and Elg, 2017). As such, in the UK, the National Institute for Health and Care Excellence (NICE) has produced a Medtech Innovation Briefing (MIB) on Granulox. The MIB is a literature review, which NICE has accepted (NICE, 2022). This is the first step in receiving national recommendation and reimbursement across the UK. In summary, the addition of Granulox as an adjunct to standard care has the potential to be cost-effective and affordable as more wounds heal and heal quicker compared to standard care alone. There is the potential for Granulox to support a reduction in cost by improving healing rates of chronic wounds in other clinical settings (Elg and Bothma, 2019).

Conclusion

Results from case studies and randomised controlled trials suggest that Granulox is effective as an adjunct to standard care to improve the healing of stagnant, non-healing wounds. Granulox has been shown to heal more wounds and heal wounds quicker when used as an adjunct to standard care, compared with standard care alone (Hunt and Elg, 2017; Elg and Bothma, 2019). The cases presented by the speakers on the role of Granulox as an adjunct therapy to standard care demonstrated accelerated healing and were similar to outcomes in published data. In doing so, it is both probable and possible for Granulox to be both cost-effective and dominant against standard of care alone (Elg and Bothma, 2019). WINT

REFERENCES

Bishop A (2008) Role of oxygen in wound healing. *J Wound Care* 17(9): 399–402

Brüggerjürgen B, Hunt S, Eberlein T (2017) Wound management in diabetic foot ulcer (DFU) – Incremental cost-analysis of treating diabetic neuropathic foot lesions with adjunct hemoglobin contact spray in Germany. *Gesundh ökon Qual manag* 22: 1–8

Choudhary PK, Patnaik S, Singh M et al (2013) Break-Even Analysis in Healthcare Setup. *Int J Res Foundation Hosp Healthc* 1(1): 29–32

Elg F, Bothma G (2019) Cost-effectiveness of adjunct haemoglobin spray in the treatment of hard-to-heal wounds in a UK NHS primary care setting. *J Wound Care* 28(12): 844–9

Elg F, Hunt S (2018) Hemoglobin spray as adjunct therapy in complex wounds: Meta-analysis versus standard care alone in pooled data by wound type across three retrospective cohort-controlled evaluations. *SAGE Open Med* 6: 2050312118784313

Dissemond J, Kröger K, Storck M et al (2015) Topical oxygen wound therapies for chronic wounds: a review. *J Wound Care* 24(2): 53–4, 56–60, 62–3

Dissemond J, Assenheimer B, Engels P et al (2017) M.O.I.S.T. - a concept for the topical treatment of chronic wounds. *J Dtsch Dermatol Ges* 15(4): 443–5

Gottrup F, Dissemond J, Baines et al (2017) Use of oxygen therapies in wound healing. *J Wound Care* 26(Sup 5): S1–S43

Gunawansa N (2017) Atraumatic Acute Limb Ischemia: Clinical Presentation, Classification, Assessment and Management- A Review. *Int J Vasc Surg Med* 3(3): 046–052

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

Hunt S, Elg F (2016) Clinical effectiveness of hemoglobin spray (Granulox®) as adjunctive therapy in the treatment of chronic diabetic foot ulcers. *Diabet 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): 558–68

Hunt S, Elg F, Percival S (2018) Assessment of clinical effectiveness of haemoglobin spray as adjunctive therapy in the treatment of sloughy wounds. *J Wound Care* 27(4): 210–9

Lakdawalla DN, Doshi JA, Garrison LP Jr et al (2018) Defining Elements of Value in Health Care-A Health Economics Approach: An ISPOR Special Task Force Report [3]. *Value Health* 21(2): 131–9

National Institute for Health and Care Excellence (2022) *Granulox for managing chronic non-healing wounds*. Available at: https://www.nice.org.uk/advice/mib296 (accessed 31.05.22)

Petri M, Stoffels I, Jose J et al (2016) Photoacoustic imaging of real-time oxygen changes in chronic leg ulcers after topical application of a haemoglobin spray: a pilot study. *J Wound Care* 25(2): 87: 89–91

Rutherford RB (2009) Clinical Staging of Acute Limb Ischemia as the Basis for Choice of Revascularization Method: When and How to Intervene. *Semin Vasc Surg* 22(1): 5–9