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USE OF TOPICAL OXYGEN THERAPY IN WOUND HEALING

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Panel

Panel chair

Robert Frykberg, DPM MPH, Adjunct Professor, Midwestern University, Glendale, Arizona, US

Authors

Charles Andersen, MD, FACS, FAPWCA, Chief of the Vascular/Endovascular Surgery Service and Medical Director of the Wound Care Clinic, Madigan Army Medical Center, US

Paul Chadwick, MSc, PhD, Visiting Professor Birmingham City University, Honorary Consultant Podiatrist Manchester and Director Curativo WoundCare Consultancy

Paul Haser, MD FACS FRCSC, Chief of Vascular Surgery, ONE Brooklyn Health System, New York, US

Sandra Janssen, MSc PhD, Nurse Specialist, Wound Care, Elkerliek Hospital Helmond/Deurne, Netherlands

Aliza Lee, DPM MS DABPM, Clinical Research Investigator and Director of Podiatric Medical Education, VA Hospital in Salem, Virginia, US

Jeff Niezgoda, MD, FACHM, MAPWCA, CHWS, CMO Kent Imaging, President/CMO WebCME.net, American Professional Wound Care Association, RxOS Medical and Auxillium Heath, US

Thomas Serena, MD FACS, Founder and Medical Director, Serena Group, US

Duncan Stang, MCPod FCPodMed FFPM RCPS (Glasg), Podiatrist, Lanarkshire NHS Scotland; Diabetes Foot Coordinator for Scotland and Executive Committee Member, Foot in Diabetes UK, UK

Review panel

Animesh Agarwal, MD, FAOA, FAAOS; Professor, Division of Orthopaedic Traumatology, University of Texas Health Science Center, San Antonio, Texas, US

Windy Cole, DPM CWSP FACCWS, Director of Wound Care Research, Kent State University College of Podiatric Medicine; Global Medical Affairs Director , NATROX Wound Care, UK

Joachim Dissemond, MD, Department of Dermatology, Venerology and Allergology, University of Essen, Germany

John Kirby, MD, Acute and Critical Care Surgeon, Washington University in St Louis, Missouri, US

John Lantis, MD, Chief and Professor of Surgery, Mount Sinai West Hospital and the Icahn School of Medicine, New York, US

Lawrence Lavery, DPD, Professor, Department of Plastic Surgery, University of Texas Southwestern Medical Center; Medical Director, Diabetic Limb Salvage Program, Parkland Memorial Hospital, Texas, US

Jose Lazaro Martinez, DPM MSc PhD, Professor of Podiatric Surgery, Podiatry College; Clinical Director and Head of Diabetic Foot Unit, Podiatric Clinic, Complutense University of Madrid, Spain

Thomas Wild, MD, Clinic of Plastic, Hand and Aesthetic Surgery, Burn Center, BG Clinic Bergmannstrost, Halle (Saale, Germany); Medical University Halle, Outpatient and Operating Center, Martin-Luther University, Halle (Saale), Germany; University of Applied Science Anhalt, Institute of Applied Bioscience and Process Management, Head of Academic Wound Consultant Education Course, Koethen, Germany

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MA Healthcare

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Design: **Fonthill Creative**
Head of Projects: **Camila Fronzo and Chris Beck**
Associate Publisher: **Tracy Cowan**
Sales Director: **Emma Blick**
Managing Director: **Anthony Kerr**

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+44 (0)7979 520828
anthony.kerr@markallengroup.com

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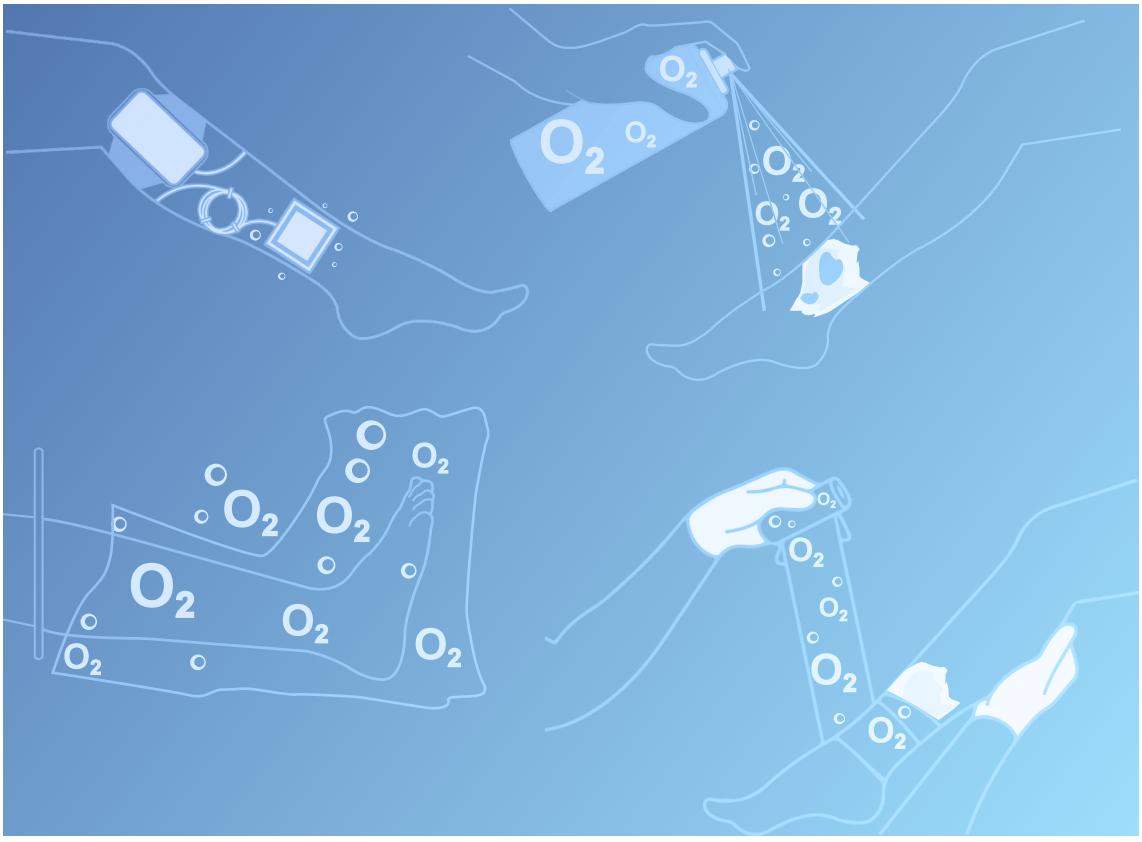
Introduction



Hard-to-heal wounds, also referred to as chronic, non-healing or complex wounds, are defined as 'wounds that do not heal properly during an amount of time that normally should be sufficient for healing'.[1] In the US, hard-to-heal wounds affected about 8.2 million Medicare beneficiaries in 2018, and cost projections for all wounds ranged from $28.1 to $96.8 billion.[2] UK estimates for all wounds in 2017/2018 were £8.3 billion. Between 2012/2013 and 2017/2018, the prevalence of wounds in the UK increased by 71%, accompanied by substantial increases in resource use and a 48% increase in patient management costs.[3] It is estimated that around 1–3% of the total healthcare expenditures in developed countries is devoted to chronic wounds.[4] In Wales alone, it was estimated that 5.5% of the UK's National Health Service (NHS) expenditures are devoted to wound care.[4] Incidence rates and costs are growing due to aging populations with concurrent increases in their comorbidities, such as diabetes, obesity, arterial hypertension and peripheral vascular disease,[5] as well as general inflationary pressures on the healthcare system. The rising population of patients with hard-to-heal wounds necessitates improvements in wound treatment technology and delivery of care. Treatments that empower patients in their home setting will be especially impactful.

Wound healing requires, among other things, the restoration of macro- and micro-circulation. Adequate blood flow delivers many key components to the site of a wound; chief among those is oxygen. Oxygen plays an important role in the reconstruction of new vessels and connective tissue, as well as the migration of epithelial cells, and it allows for normal local metabolism while facilitating resistance to

infection. One way of locally delivering more oxygen to a wound is using topical oxygen therapy (TOT), an umbrella term for several modalities for topically administering oxygen to wounds or ulcers to promote tissue healing.

In 2022, an expert panel of nine key opinion leaders from the US and Europe met to discuss the clinical evidence in support of TOT in the care and treatment of hard-to-heal wounds, with the aim of providing expert consensus recommendations on best practices. The meeting resulted in this consensus document, which is intended to be an update on a 2017 document on oxygen therapies in wound healing published by the European Wound Management Association (EWMA).[6]

This consensus document first explains the role of oxygen and its derivatives in normal wound healing, including the impact of hypoxia. It then introduces TOT and its specific modalities, detailing their mechanisms of action with an overview of treatment options. This document includes a thorough assessment of the best available evidence for the utility of TOT in hard-to-heal wounds (*Box 1*).[7] However, it does not directly compare the various TOT modalities and devices or provide a comprehensive review of systemic hyperbaric oxygen therapy (HBOT). It does examine the practical incorporation of TOT into wound care clinical practice, engaging with current discussions on the topic and the recommendations of internationally recognised organisations. Its final sections explore patient perspectives on TOT, the cost-effectiveness of TOT and gaps in the evidence on TOT, with suggestions for future actions.

Box 1. Research rating method

The panel rated the quality of evidence available (confidence in the estimates) and the strength of recommendations based on the American Diabetes Association (ADA) Grades of Recommendation Assessment, Development and Evaluation (GRADE) system. This system, last updated by the ADA in 2023,[7] provides ratings of A, B or C, depending on the quality of the grade. Expert opinion E is a separate category for ratings where there is no clinical trials evidence, trials are impractical or there is conflicting evidence. The E grades are informed by key opinion leaders identified by the ADA. All standard-of-care recommendations evaluated herein receive a rating for the strength of the evidence and not for the strength of the recommendation. Recommendations with A-level evidence are based on large, well-designed randomised controlled trials (RCTs) or well-conducted meta-analyses of RCTs. Generally, these recommendations have the best chance of improving outcomes when applied to the appropriate population. Recommendations with lower levels of evidence may be equally important but are not as robustly supported. The 2023 ADA Standards of Care for the first-time recommended topical oxygen therapy (TOT) for the treatment of chronic diabetic foot ulcers, with the highest level of evidence grade (A).[45] The 2022 panel review initiated with all the publications included in the 2017 European Wound Management Association document.[6] Panelists discussed the relevant research published in the intervening 5 years and included over 45 additional peer reviewed articles deemed to impact the knowledge and usage of TOT into this 2023 analysis.

