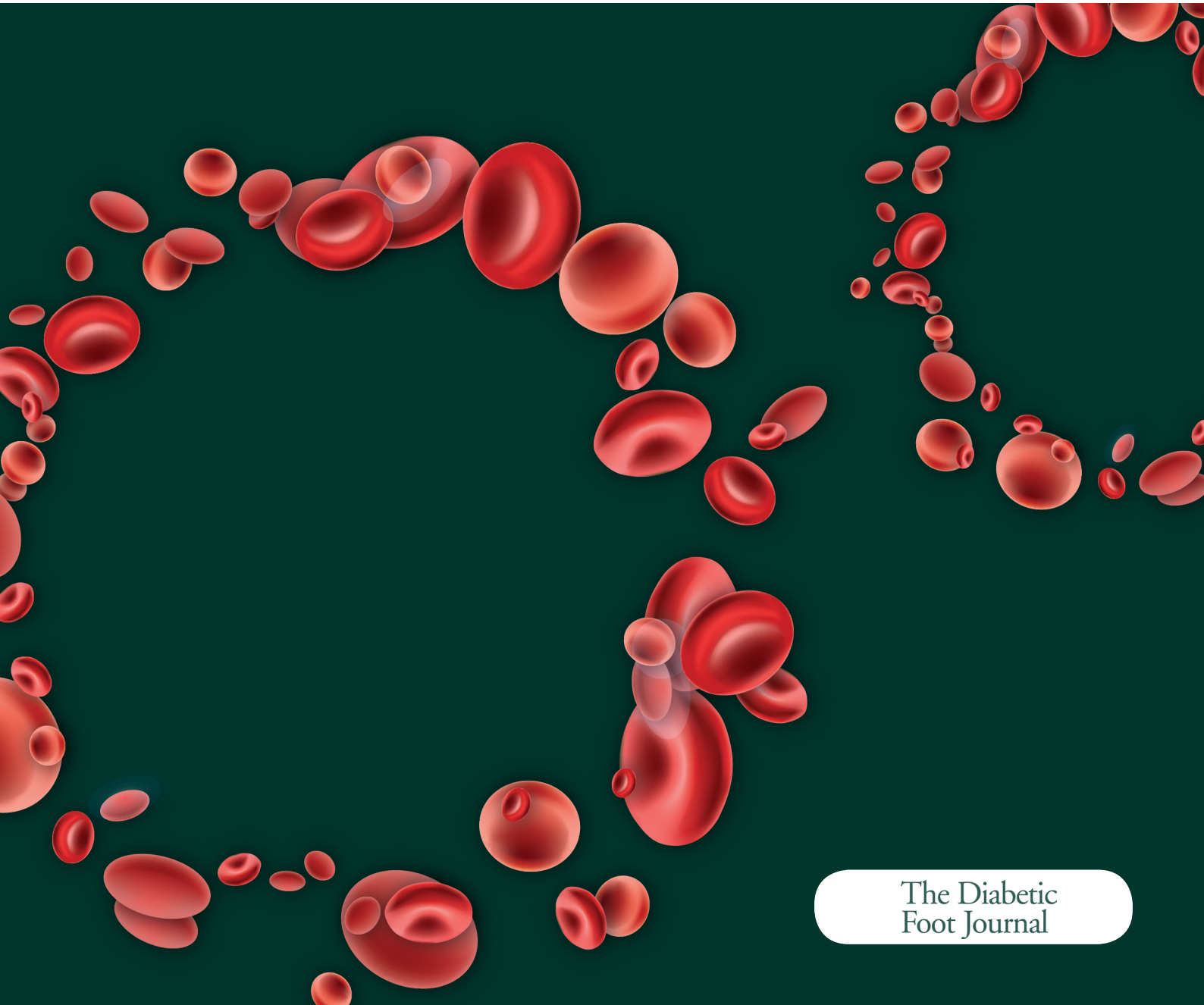
EXPERT PANEL REPORT

Expert panel report:
The role of topical oxygen therapy in the management of diabetic foot ulcers



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Foreword

This document covers the role, current evidence and practicalities of topical oxygen therapy (TOT) in diabetic foot care in the UK. Diabetic foot ulcers (DFUs) are complex chronic wounds that have a major long-term impact on the morbidity, mortality and quality of patients' lives (Wounds International, 2013).