Generally, RCTs are considered level 1, cohort studies level 2, case studies as level 3 and case reports level 4 evidence. After assessment of availability and levels of evidence, the evidence level that supports each recommendation is graded as follows:

A. Clear evidence from well-conducted, generalisable RCTs that are adequately powered
B. Supportive evidence from well-conducted cohort studies
C. Supportive evidence from poorly controlled or uncontrolled studies
D. Expert consensus or clinical experience.

Role of molecular oxygen in wound healing

Understanding TOT requires an understanding of the role of molecular oxygen and its derivative molecules in wound healing.

Flow of oxygen in the body

Oxygen delivery to tissues begins with oxygenation of arterial blood in the lungs. The oxygen is then transported by haemoglobin through the blood and delivered to the tissues. The balance between the arterial blood flow to the tissues and the rate of oxygen consumption in the tissue is known as oxygen tension (or partial pressure of oxygen).[8] In the small intercapillary distances of the muscle where there is high consumption of oxygen, the main source of oxygen is that bound to haemoglobin, rather than arterial oxygen tension.[9] However, where intercapillary distances are higher and the consumption of oxygen is relatively low, as in the subcutaneous tissue, the arterial oxygen tension is the main means of oxygenation. When a wound disrupts tissue, microcirculation diffusion distances increase, and therefore the arterial oxygen tension becomes the major means of oxygen transportation.[10]

Table 1. Roles of oxygen and oxygen derivatives in wounds

Chemical	Roles
Oxygen	· Oxidative metabolism-derived energy synthesis · Protein synthesis · Nitric oxide synthesis · Collagen maturation · Reduction of reactive oxygen species, including superoxide and hydrogen peroxide · Adenosine 5'-triphosphate synthesis
Nitric oxide	· Angiogenesis · Vasodilatation and vasoconstriction
Superoxide	· Endothelial cell signalling · Dismutation to hydrogen peroxide
Hydrogen peroxide	· Redox signalling · Peroxidation of hypochlorous acid
Hypochlorous acid	· Phagocytosis/bactericide/ bacteriostasis
Adenosine 5'-triphosphate	· Protein synthesis · Chemical energy for metabolism

Normally, the oxygen tension in healthy tissue is approximately 100 mmHg. However, upon injury there is an initial hypoxia, where oxygen consumption exceeds delivery, stimulating essential inflammatory processes. In instances where hypoxia becomes prolonged, there is wound deterioration.[11–13] Causes of hypoxia include high biological activity in the wound (which depletes oxygen), inadequate oxygen delivery and poor blood perfusion. As the oxygen tension levels in the tissue drops below 30 mmHg towards 10 mmHg, a critical hypoxic threshold is reached where low oxygen tension may lead to the development of hard-to-heal wounds.[8,14]

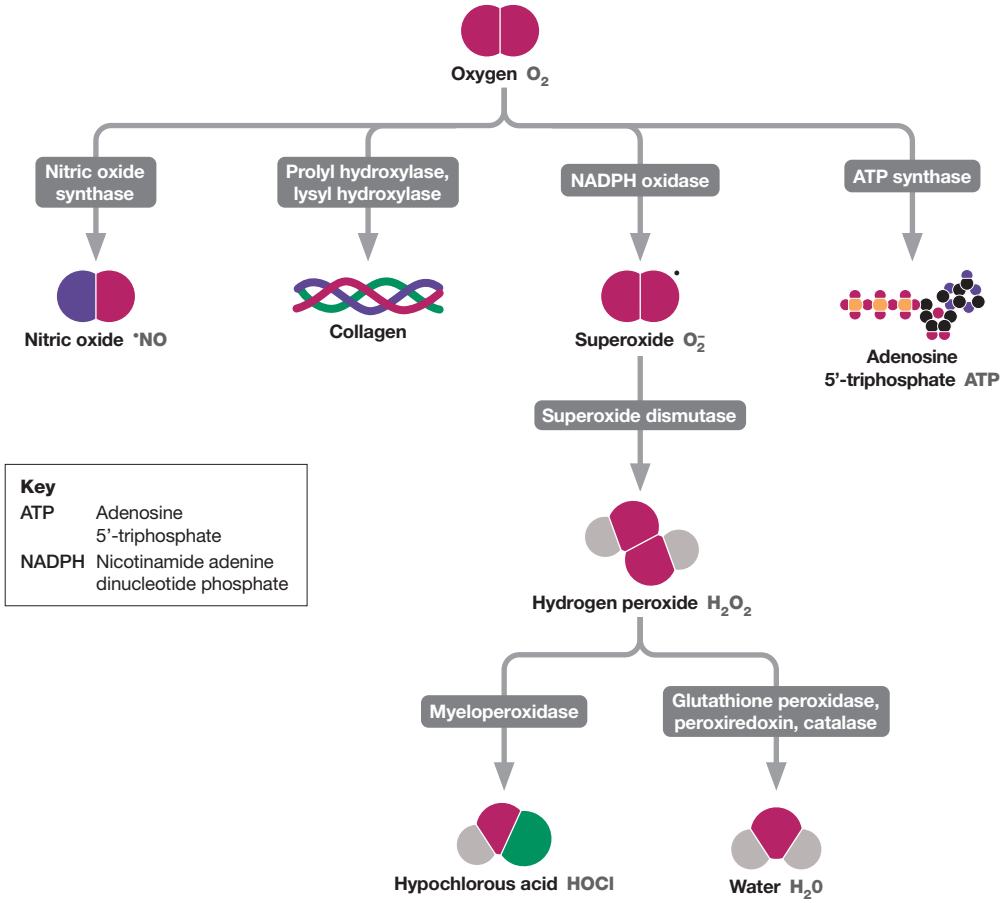
Molecular oxygen and its derivatives in wound healing

Oxygen and its derivatives affect cytokines, cell mediation and tissues and are involved in a multitude of wound-healing processes, in all wound types and aetiologies (*Table 1*), including energy generation, bacterial defenses, cell signaling, angiogenesis and collagen deposition. Various enzymes and substrates in the body react with oxygen to produce derivative molecules (*Figure 1*).

Oxygen drives the synthesis of oxidative metabolism-derived energy, proteins and nitric oxide. Nitric oxide has key roles in the regulation of vascular tone (vasodilatation and vasoconstriction) and formation of new blood vessels (angiogenesis). The availability of oxygen is key to the production of adenosine 5'-triphosphate (ATP), which is synthesised via the enzymes ATP synthase and cytochrome C and the electron transport chain in the mitochondria (*Figure 2*). ATP is used in protein synthesis, chemical energy for metabolism and many other cell functions. Oxygen is also used in the hydroxylation of other molecules, all of which are involved in wound healing; this includes the hydroxylation of mature collagen, a key substrate for wound healing that is deposited and crosslinked to form fibroblasts and extracellular matrix.

In a wound setting, oxygen is partially reduced in large quantities to form reactive oxygen species (ROS), which include the free-radical anion superoxide (the one electron-reduction product of oxygen) and the non-radical hydrogen peroxide.[14]

Figure 1. Enzymatic and molecular derivation of oxygen in wound healing



This is known as a respiratory or oxidative burst. ROS are involved in migration and phagocytosis of leukocytes, as well as the upregulation of bacteriostatic hydrogen peroxide, nitric oxide, platelet derived growth factor (PDGF) and vascular endothelial growth factor (VEGF). A major source of superoxide at the wound site is receipt of a single electron from nicotinamide adenine dinucleotide phosphate (NADPH)-oxidase in phagocytic cells, which help kill bacteria.

Superoxide generation drives endothelial cell signalling, such as is required during angiogenesis, division and migration of cells, reconstruction of connective tissue and upregulation of growth factors (e.g., fibroblast growth factor (FGF), PDGF and VEGF). In biological tissues, superoxide can rapidly and spontaneously dismutate to create hydrogen peroxide—either spontaneously or facilitated by enzymes called superoxide dismutases. Superoxide dismutase converts two superoxide molecules into a hydrogen peroxide and a water molecule. Endogenous hydrogen peroxide powers a cellular signalling network (redox signalling) to support cell migration and proliferation and angiogenesis, positively impacting important aspects of wound healing. Redox-sensitive cysteine residues can be modified by