TOT in wound care has been understood to aid wound healing since the 1960s and has been shown to be especially beneficial for DFUs where there is an ischaemic or a hypoxic element. An Expert Panel gathered in London in early 2019 to discuss the position and appropriate use of TOT in the UK today.

Burden of DFUs

Diabetic foot disease is just one complication of diabetes mellitus, which can lead to non-healing wounds and amputations if left unmanaged. Unlike other chronic wounds, DFUs are often complicated by other wide-ranging diabetic and metabolic changes, such as neuropathy and vascular disease (Wounds International, 2013), which can make them particularly difficult to manage and heal.

Each year, an estimated 2–2.5% of people with diabetes develop a DFU (Diabetes UK, 2017). In the Burden of Wounds study, it has been estimated that there were 169 000 DFUs across the UK, equating to 5% of adults with diabetes (Guest et al, 2015).

Diabetic foot disease is the largest single reason for hospital admissions among people with diabetes (Boulton et al, 2005). The NHS cost of DFUs is estimated at £1 billion per year (Kerr, 2017; Guest et al, 2018), but this does not include the additional social costs to the patient, such as reduced mobility and sickness absence, which are estimated at £13.9 billion per year. The indirect, intangible costs to the person with diabetic foot disease are also high, with many experiencing a poorer quality of life than those without foot disease (Vileikyte, 2001). Individuals who develop a DFU are also at greater risk of premature death, myocardial infarction and fatal stroke than those without a history of diabetic foot ulceration (Brownrigg et al, 2012).

With appropriate and careful management it is possible to delay or avoid most serious complications of diabetic foot ulceration (NICE, 2015).

Management of DFUs and associated challenges

Evidence-based clinical practice

To ensure consistent and standardised care throughout the UK, the application of evidence-based practice guidelines (Nube, 2016) in favour of traditional working practices should be implemented. More studies like the Explorer clinical trial, one of the first randomised double-blind clinical trials on treatments for neuroischaemic DFUs (Edmonds et al, 2018), are needed.

Standard care

Standard care for DFU management should begin with a thorough holistic assessment of the patient and wound by a competent healthcare professional following a structured, formalised process. This is important as the underlying cause(s) of DFUs will impact on the management plan (Wounds International, 2013). The management plan may include wound debridement, limb offloading, dressings and devices, and management of metabolic or glycaemic control, infection and ischaemia. The patient and wound should be assessed at least every 4 weeks to monitor for improvement or deterioration (Frykberg and Banks, 2016).

Validated clinical tool for DFU classification

To ensure holistic assessment and treatment of DFUs, the wound should be classified according to a validated clinical tool (Frykberg and Banks, 2016). Using such a tool for DFU classification ensures consistency and continuity of care locally and nationally (Box 1).

Throughout Scotland, the Texas Foot Ulcer Classification System is used and included in the Scottish Care Information Diabetes (SCI-Diabetes) ulcer management system – the system to record diabetes foot ulceration in Scotland. In England and Wales, there is currently no universally accepted DFU classification system; however, NICE (2015) advocate use of either the Texas Classification or SINBAD. The SINBAD score is used as the measure of DFU severity in the National Diabetes Audit.

BOX 1. EXAMPLES OF VALIDATED CLINICAL TOOLS FOR DFU CLASSIFICATION

- TEXAS Classification (Lavery et al, 1996)
- SINBAD: Site, Ischaemia, Neuropathy, Bacterial Infection, Area and Depth (Ince, 2008)
- WIFi: Wound, Ischaemia and foot Infection (Mills et al, 2014)
- Wagner classification (Wagner, 1981)

Prompt referral

85% of amputations are preceded by an DFU (Edmonds, 2013), which can deteriorate quickly if not managed efficiently. Therefore, NICE (2015) recommend that patients should be referred promptly to a specialist multidisciplinary foot team within 1 working day to reduce the risk of amputation and cost of treatment. However, this can be a challenge; a recent analysis suggested only 22% of newly diagnosed DFUs were referred, or had access, to a specialist DFU clinic (Guest et al, 2018).