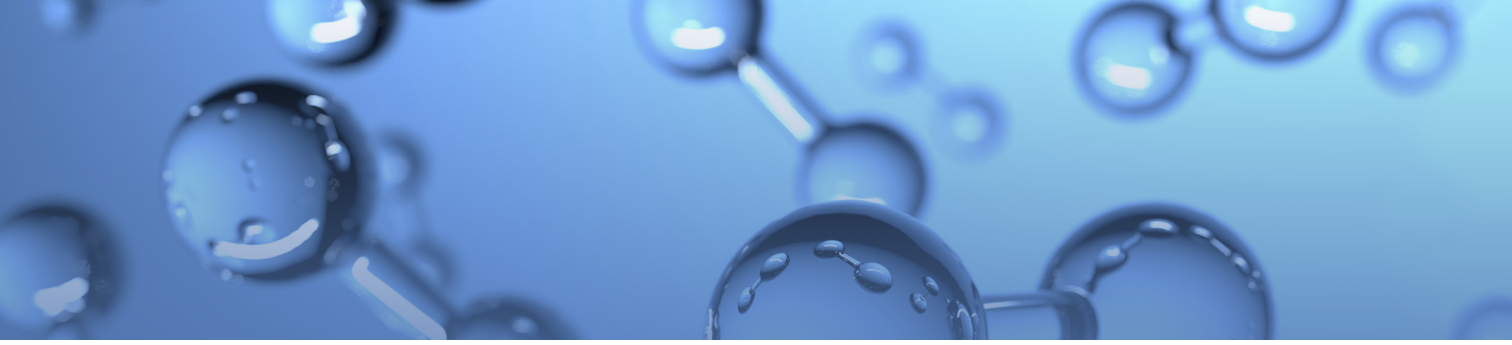
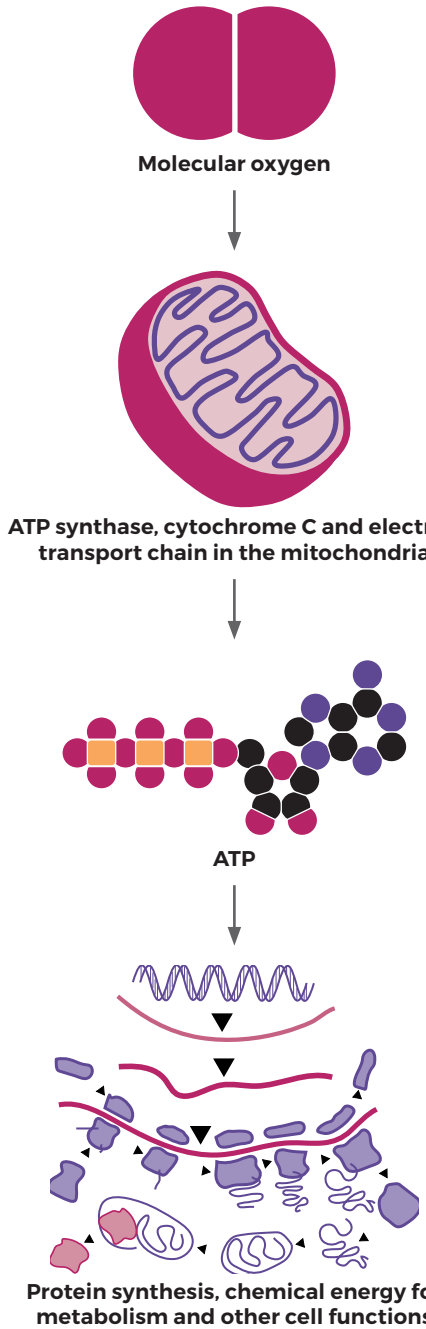


Figure 2. Oxygen and adenosine 5'-triphosphate (ATP)



hydrogen peroxide to change cellular signalling. Hydrogen peroxide may be used by myeloperoxidase within neutrophils to mediate chloride ions, resulting in the formation of hypochlorous acid, a potent disinfectant, antimicrobial and bactericidal agent in phagocytic cells. Reduction of hydrogen peroxide to water occurs by glutathione peroxidases, peroxiredoxins or catalase.[14]

Effects of bacterial burden on local oxygen consumption

Physiological features of wounds that affect oxygenation include high metabolic activity in the tissue, oedema, poor blood circulation, diffusion constraints (surface area vs volume) and bacterial oxygen consumption. It is the physical damage of a wound that injures the microvasculature and reduces tissue perfusion. Following microvascular injury, tissue oedema and venous outflow congestion contribute to ischaemia-reperfusion tissue injury.[15] Additionally, biofilms produced by both gram-positive and gram-negative bacteria impact oxygen consumption and have gained increasing attention as a contributor to wound chronicity.[16–18] Neutrophils have been shown to accumulate in biofilms in mouse-wound models.[19] In response to an infection, neutrophils activate NADPH-oxidase to produce ROS and reduce oxygen through NADPH oxidase-2, all of which will deplete the levels of oxygen. Indeed, steep gradients of oxygen are detected in biofilms, with little or no oxygen measured 100 µm below the surface.[20,21] Alternatively, once neutrophils clear microorganisms and macrophages remove debris, their activation comes to an end, inflammation diminishes, consumption of oxygen decreases and the wound can progress towards closure. Complications arise when the bacterial biofilm persists and attracts activated neutrophils, creating an environment of depleted oxygen and decreasing the opportunity to create the ROS needed for antimicrobial activity.[18] Wound healing is impaired by biofilms, which promote wound chronicity by contributing to and maintaining low oxygen tension via bacterial metabolism and recruitment of oxygen-consuming neutrophils.[18,22]

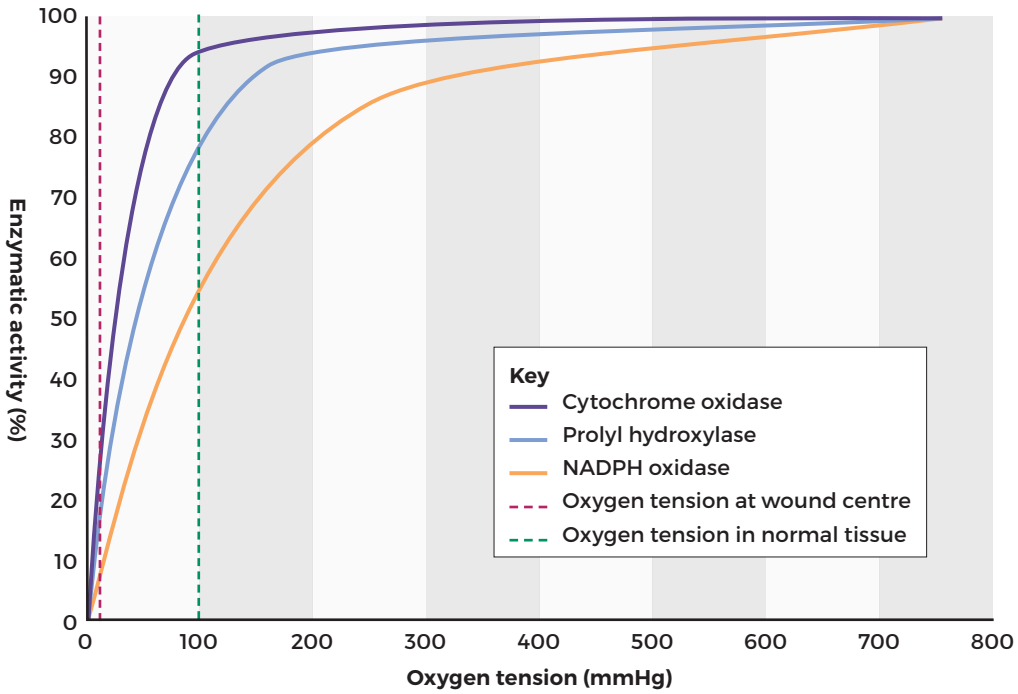
When the oxygen tension becomes suboptimal, enzymes involved in these wound-healing processes are less efficient, contributing to impairment of wound healing.[11,12] The depletion of oxygen has a direct effect on the efficiency of many enzymes (*Figure 3*).[23] Typical oxygen tension in normal tissues is approximately 100 mmHg, which supports enzymatic activity levels relative to maximal efficiency of around 95% for cytochrome oxydase (involved in ATP synthesis), 80% for prolyl hydroxylase (involved in collagen synthesis) and 60% for NADPH oxidase (involved in antimicrobial activity).[24] Conversely, typical oxygen tension at the centre of a wound is closer to 10 mmHg, which reduces activity of these enzymes to 10–30% of their maximal efficiency, with infection-fighting enzymes being most susceptible to low oxygen tension.[25]

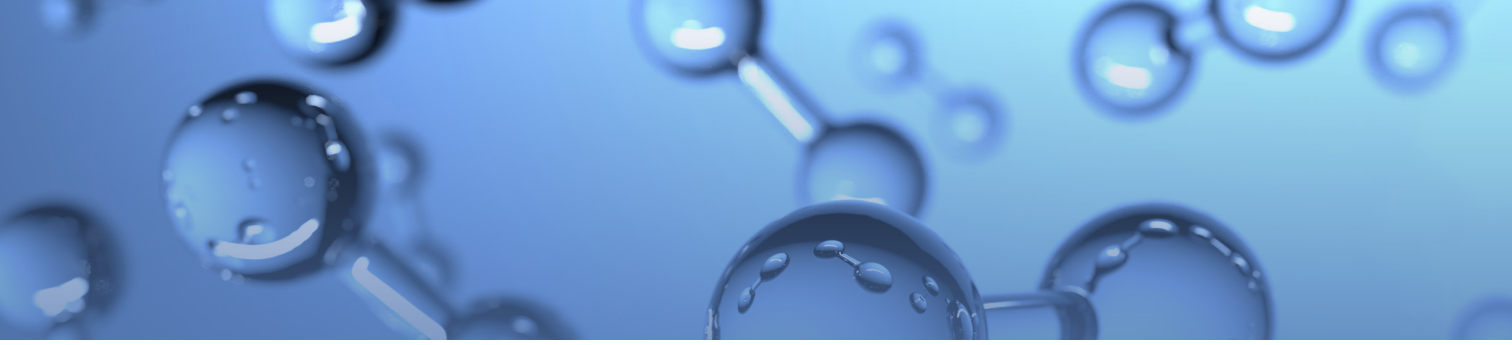
In clinical practice, there are several indicators of low oxygen in a wound. The presence of facultative aerobic and strictly anaerobic bacterial species can serve as a surrogate biomarker for persistent hypoxia in hard-to-heal wounds.[26,27] Investigators have also observed that the biochemical composition of wound exudate compared to serum, specifically high lactate

Key points

- Oxygen and its chemical derivatives are essential for many wound-healing processes
- Healing is impeded by lack of oxygen in a wound (hypoxia), caused by high biological activity and poor oxygen delivery and perfusion
- Enzymatic activity is affected by oxygen levels
- Bacterial burden impacts oxygen consumption
- Facultative aerobic and strictly anaerobic bacterial species can be surrogate biomarkers for hypoxia
- Several methods for measuring levels of oxygen in wounds can be used to estimate oxygenation and treatment efficacy

Figure 3. Enzymatic activity by oxygen tension[23]





concentratons,[28] indicate hypoxic metabolic conditions from anaerobic glycolysis and neutrophil activity.