Knowledge gaps

A recent review of postgraduate medical and surgical curricula showed the term 'diabetes' was not specifically mentioned in Foundation training (FP) curriculum, and that it appeared only three times in core surgical training (CST) and 16 times in core medical training (CMT) (Skervin et al, 2019). The article concluded that a FP, CST, CMT or early year emergency medicine trainee may complete training without understanding the presentation, urgency or treatment of diabetes. There is an opportunity to improve the knowledge of diabetes within the medical field to ensure prompt referral. Campaigns to improve knowledge of the diabetic foot among the public wound also be beneficial.

Multidisciplinary service

The multidisciplinary service has been an established approach to DFU care for over 30 years (Edmonds et al 1986; Edmonds, 2011) (Box 2). The multidisciplinary approach incorporates not only the clinic, but also the service and patient, including the carers and family. One clinical specialty cannot treat diabetic foot alone, and it is the podiatrist who usually assumes the role of 'navigator' or 'gatekeeper' of the multidisciplinary service. However, the number of qualified podiatrists has dropped over the past 7 years from 3000 in 2012 to 2400 in 2019. A 25% reduction in university applications may be linked to bursary reforms for new students applying for podiatry and other allied health professions (Department of Health and Social Care, 2017).

One of the biggest positive changes to the multidisciplinary service of recent times has been the addition of the vascular team, ensuring rapid access to revascularisation necessary to overcome the ischaemic element common in diabetic foot ulceration, and reduce risk of amputation. However, the introduction of vascular surgery as a stand-alone speciality and centralisation of vascular services away from spoke hospitals has challenged patient access (NICE, 2015).

BOX 2. MEMBERS OF THE CLINICAL MULTIDISCIPLINARY TEAM

Diabetologists, vascular surgeons, orthopaedic surgeons, plastic surgeons, medical staff, GPs, microbiologists, radiologists (diagnostic and interventional), podiatrists, diabetes specialist nurses, plaster technician, 'other' nursing staff, orthotists.

Measures in progress

An accepted measure or prediction of DFU healing is a percentage wound area reduction of 10–15% per week or 40% after 4 weeks of treatment (Frykberg and Banks, 2016; Hingorani et al, 2016).

A reduction in amputation rate is used as a driver of progress in the National Diabetes Audit, but it is important to remember that, in some cases, the primary treatment should be a minor or major amputation and that not all amputations are preventable. In some circumstances, amputation can be an improvement to a patient's quality of life.

Diabetic foot ulceration management is multifactorial and can be challenging. Innovations in practice and products, and developments in policy and organisational process may help to overcome some of these challenges.

Aetiology of DFUs

In most patients with a DFU, peripheral neuropathy, ischaemia or both, are contributory factors to the ulceration aetiology (Box 3).

BOX 3. THREE KEY AETIOLOGIES THAT INFLUENCE ASSESSMENT, TREATMENT OF THE UNDERLYING CONDITION AND MANAGEMENT OF DIABETIC FOOT ULCERATION

- Peripheral neuropathy
- Ischaemia
- Neuroischaemia

Ischaemia is a restriction in blood supply to tissues and can be local to the wound or systemic, as in peripheral arterial disease (PAD). Patients with both peripheral neuropathy and PAD (neuroischaemia) have been shown to have higher re-ulceration and amputation rates than those with peripheral neuropathy alone (Lewis and Lipp, 2013).

Estimates show PAD is a complicating factor in the management of nearly 65% of all DFUs (Bus et al, 2016). In PAD, the lower limbs have an inadequate supply of oxygenated blood leading to numbness or coldness, pale or blue-tinged legs and hair loss on the legs and feet. There is also an increased likelihood of infections or wounds that are slow-healing.

Appropriate vascular evaluation and an individualised management plan to improve or monitor the effects of ischaemia on the lower legs must be used to aid wound healing and avoid or delay future amputation in all patients presenting with diabetic foot ulceration (Wounds International, 2013). Revascularisation intervention or survey may be appropriate for people with lower limb ischaemia, decreased perfusion or impaired circulation.

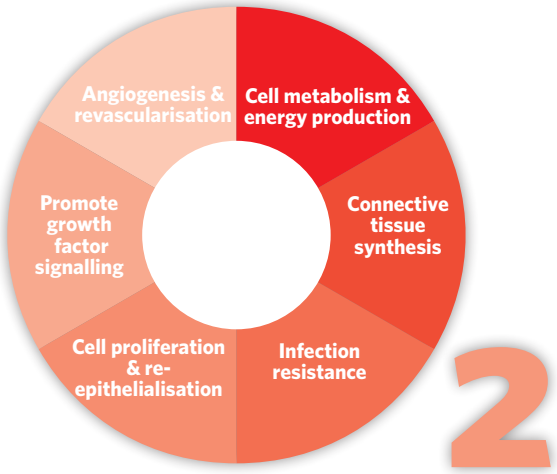
However, some patients with DFUs are not good candidates for revascularisation surgery due to complications arising from comorbidities, late presentation, or chronic ischaemia associated with irreversible tissue injury (Yu et al, 2016).

For some patients, revascularisation may not be suitable or successful. Delivering oxygen by an alternative mechanism, such as topical oxygen therapy, can be an option to improve oxygen content for these patients with slow-healing wounds.

The role of oxygen in wound healing

Oxygen is a well-known requirement in wound healing. It is critically important for cell metabolism and pathways for wound healing, such as the angiogenesis and revascularisation, cell metabolism and energy production, synthesis of connective tissue and infection resistance (Figure 1).

Figure 1: Roles of oxygen in wound healing



Chronic wounds have been shown to have reduced oxygen at the wound bed (Dissemond et al, 2015), which is worsened by factors such as PAD. Throughout healing, wounds are generally hypoxic at the centre, with an increasing oxygen gradient towards the intact tissue. Wound hypoxia may result when consumption of O_2 is above the delivery of O_2 to the wound. The hypoxic state lasts until angiogenesis is complete and blood supply is restored at the end of proliferative phase (Bishop, 2008).

Although gaseous oxygen can diffuse through any permeable surface, only a very small amount of oxygen used in wound healing enters the body via the skin or wound exudate (Jamnongwong et al, 2010). This is related to the thickness of the skin and the liquids in the wound bed, which act as an oxygen diffusion barrier (Stücker et al, 2002; Dissemond et al, 2015). High metabolic activity in healing wounds and the presence of infection will also reduce the overall levels of tissue oxygen content.

Sustained oxygen delivery, either intrinsically from the blood supply or extrinsically via topical oxygen, is vital for the healing of non-healing wounds, especially for wounds associated with PAD and DFUs (Dissemond et al, 2015).

Wounds often have poor oxygen delivery from capillaries, and oxygen diffusion from the atmosphere is limited by exudate (Jamnongwong et al, 2010). Sustained oxygen delivery to the wound bed has been shown to aid healing in non-healing wounds associated with PAD and DFUs (Dissemond et al, 2015). Oxygen delivery via topical oxygen therapy may pose a useful adjunct to best practice for these types of wounds and patient groups. Body temperature and hydration status affect tissue oxygenation so should be closely monitored alongside adjunct therapies to ensure optimal oxygenation.