Several methods for measuring levels of oxygen in wounds are used to estimate oxygenation and the efficacy of treatments (*Table 2*).[15,29–37] These methods measure local hypoxia, but they offer no estimate on the activity level of neutrophils. Although not necessary for TOT therapy management monitoring oxygen levels has the potential to provide guidance on whether a non-healing wound is associated with a lack of oxygen and if supplemental oxygen is likely to result in improved healing. One method, transcutaneous oximetry ($TCPO_2$), has been validated mathematically to predict failure-to-heal rates for diabetic foot ulcers (DFUs) treated with HBOT,[6] and it holds promise for TOT.[34] Near-infrared spectroscopy (NIRS), remission spectroscopy and tissue oxygen tension measurements have also been favourably reviewed.

Table 2. Methods for measuring levels of oxygen in wounds

Method	Parameters	Mechanism	Advantages (+) and limitations (–)
Near-infrared spectroscopy	Light reflectance and absorbance at 760–1100 nm	Computerised algorithms measure skeletal muscle oxygen saturation of tissue, correlating to tissue perfusion, using oxygenated and deoxygenated haemoglobin as the primary absorbers (chromophores)[31,32,35]	+ Colour visualisation; completed in a few minutes; noninvasive – Disposable costs; potential of presence of dermal melanin to limit accuracy
Tissue oxygen tension	Local oxygen tension in a specific tissue volume around the probe	Measurements are based on polarography, in which tissue oxygen passes through a semipermeable membrane and is reduced to hydroxide ions on a noble-metal cathode polarised by an anode; the electrochemical reduction of oxygen produces a current that is directly proportional to oxygen tension in the tissue[15,29,33]	+ Minimally invasive, continuous measurement – Dependency of electrode currents on tissue temperature, patient movement; reading errors due to tissue trauma and oedema by electrode insertion or misplacement of oxygen sensors
Transcutaneous oxygen tension measurement	Blood perfusion in tissue immediately below skin	Measures oxygen tension of the skin, as cutaneous oxygen-tension values reflect arterial oxygen-tension values; heated Clark electrodes provide a practical method to monitor skin-surface (transcutaneous) oxygen tension[31,34–36]	+ Measures oxygen tension; correlation with local microcirculation status – Reading errors due to tissue oedema and states of inflammation and infection; potential for readings to be affected by temperature
Remission spectroscopy	Hyperspectral imaging; complete remission spectra; spatial frequency domain imaging	Hyperspectral (multispectral) imaging provides complete 3D remission spectra in the visible–near-infrared region in the form of theta perfusion depth profiles, compiled by advanced model-based data processing; classifies and segments different types of tissue (e.g., necrosis, granulation and epithelium); estimates perfusion in the superficial tissue, wound depth and surrounding tissue[110]	+ Contact-free; high information content – Lack of continuous measurement; sensitivity to environmental light influence

Topical oxygen therapy

The panel defined TOT as 'the administration of oxygen applied topically to wounds by either mechanical or non-mechanical means to promote tissue healing'. Distinct from HBOT (*Box 2*), TOT can be provided by a clinician or self-administered, and it is easily used in a variety of settings, from long-term care and acute hospitals to skilled nursing facilities and home care.[38]

TOT works on the rationale that higher oxygen tension has been demonstrated to reverse local hypoxia.[39] High oxygen concentrations are detrimental to anaerobic bacteria, while other pathogens are more readily cleared by leukocytes activated by oxygen.[40,41] Furthermore, wounds stalled in the inflammatory phase of wound healing can benefit, and oxygen can proceed to upregulate angiogenic growth factors (e.g. VEGF and FGF-2).[41] As angiogenesis progresses with enhanced fibroblast activity, wound-bed granulation and tissue collagen formation ensues, with the growth of new blood vessels, ultimately leading to wound healing.[13,41,42] Multiple modalities of TOT can be used to restore oxygen tension to levels necessary to support the enzymatic processes required for tissue regeneration.[14]

A study on DFUs investigated the impact of one TOT modality, continuous delivery of oxygen (CDO) (*Figure 4*), on inflammatory cytokines (IL-6, IL-8 and TNF-α), growth factors (VEGF, PDGF, IGF and TGF-β) and perfusion changes in the peripheral wound bed over 3 weeks.[43] Significant increases in cytokines, growth factors and $TCPO_2$ measurements were observed 1 week after CDO application. The study also measured perfusion, bacterial load and healing. Growth factors significantly increased from 280% to 820% in the first week. Several cytokines increased over 400% in the first 2 weeks before decreasing. Significant increases in $TCPO_2$ indicated increased oxygen perfusion in the wound periphery. Over half the wounds healed at least 50% in 3 weeks.[43] An earlier mechanistic study[13] further demonstrated that pressurised topical oxygen penetrated to at least 2 mm below the wound bed and increased oxygen tension eightfold in 4 minutes. These results demonstrate the effects of rapid oxygen delivery into the wound bed and periphery, as well as its significant positive impacts on multiple factors involved in wound healing.

Evidence

Historically, there has been a lack of the highest-level evidence for wound care in general and TOT specifically. This can be attributed to several factors, such as complex biological mechanisms of action, difficulties in clinical trial design, commercial barriers to serving target patient populations and a regulatory landscape that changes over time and differs across agencies (e.g., the US Food and Drug Administration

Box 2. Hyperbaric oxygen therapy

Hyperbaric oxygen therapy (HBOT) is a systemic therapy in which the patient inhales oxygen within a hyperbaric chamber. This provides super-physiologic oxygen tension—over 1800 mmHg at 2.4 ATA—which translates to different clinical and treatment indications from those of topical oxygen therapy (TOT). However, in principle, HBOT and TOT are not competing therapeutic methods and could be used together or sequentially.

HBOT has been in use for decades[111–113] and thus has a greater recognition and usage in the medical community than TOT. However, HBOT has the practical limitations of being relatively expensive and only accessible in a specialised care facility.[114] There has been tremendous variation in the accessibility of HBOT, on a country by-country basis and frequently by insurer as well, although the US Centres for Medicare and Medicaid Services have recognised HBOT use and provided coverage for several clinical indications, including diabetic foot ulcers (DFUs).[115]

The data on HBOT is inconsistent on its efficacy for various reasons. Reported trials in DFUs have been heterogenous, with inconsistent results and high drop-out rates due to inconvenience or complications.[111–113] Consequently, routine use of HBOT for chronic superficial non-ischaemic, non-infected DFUs is not recommended.[114] Two RCTs comparing HBOT to placebo in leg ulcers found significant improvements in wound-area reduction but not in overall healing.[116,117] The latest Cochrane review on HBOT found no eligible studies in pressure ulcers.[114]

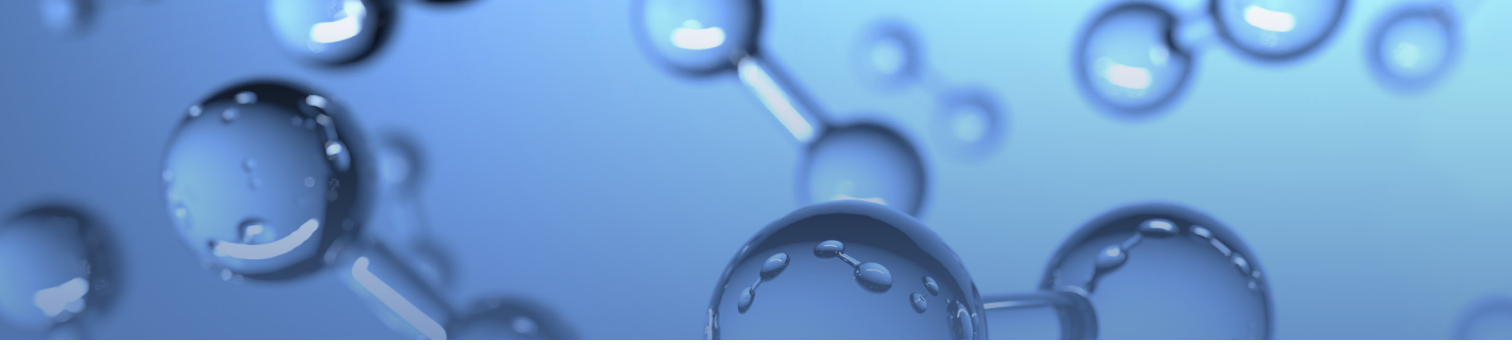
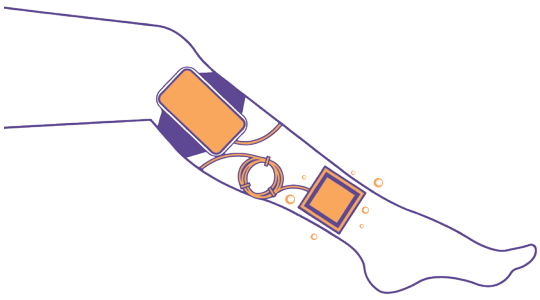
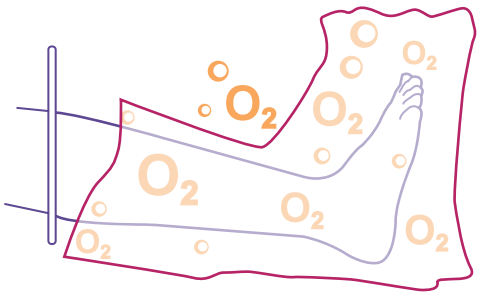


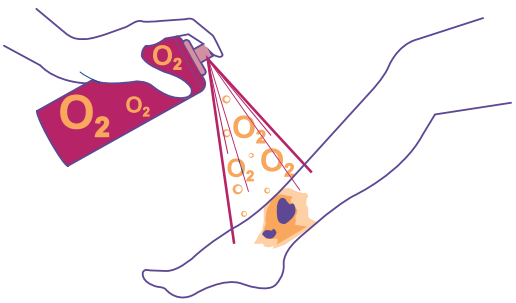
Figure 4. Topical oxygen therapies



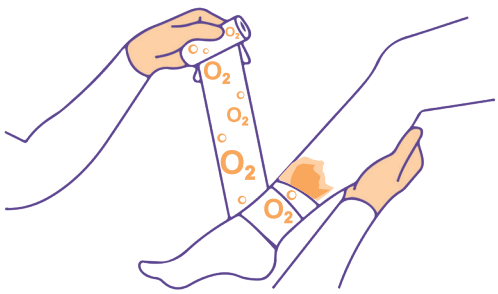
Continuous delivery of oxygen



Higher cyclical or low constant pressure oxygen



Haemoglobin spray



Oxygen wound dressing

(FDA), US Centers for Medicare and Medicaid Services, European Medicines Agency, Japan Pharmaceuticals and Medical Devices Agency and commercial payers). While most studies to date are supportive of TOT, other, mostly earlier studies present conflicting reports on this therapy. As knowledge of wound healing has advanced, so too have trial designs. Patient- and wound-selection issues, duration of treatment, durability of wound closure and defining appropriate standard of care (SoC) have remained challenges for clinicians, academics and industry to standardise.[44] Nonetheless, in recent years, a series of randomised controlled trials (RCTs) and systematic reviews have validated many aspects of TOT.

Due to the quality of recent TOT clinical trials and the positive results in the aforementioned systematic reviews, the ADA gave TOT the highest-level evidence rating for the first time in its 2023 'Standards of Care' guideline.[45] Equally important, the International Working Group on the Diabetic Foot (IWGDF) for the first time in 2023 made a recommendation to consider adjunctive TOT for hard-to-heal DFUs.[46]

Recommendations

There is an expanding evidence base for improved wound healing after treatment with TOT products, especially in a subset of patients with hard-to-heal wounds who failed to achieve adequate closure with SoC. Therefore, the panel endorses the adjunctive administration of TOT in particular for hard-to-heal wounds. Some products have completed multicentre prospective placebo-controlled trials affirming their clinical efficacy. Expanded studies to include additional clinical subpopulations (e.g. venous leg ulcers, pressure ulcers or some post-surgical wounds) and affirming studies for some products remain to be completed, although the requirement for and impact of oxygen in wounds of different aetiology is the same.

Key points

- Topical oxygen therapy (TOT) aims to increase oxygen tension to support tissue regeneration
- Rapid oxygen delivery has significant positive impacts on wound healing
- Unlike hyperbaric oxygen, TOT can be administered by clinicians or patients in various settings

Methods of topical oxygen therapy

There are several TOT modalities available (*Table 3*), with different methods of increasing wound oxygenation, and some of these modalities can be delivered by different devices (*Table 4*). More established modalities are supported by evidence from multiple reasonably robust RCTs, systematic reviews and meta-analyses.[47–54] More recently introduced modalities are also mentioned in these systematic reviews and are supported in most instances by evidence at the level of controlled cohort studies. TOT modalities are not all the same, and variations in the delivery of oxygen results in different oxygen tension applied to wounds, with observed differences in outcomes.[55] In order to evaluate these modalities, the most recent or highest-grade studies from each technology were identified by the panel members. Following is a summary of the representative evidence from each modality that met the panel's criteria.

Continuous delivery of oxygen

Continuous delivery of oxygen (CDO) devices deliver a continuous low flow of pure, humidified, low-pressure oxygen to blanket the wound, 24 hours a day, 7 days a week. The oxygen is generated from the surrounding air using compression-stack electrochemical oxygen generator units, which are small (about the size of a cell phone), rechargeable, wearable and silent. The oxygen is then delivered through a thin flexible tube (cannula) to either an

Table 3. Topical oxygen therapy modalities

Modality	Mode of delivery	Treatment time	Treatment frequency	ADA grade[7]
Continuous delivery of oxygen	Continuous flow of pure oxygen delivered from a generator, through a cannula, to an oxygen diffuser or diffusion dressing on the wound bed	24 hours a day	7 days a week	A (4 RCTs[56–59] and 3 CCSs[43,60,61])*
Disposable continuous delivery of oxygen	Continuous flow of pure oxygen delivered from a disposable generator, through a cannula, to an open end below an occlusive dressing	24 hours a day	7 days a week	C (1 RCT[62])*
Higher cyclical pressure oxygen	Humidified oxygen provided under cyclical pressure, managed by a controller unit connected to an oxygen concentrator, delivered via a disposable plastic chamber around the wound	90 minutes a day	5 days a week	A (3 RCTs[12,65,66] and 2 CCSs[67,105])*
Low constant pressure oxygen	Oxygen delivered at a constant pressure from a concentrator to a disposable plastic chamber around the wound	60–90 minutes a day	3–7 days a week	C (1 CCS[41])
Haemoglobin spray	Liquid with 10% purified haemoglobin sprayed onto the wound bed and covered with a non-occlusive dressing	24 hours a day	7 days a week	B (1 RCT,[75] 5 CCSs[73,76,77,118,119] and 1 meta-analysis[49])†
Oxygen dressings	Continuous-release dressings: pure oxygen in an occlusive dressing is dissolved on contact with moisture and released across a semipermeable membrane Hydrogel dressings: oxygen is released from chemical reactions on combining the two parts of a hydrogel primary dressing	24 hours a day	7 days a week	C (1 PCS[79])

Note: ADA=American Diabetes Association; CCS=controlled cohort study; PCS=prospective comparative study; RCT=randomised controlled trial; *these devices were considered in five systematic reviews or meta-analyses all supportive of the efficacy of TOT in healing hard-to-heal wounds;[50–54] †>50,000 documented treatments in more than 20 countries

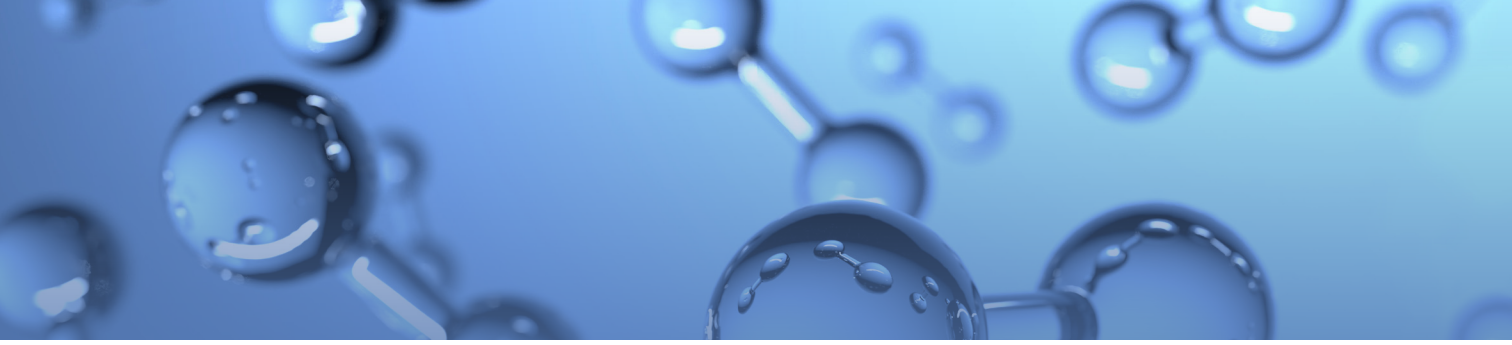


Table 4. Topical oxygen therapy devices

Device	Manufacturer	Modality	Flow rate	Pressure
NATROX O_2	Inotec AMD	CDO with oxygen diffuser	Low, ~12–15 ml/h	n/a
OxyGeni	EO_2 Concepts	CDO with diffusion dressing, pressure monitor and adjustable flow	Low, 3–15 ml/h	n/a
EpiFlo	Ogenix	Disposable CDO	Low, 3 ml/h	n/a
TWO_2	AOTI	Higher cyclical pressure oxygen	High, 10 l/min	10–50 mbar
O_2 TopiCare	OxyCare GmbH	LCPO with extremity chamber	High, 2–5 l/min	<22 mbar
O_2Boot and O_2Sacral	GWR Medical	LCPO with extremity or sacral chamber	High, 2–5 l/min	<29 mbar
Granulox	Hälsa Diapharm/ Mölnlycke	Haemoglobin spray	n/a	n/a
OxyBand	OxyBand Technologies	Continuous-release oxygen wound dressing	n/a	n/a
OxyGenesys	AcryMed/ Kimberly Clark	Continuous-release oxygen wound dressing	n/a	n/a
Oxyzyme	Crawford Healthcare	Hydrogel oxygen wound dressing	n/a	n/a

Note: CDO=Continuous delivery of oxygen; LCPO=low constant pressure oxygen

occlusive oxygen diffusion dressing or an oxygen diffuser (below a semi-occlusive dressing), placed in direct contact with the wound bed.

As previously mentioned, a clinical study of CDO in DFUs showed significant increases in cytokines and growth factors 1 week after application.[43]

A double-blind multicentre study using CDO with oxygen diffusion dressings on 146 non-healing DFUs with placebo controls and a 12-week endpoint found significant improvement with CDO compared to control.[56–58] A significantly higher proportion of wounds, more than twice as many (204%), healed in the CDO arm compared to the placebo (46% vs 22%, p=0.016). Frequent debridement increased the relative performance to 240% (51% vs 21%, p=0.006). The relative performance became greater as wounds were larger (273%), more chronic (334%, p=0.008) and weight-bearing (plantar, 465%, p=0.003). Patients with CDO experienced significantly faster rates of healing relative to the placebo (p<0.001), with the time to 50% wound healing being almost halved with CDO.

In another study, a 12-week, multicentre, open-label, community-based RCT of 145 patients with DFUs or minor amputation wounds treated with total contact casting and SoC compared those who were and were not receiving adjunctive CDO with an oxygen diffuser.[59] Primary endpoints were the number of patients to achieve complete wound closure and percentage change in wound size. This study demonstrated that adjunctive CDO to SoC supports wound closure in patients with non-healing DFUs. At 12 weeks, 18/64 (28.1%) patients healed in the SoC group vs 36/81 (44.4%) in the SoC plus CDO group (p=0.044). Additionally, the mean wound area reduction for the SoC cohort (40% +/-72.1), compared with the SoC plus CDO cohort (70% +/-45.5), was significantly lower (p=0.005).