Available oxygen therapies

Hyperbaric oxygen therapy (HBOT) was first used in the field of wound care in the 1960s following the discovery that the burns of patients who received treatment for carbon monoxide poisoning healed more quickly than those who did not (Wada et al, 1965). Today, HBOT is not widely available in the UK. However, there are portable, TOT products that carry or deliver oxygen to the wound bed. The published research on TOT is growing and findings to date have been positive (Gottrup et al, 2017):

Oxygen carrier system

Oxygen transfer using haemoglobin as a physical transporter of oxygen is known as facilitated delivery. A haemoglobin spray (Granulox®, Mölnlycke), produced from highly purified porcine haemoglobin products, binds atmospheric oxygen and transports it to the wound bed, where it is released. Haemoglobin spray application is indicated every 3 days and not necessarily at every dressing change (if dressing changes are more often and no debridement or washout has taken place). A standard dressing regimen should be continued with a breathable/non-occlusive wound dressing.

A European Wound Management Association (EWMA) evaluation of the currently available oxygen therapies in wound care awarded haemoglobin spray a Grade 1B, indicating a positive benefit–risk value with moderate quality of evidence (Table 1; Gottrup et al, 2017).

In a single-blinded randomised controlled trial, on 72 patients with venous leg ulcers (VLUs), there was an average wound size reduction of 53% at 13 weeks ($p<0.01$) in the group treated with the haemoglobin spray. There was no statistically significant reduction in wound size observed in the control group (Arenbergenova et al, 2013). For DFUs, studies have shown a reduction in size when haemoglobin spray is used as an adjunct to standard care (Bateman, 2015; Haycocks et al, 2016; Hunt and Elg, 2017). Wounds that have been sloughy or painful have also been found to respond well to the application of haemoglobin spray.

TABLE 1. GRADE APPROACH TO TREATMENT RECOMMENDATIONS (GOTTRUP ET AL, 2017)

Recommendation	Quality of evidence
1A	**High**: Consistent results from RCTs or observational studies with large effects
1B	**Moderate**: RCTs with limitations and very strong observational studies
1C	**Low:** Observational studies **Very Low**: Case series, descriptive reports, expert opinion
2A	**High:** Consistent results from RCTs or observational studies with large effects
2B	**Moderate:** RCTs with limitations and very strong observational studies
2C	**Low:** Observational studies **Very Low:** Case series, descriptive reports, expert opinion

RCT=randomised controlled trial.
Adapted from Guyatt G, Schunemann HJ, Cook D, Jaeschke R, and Pauker S. Applying the grades of recommendation for antithrombotic and thrombolytic therapy. Chest 2004; 126; 179S-187S

Higher cyclical pressure oxygen

The Topical Wound Oxygen (TWO_2, Aoti Inc) system applies a higher topical O_2 pressure between 5mmHg and 50mmHg in a cyclical pressure waveform, combined with humidification. The open wound is placed in a single-use or reusable chamber or bag for a treatment time of 60–90 minutes.

Several prospective clinical studies have been conducted using the device on both VLUs and DFUs, and the device was awarded a Grade 1B on available evidence (Gottrup et al, 2017). Since this evaluation, a multinational, multicentre, prospective, double-blinded, randomised, placebo-controlled trial of 73 patients exploring the efficacy of TWO_2 homecare therapy in DFUs that had failed to heal with gold standard-of-care alone showed nearly 4 times the likelihood of wound healing compared to standard-of-care alone at 12 weeks (Frykberg et al, 2018).

Continuous delivery of oxygen systems

A battery-powered device (Natrox® Oxygen Delivery System, Inotec AMD) delivers continuous topical oxygen 24 hours a day through either small cannulas or thin tubes to occlusive wound dressings (Gottrup et al, 2017). The wound dressings are typically changed weekly, and the oxygen generators are generally replaced after 1–2 weeks of continuous use.

Recent studies have shown that continuous oxygen delivery to DFUs have a positive effect on non-healing DFUs (Yu et al, 2016; Kaufman et al, 2018; Jones et al, 2018). In a randomised trial of 20 patients comparing Natrox and non-placebo control group with regular dressings and standard care, 30% of the control group healed while 90% healed in the NATROX arm after 8 weeks of treatment (Yu et al, 2016). Natrox has also been shown to be well-tolerated by patients. In 2017, Gottrup et al awarded Natrox a Grade 2C in terms of evidence. A multicentre randomised controlled trial on healing rate of DFUs is currently underway.