Results from a non-comparative prospective trial of 20 patients to investigate reduction in pain in patients with 23 hard-to-heal lower-extremity wounds found that subjects experienced wound-associated pain relief quickly after starting CDO.[60] Over half the patients experienced at least a 75% reduction in pain relief by the first follow-up visit (median of 4 days), and over 90% had noticeable pain reduction (>25%) by the first follow-up visit. All patients (100%) experienced complete pain relief regardless of wound closure rate while the wounds were open. Patients with wounds as large as 117 cm^2 experienced complete pain relief by the first follow-up visit from a baseline pain score of 10/10. Multiple

subjects reported complete pain relief within hours of application of CDO. Subjects also reported being able to cease using narcotics with CDO. Overall, 83% of wounds experienced complete or significant wound closure. Pain relief was also reported in a retrospective analysis of 20 patients in which 76% of patients had 'substantial, rapid pain relief', and 69% stopped taking opioids completely.[61]

Disposable continuous delivery of oxygen

Disposable CDO devices, introduced in the mid-2000s, also deliver a continuous, low flow of pure oxygen to the wound. They differ from other CDO devices in that the entire system is disposable and intended to be used for up to 15 days before being thrown away and replaced with a new device and tubing. Oxygen is generated from ambient air using fragile,[54] tape-based electrochemical generators and delivered through a cannula, with an open end placed within a moist occlusive wound dressing. Disposable CDO devices are small, lightweight, wearable and completely silent.

A prospective, randomised, blinded, multicentre, parallel study, conducted from October 2009 to November 2012, evaluated healing time and the proportion of DFUs healed after 12 weeks of moist wound therapy with or without disposable CDO.[62] While the study showed some improvements in healing, none were statistically significant. A meta-analysis of studies on TOT identified reasons for these results, including the fragile construction of the oxygen generator, which can result in the unit failing in low humidity, and improper offloading by the patient, with no alert to the user.[54] The meta-analysis went further to state that, if the results of the disposable CDO study are removed from the meta-analysis on the basis of suspected premature failure, the heterogeneity disappears, and the meta-analysis yields statistically significant results.

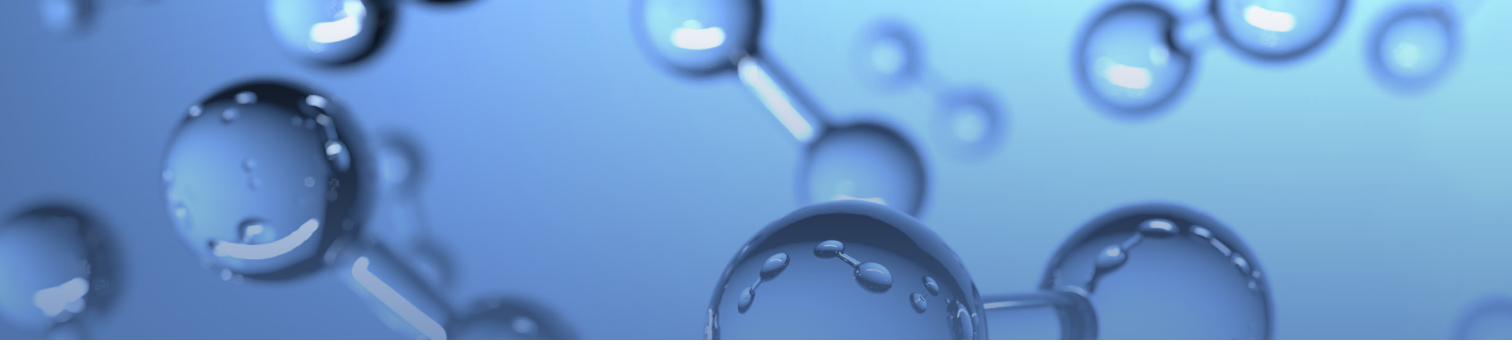
Disposable CDO is one of the few TOTs that has also been evaluated for pressure ulcers in an RCT. An RCT, conducted in Iran, randomly assigned 100 patients with stage II–IV pressure ulcers on the sacral or ischial areas to either control or experimental groups. The experimental group received 12-days of disposable CDO and demonstrated a total mean reduction in wound area that was significantly lower than the control group (p=0.0011).[63]

Higher cyclical pressure oxygen

Higher cyclical pressure oxygen (HCPO) devices deliver oxygen at variable pressure, cycled between 10 mbar and 50 mbar (1.07 ATA). These cycles are generated in a computer-controlled concentrator, where oxygen can be combined with humidification if desired, and delivered in a disposable plastic chamber placed around the wound, either as a boot-like extremity chamber or a patch. This modality is based on the theory that higher pressure gradients result in oxygen molecules diffusing deeper into the hypoxic wound tissue to enhance various molecular and enzymatic functions.[13,64] The cyclical pressure applied creates sequential non-contact compression of the limb that helps to reduce peripheral oedema and stimulates wound site perfusion further.[65,66] As with wearable CDO devices, HCPO can be delivered at home or in long-term care settings. Unlike CDO devices, HCPO is applied for only 90 minutes per day, 5 days per week.

A multinational, multicentre, prospective, double-blinded, placebo-controlled RCT evaluated the efficacy of HCPO with SoC vis sham therapy and SoC in the treatment of hard-to-heal DFUs.[12] SoC was a foam dressing, hydrogel and a diabetic offloading boot, equivalent to total contact cast. The patients self-treated 5 days a week for 90 minutes. The primary outcome measure was the intention-to-treat percentage of ulcers in each group achieving 100% closure at 12 weeks. A group sequential design was used for the study, with three predetermined analyses and hard-stopping rules once 73, 146 and ultimately 220 patients completed the 12-week treatment phase. This RCT demonstrated that, at both 12 weeks (intervention closure rate of 41.7% compared with 13.5%, p=0.007) and 12 months (56% intervention closure rate vs 27%, p=0.013), adjunctive HCPO was superior in healing hard-to-heal DFUs compared with SoC alone.[12]

Additionally, a retrospective cohort analysis of over 200 DFU patients was undertaken using



de-identified patient medical records from two US Department of Veterans Affairs (VA) hospitals.[67] Patients were allocated to control or HCPO cohorts based on their treatment records. The control arm had received appropriate SoC, potentially including other advanced wound treatments, such as cellular, acellular and matrix-like products (CAMPS)—formerly known as skin substitutes or cellular and/or tissue-based products (CTPs)[68]—negative pressure wound therapy (NPWT) and growth factors. Primary outcome measures were rates of hospitalisation and amputation within 360 days, with additional analysis in propensity-matched groups of 140 patients. The study found that treating DFU patients with HCPO in a real-world setting led to an 82% reduction in hospitalisations (p<0.0001) and 73% fewer amputations (p<0.0007). Additionally, when compared with other advanced wound treatments, HCPO demonstrated an 88% reduction in hospitalisations (p<0.0001) and a 71% reduction in amputations (p=0.016) at 12 months.[67]

Several further prospective clinical studies have been conducted using cyclically pressurised topical oxygen on both venous leg ulcers (VLUs) and DFUs. One non-randomised parallel arm study of 83 patients was conducted on VLUs to measure the effect of HCPO compared with conventional compression dressings (CCD) on wound healing with primary outcome measures of ulcers healed at 12 weeks (80% HCPO closure vs 35% for CCD).[65] The median time to full closure was 45 days in the study arm and 182 days in CCD arm. Criticism of patient-selection bias led the authors to conduct another comparative study of HCPO versus CCD in the management of refractory non-healing VLUs with a duration of at least 2 years.[66] In this study, 67 non-randomised patients were enrolled (mean age: 69 years) using HCPO and 65 patients (mean age: 68 years) using CCDs for 12 weeks or until full closure. At 12 weeks, 76% of the HCPO-managed wounds had completely healed, compared with 46% of the CCD-managed wounds (p<0.0001), with a median time to full healing of 57 days and 107 days, respectively (p<0.0001). Importantly, wounds colonised by methicillin-resistant *Staphylococcus aureus* (MRSA) were eliminated in 46% of patients managed with HCPO and 0% of patients managed with CCD. After 36 months follow-up, 14 of the 30 CCD-healed ulcers showed recurrence, compared with only three of the 51 HCPO-healed ulcers (p<0.0001).[66]

Low constant pressure oxygen

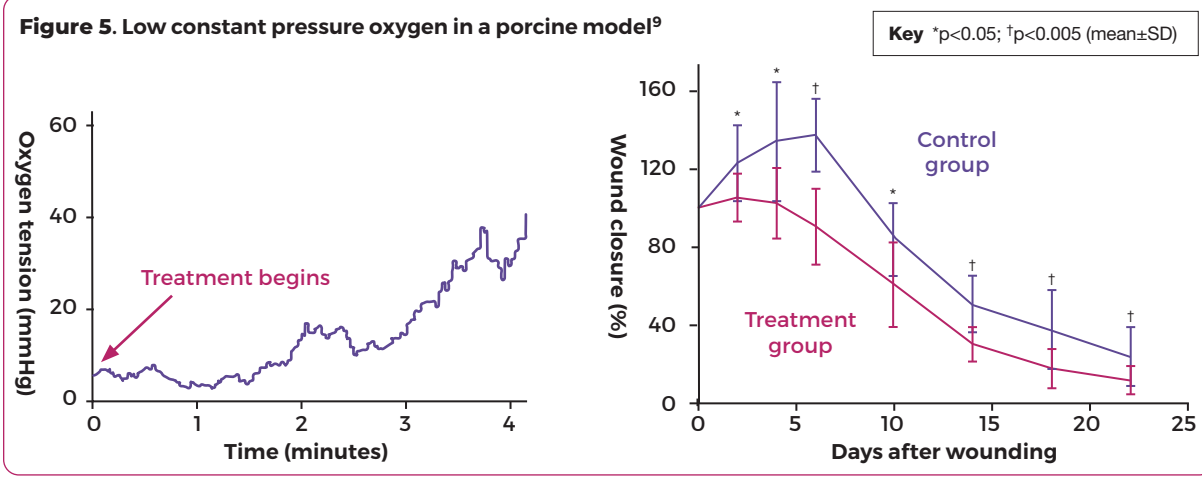
Low constant pressure oxygen (LCPO) devices deliver a high flow (2–5 l/min) of low-pressure oxygen, maintaining constant pressures of up to 29 mbar. Oxygen is delivered from a concentrator to a disposable plastic chamber (extremity chamber or patch) placed around the wound.