Oxygen release through dressings or gels

Oxygen-containing dressings or gels have embedded O_2 that is released via a chemical or biochemical reaction. Hydrogen peroxide is a reactive oxygen species that is often present, and is converted to water and dissolved O_2 that diffuses to the wound bed, as in the case of SurgihoneyRO™ (H&R Healthcare). Hydrogel dressings (e.g. ActiFormCool [L&R], Intrasite Gel [Smith & Nephew]) release O_2 for up to 6 days, and a non-absorbent dressing is used to secure it in place.

Several case study reports demonstrate improvements in the healing of different wound types. Dressings or gels that release oxygen have been awarded a Grade 2B in terms of evidence, meaning there is a moderate quality of evidence for their use (Gottrup et al, 2017).

The evidence for topical oxygen therapy is still growing, but it can be used as an adjunct to best practice. Initiation of topical oxygen therapy is a specialist action to be undertaken by the multidisciplinary foot care service or clinician experienced in diabetic foot care, which can be continued in the community.

Algorithm for the use of topical oxygen therapy

The Expert Panel Report Working Group developed and updated an algorithm developed by Stang et al (2018) for the initiation of a haemoglobin spray in DFU care in Scotland, to be relevant for TOT options. TOT is an adjunct to standard care and should be after 4 weeks of standard care if non-healing is apparent (Figure 2).

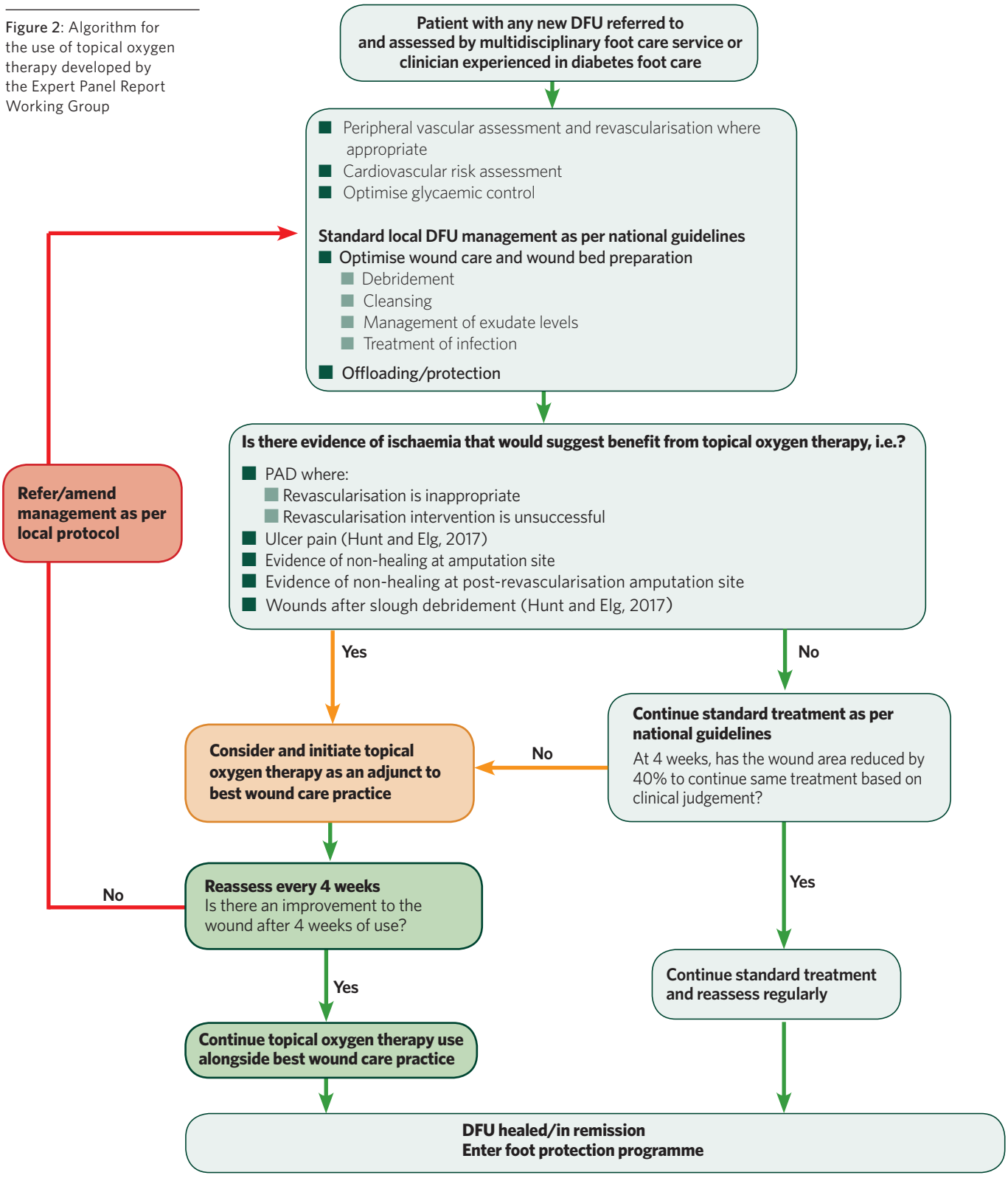
However, there are patient comorbidities, complications or wound characteristics that would suggest early use of TOT (prior to 4 weeks of standard care) could be beneficial to healing and lead to quicker wound healing:

- PAD where:
  - Revascularisation is inappropriate
  - Revascularisation intervention is unsuccessful
- Ulcer pain (Hunt and Elg, 2017)
- Evidence of non-healing at amputation site
- Evidence of non-healing at post-revascularisation amputation site
- Wounds after slough debridement (Hunt and Elg, 2017).

The group agreed that it would not be suitable to consider early use of TOT in the presence of wound or patient deterioration (e.g. size, pain, worsening infection).

Topical oxygen therapy is an adjunct to standard care and should be considered after 4 weeks of standard care if non-healing is apparent. There are patient and wound factors that would suggest early initiation of topical oxygen therapy, such as the presence of PAD, ulcer pain, non-healing after amputation, or wounds following debridement.

Figure 2: Algorithm for the use of topical oxygen therapy developed by the Expert Panel Report Working Group



Future plans for diabetic foot care and topical oxygen therapy

Diabetic foot disease is a serious condition with potentially life-changing outcomes, which are preventable with correct, individualised care. The group agreed that appropriate government policies and penalties for missed targets, like those for cancer care, should be in place. There is an ongoing need to educate clinicians and patients of the risk of diabetic foot ulceration. Public campaigns should be initiated to remove the stigma associated with diabetes (i.e. it is caused solely by poor lifestyle), and to raise awareness that diabetic foot complications and amputations are not inevitable.

Advanced treatments are needed, as healing rates under standard-of-care are often poor. As such, more randomised controlled trials for diabetic foot disease treatment are needed, including those for TOT. A drive to collect more data from clinicians using TOT would also be a step in the right direction.

According to a EWMA report, diagnostic tools for measuring local hypoxia (e.g. pulse oximetry) have not been adequately used (Gottrup et al, 2017). For more accurate clinical decisions, it would therefore be pertinent to encourage the regular use of these tools, and to improve such techniques.

Conclusion

Nearly 65% of all DFUs are complicated by PAD (Bus et al, 2016), which presents a challenge when not all patients are suitable for vascular intervention. Additionally, local ischaemia can exist independently of PAD. Topical oxygen therapy is an option for the management of chronic, non-healing wounds where ischaemia is a contributing factor.

Patients with diabetic foot ulceration and PAD where revascularisation is inappropriate or has been unsuccessful may benefit from topical oxygen therapy. Evidence also suggests that topical oxygen therapy may be of assistance to reduce ulcer pain and for use after slough debridement (Hunt and Elg, 2017), as well as on post-revascularisation amputation sites that are not healing.