LCPO has shown good clinical efficacy in several studies conducted over the past four decades. The mechanism of action was explored in multiple tests, including a pre-clinical porcine dermal excision wound model.[13] Ten porcine open full-thickness dermal wounds were split into control (exposed to open air) and intervention (LCPO at 3–6 l/min for 3 hours a day for 7 days). An oxygen electrode placed at 2 mm depth in the centre of the wound bed monitored the oxygen tension, and 3 mm punch biopsies were taken for histology from two animals from each cohort. The data show that exposure of the open dermal wounds to LCPO increased tissue oxygen tension of superficial wound tissue from a baseline of 5–7 mmHg to >40 mmHg in as little as 4 minutes. Histological evidence for improvement was observed, and LCPO-treated wounds showed signs of improved angiogenesis and tissue oxygenation. Repeating the treatment accelerated wound closure significantly over controls (*Figure 5*).[13] However, no high-quality RCTs have been completed, and the majority of data supporting the use of LCPO comes from case series or uncontrolled trials.[41]

Haemoglobin spray

Topical haemoglobin spray, also known as oxygen diffusion enhancement or oxygen transfer, involves spraying the wound bed with a thin layer of a liquid containing 10% purified haemoglobin. The haemoglobin molecules increase the local delivery of oxygen by facilitating diffusion, rather than by a pharmacological or metabolic effect.[69] During treatment of a wound, the haemoglobin spray should

Figure 5. Low constant pressure oxygen in a porcine model[9]

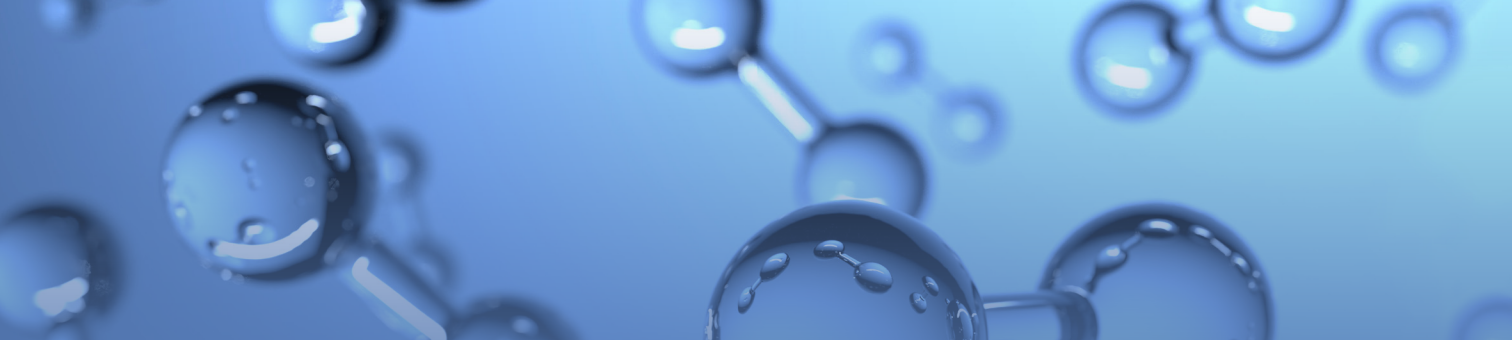


be applied adjunctively to SoC, after wound-bed preparation, before the wound is covered by a non-occlusive dressing. Haemoglobin spray can be applied from twice weekly up to once daily, to coincide with routine dressing changes, depending on wound status. Applications take less than 5 seconds, and a standard container has around 30 applications, for a wound with an area of 6 cm^2. Haemoglobin spray can be used concomitantly with most wound treatments, but occlusive dressings should be avoided.[70]

Haemoglobin spray was verified in an initial pilot study where researchers using photo-acoustic tomography were able to visualise the conversion of carboxy-haemoglobin to oxy-haemoglobin in under 20 minutes after application. Furthermore, they observed an increase of haemoglobin oxygenation in the tissue, concluding that the increased diffusion of oxygen was facilitated by the haemoglobin spray.[71,72]

In another set of recently collected data cohorts, patients were recruited prospectively from sequentially presented diverse hard-to-heal wounds, in particular, sloughy wounds. The number of patients recruited to each cohort was 20, 50 and 100, respectively. As a control group, data from clinical notes of an equal number of patients were collected retrospectively. These were selected sequentially by date in the notes without reported as matching to prospective cases. The DFU cohort was treated in a hospital setting, and the hard-to-heal wound and sloughy wound cohorts were treated in primary care. All three cohorts shared the inclusion criterion of a wound that failed to heal (defined as a <40% reduction in area in the previous 4 weeks). In the DFU cohort, the mean wound size reduction was greater in the haemoglobin spray group at week 4 (–63% vs –21%), week 16 (–91% vs –43%) and week 28 (–95% vs –63%). At week 28, 15/20 patients in the haemoglobin spray cohort had complete healing, compared with 8/20 in the control cohort. The hard-to-heal wound cohort reported mean wound size reductions of –73% in the haemoglobin spray group compared with –12% in the control group at 4 weeks. The benefit persisted at 8 weeks (–87% vs –14%) and the final 26-week follow-up (–89% vs –75%). Altogether, 45/50 patients had complete healing at the final 26-week follow-up compared with 19/50 in the control group. The sloughy wound cohort results were reported in a more limited fashion. At week 8, there was a mean wound size reduction of –93% in the haemoglobin spray group compared with –32% in the control group. At week 6, complete wound closure was observed for 65/100 patients in the haemoglobin spray group and 37/100 patients in the control group.[73,74]

A single-blinded prospective RCT included 72 patients with VLUs and compared adjunctive haemoglobin spray therapy on wound size reduction



in hard-to-heal wounds to an SoC-only cohort (moist wound treatment and compression therapy).[75] After 13 weeks of treatment, the group receiving haemoglobin spray demonstrated a mean wound size reduction of 53% (40%–62%, $p<0.01$) with significant and continuous healing noted throughout. In contrast, no statistically significant reduction in wound size was demonstrated in the control group.[75]

Additional, less robust studies on DFUs have also shown a wound size reduction when haemoglobin spray is used as an adjunct to SoC[73,76,77] However, no large, well-designed RCTs corroborating earlier findings for this modality have been published to date.

Oxygen wound dressings

Oxygen wound dressings deliver topical oxygen directly to a wound without the need for gaseous diffusion. There are two main types:

- Continuous-release oxygen dressings are occlusive dressings that contain pure oxygen embedded in a reservoir at >2800 ppm or in foam vesicles. Contact with moisture from the wound exudate dissolves the oxygen, allowing it to be continually released to the wound bed for up to 5 days through direct diffusion across a semipermeable membrane. In vitro experiments with these dressings have measured significant increases in oxygen levels in the wound.[78] A 17-patient RCT on the treatment of larger donor-site wounds in burn patients observed a decrease in healing time and reported pain scores in dressings with a reservoir compared to SoC alone.[79] No further clinical data are available in the public domain.
- Hydrogel oxygen dressings increase the dissolved oxygen concentration at the wound bed via a chemical or biochemical reaction.[70] In one example, an occlusive dressing with a hydrogel containing 0.3% hydrogen peroxide generates water and dissolved oxygen, which can diffuse via a permeable separator to the wound bed. Another example is a hydrogel primary dressing with two component sheets: the first containing glucose and a low-concentration gel matrix with less than 0.04% w/w of iodide ions and the second containing glucose oxidase. In the presence of oxygen, the glucose oxidase catalyses the oxidation of β-D-glucose to D-gluconic acid and hydrogen peroxide. The released hydrogen peroxide is thought to diffuse through the dressing and either oxidise any available iodide ions to free iodine and oxygen or, if it reaches the wound surface, metabolise to water and oxygen.[70] Used in early stage wound treatment, oxygen is released when both layers are attached to each other. This modality may also benefit from the antimicrobial effect of iodine. Clinical data from several case studies have shown improved healing of different wound types.[80,81] No RCTs have been carried out to date.