Topical oxygen therapy should be considered as an adjunct to best practice for DFUs as it has been shown to be beneficial and improve outcomes in suitable patients.

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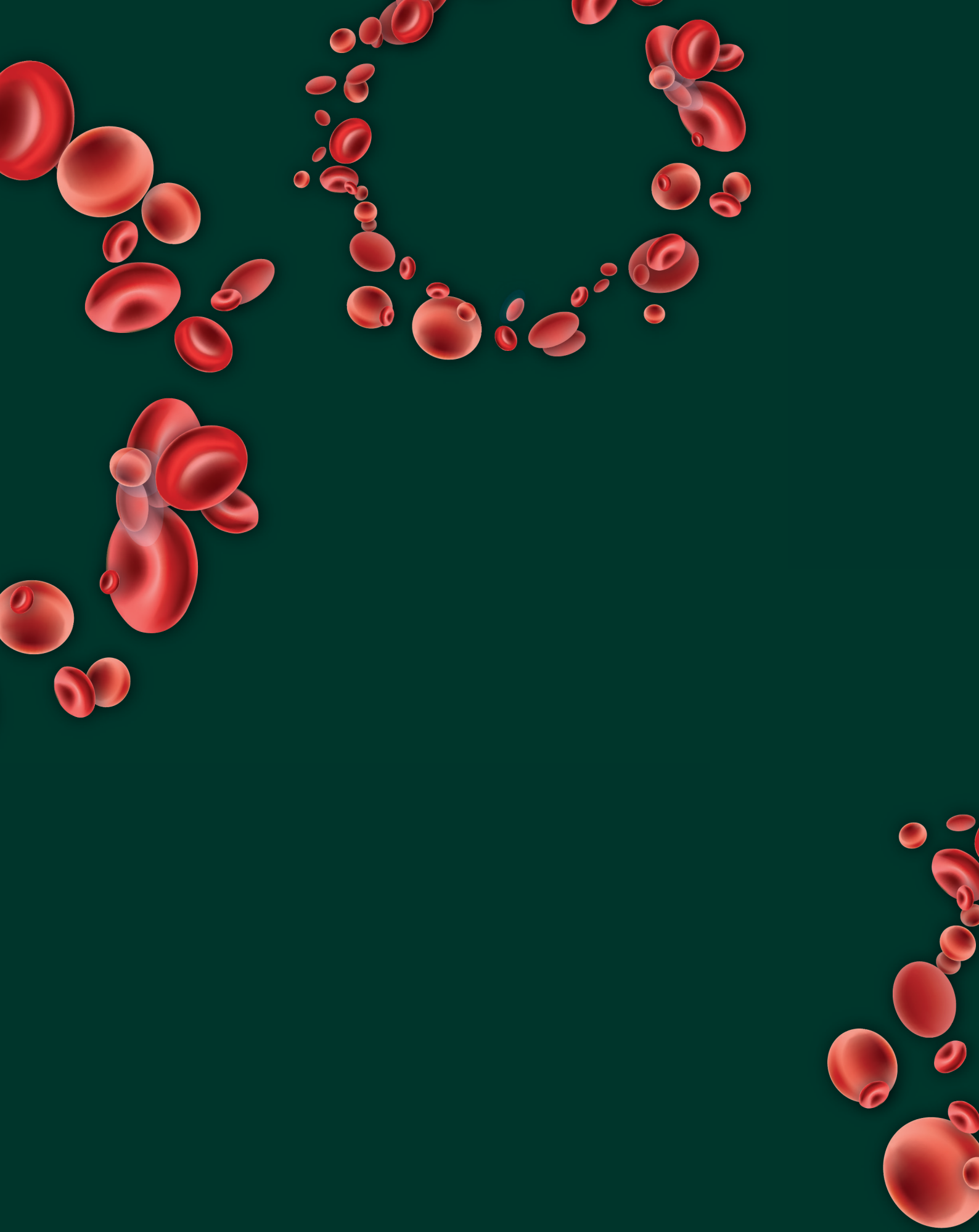
Notes



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