Key points

- Topical oxygen therapy is an umbrella term for several different modalities and devices
- Continuous delivery of oxygen (CDO) and disposable CDO devices are worn 24 hours a day, 7 days a week and deliver oxygen from a wearable generator to the wound bed
- Higher cyclical and low constant pressure oxygen (HCPO and LCPO) devices deliver a relatively high flow of pressurised oxygen to a disposable plastic chamber around the wound for 90 minutes a day, 5 days a week; in HCPO devices, this pressure varies in cycles
- Haemoglobin spray with 10% purified haemoglobin is sprayed on the wound bed and covered with a non-occlusive dressing; in continuous-release dressings, oxygen in an occlusive dressing is dissolved on contact with moisture and released across a semipermeable membrane, while, in hydrogel dressing, oxygen is released from chemical reactions on combining the two parts of a primary dressing
- The supporting evidence is strongest (grade A) for CDO and HCPO, followed by haemoglobin spray (grade B)

To optimise conditions for use of oxygen wound dressings, the wound should be regularly debrided and cleansed. The interval depends on the wound status and any other adjunctive therapies. In general, these dressings should be replaced no less frequently than at each debridement. An improvement of wound healing within 4 weeks should be used as an indicator to maintain therapy.[70]

Optimising topical oxygen therapy in clinical practice

To date, most evidence on TOT comes from studies of patients with DFUs. Recent review panels have suggested that ischaemic ulcers, DFUs and VLUs are all anticipated to be responsive to TOT, [82] since hard-to-heal wound require oxygen (as detailed earlier in this document) and are typically hypoxic, and, therefore, they should benefit from TOT. From this evidence, the panel makes the following recommendations:

- TOT is an appropriate adjunctive therapy for wounds that have failed to reduce in size by 50% or more after 4 weeks of optimal SoC
- TOT is generalisable to most kinds of non-neoplastic hard-to-heal wounds (not just DFUs)
- Earlier consideration of TOT usage, rather than later, is appropriate for those with hard-to-heal wounds; such efforts will notably improve with the development of assessment tools to identify regional ischaemia to guide the decision of when to implement TOT
- In patients with critical limb ischaemia, there is insufficient evidence to support the use of TOT; however, the therapy has been used anecdotally in patients with no option for revascularisation, and patients were only able to be partially revascularised, including revascularisation of a non-contiguous angiosome
- TOT can be considered for early treatment of ischaemic DFUs
- Broad access to TOT should be available, with appropriate reimbursement by payers and healthcare systems
- As the clinical data expands, then TOT might also be used as a first-line therapy.[11,12]

Incorporation of topical oxygen therapy into practice

Every patient should undergo an initial validated wound assessment, on which their progress is based. The panel generated a treatment algorithm to guide the incorporation of TOT into practice (assuming universal access) (*Figure 6*). Patients who progress <50% wound closure in 4 weeks should have good wound practice continued and adjunctive TOT initiated. Wounds that are healing sufficiently can continue SoC without TOT. Re-evaluation of progress at weekly-to-biweekly intervals should be maintained until wound closure. When wounds stall after initial progress, they should be re-evaluated and then also considered for TOT to assist in wound healing.

Of note, a 2022 study on patients with DFUs demonstrated that patients are 8.7 times more likely to be hospitalised and 4.5–5.0 times more likely to have an amputation if they did not use HCPO compared with those who had the benefit of the therapy. Additionally, once a wound closed, enhanced durability of healing was demonstrated with HCPO (a low wound recurrence rate).[12] Additional studies support the use of TOT in VLUs and pressure ulcers as well.[60,63,65,66]

Standard of care

The panel recommends that patients should have noninvasive vascular studies performed as part of their initial assessment. The wound aetiology and the presence of any vascular issues or other physical deformities must be considered. The patient should be treated for any contributing comorbidities and provided with medical management of cardiovascular issues, glucose levels and nutrition. A 2022 consensus document had 75–100% support for assessment of limb perfusion, nutrition and infection, as well as management of oedema, debridement and offloading.[82] The consensus of this review is that vascular intervention should be provided when necessary.

For most kinds of hard-to-heal wounds, TOT should be considered as an adjunctive therapy to promote wound healing where 4 weeks of optimal SoC has failed to reduce wound size by 50% or more. Wound care should also include frequent and adequate debridement,[83] effective offloading, compression as required, management of any infections (including osteomyelitis) and management of patient pain. The panel emphasises the need for a multidisciplinary approach, since this structure of care has been shown to provide optimal long-term results.[84]

Appropriate education of patients and caregivers has been seen to activate patient engagement in their care and provide for effective treatment. The patient should receive appropriate education on wound care

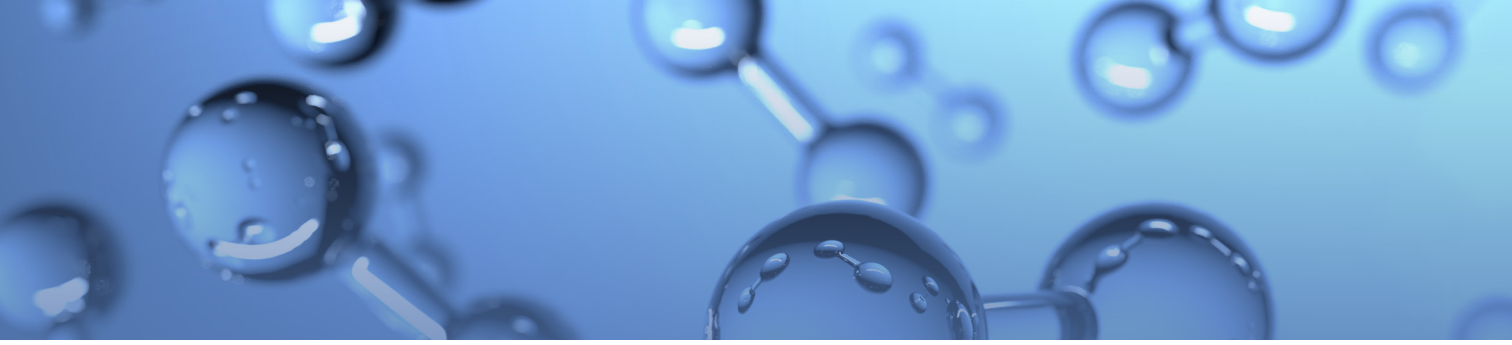
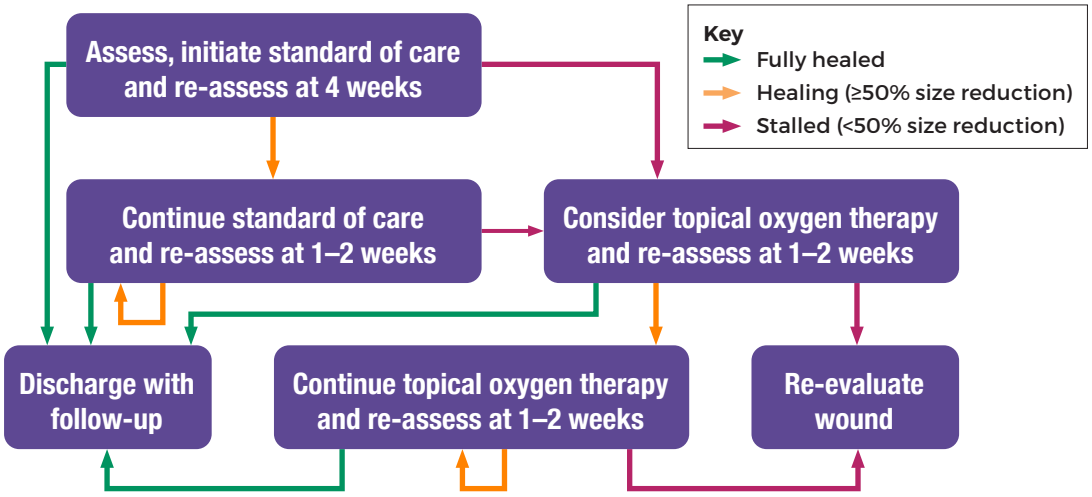


Figure 6. Treatment algorithm for topical oxygen therapy in hard-to-heal wounds



and of any underlying comorbidities or deformities they may have. The patient should understand that hard-to-heal wounds often take longer to heal than they might expect. Education should include managing the patients' expectations and making them aware of important lifestyle changes, such as smoking cessation. Involving patients and their families in their care is viewed as key to compliance, so clinicians should discuss the rationale for using a specific therapy, device-specific recommendations and the importance of maintaining adherence to both SoC and any indicated advanced therapies, including TOT, for maximal benefit. The use of NIRS imaging to demonstrate the response of the tissue to TOT can enhance patient education efforts and foster adherence to treatment plan of care.

There are few contraindications and precautions for TOT, but the limits are still under investigation. Patients should be provided consultation in the following circumstances:

- Upon initial presentation, the provider anticipates perfusion will not support wound healing by TOT
- The wound is completely covered with eschar or fibrin
- Presence of fistulae or deep sinus tracts where the end cannot be probed
- The patient will not agree to refrain from smoking during TOT.[85]

The panel notes that TOT should not be used on wounds with an untreated infection or osteomyelitis, in the presence of a malignancy and in un-debrided or necrotic wounds. TOT treatment is also not advised without a vascular assessment and appropriate intervention. Lastly, hydrogels, foam dressings, mutilayer compression, petrolatum-based salves or occlusive dressings underneath the chosen treatment modality that can prevent access of oxygen to the wound should be avoided.[85]

Key points

- Compression, offloading and vascular intervention should be provided as required, while pain and infection should be managed as appropriate
- Wound care should include frequent and adequate debridement
- Adjunctive topical oxygen therapy (TOT) should be considered where standard of care alone has not achieved ≥50% wound closure after 4 weeks
- Patient progress should be based on an initial wound assessment and re-evaluated every 2 weeks
- Optimal long-term results can be achieved with a multidisciplinary approach

Patient perspectives on topical oxygen therapy

Most research on oxygen therapy has been for HBOT and pulmonary delivery of oxygen.[86–89] Lessons from these related treatments demonstrate that patients' understanding of and concerns about oxygen therapy are important and will likely impact their use of home therapy.[88] Health professionals providing information and education on oxygen delivery methods do influence patients trying to decide the best path for their healing needs. Ultimately, the patient's own experience of TOT and the progress of their wound will dictate the perspectives on TOT that they hold and share with others. However, both patients and providers may not find the information they want. Much of the discussion presented here is extrapolated from related oxygen therapies and lower-level studies.

Patient-centred outcomes

Outcomes that are important to patients have been measured in the Wound-QoL, a validated tool for longitudinal assessment of quality of life (QoL) in patients with hard-to-heal wounds.[90–92] The questionnaire was validated on 277 patients, with indications including VLUs, pyoderma gangrenosum, diabetic or ischaemic foot ulcers and pressure ulcers, and it is suitable for use in clinical trials and quality-of-care studies.[90] However, endpoints specifically identifying the patient's perspective on TOT need to be added to show improved disease-related QoL.

Patient education

Information and education shape a patient's perspective about the treatment they are about to undertake, necessitating straightforward education be provided to the patient[93] before any collaborative healthcare decision is made. Other researchers have suggested four 'rights' of health literacy: the right information, the right literacy level, the right modality and the right time, with 'due respect for any cultural, language and socioeconomic barriers'.[94]

TOT education is based on the essential tenets of education and right to know, which enable patients to commence the TOT modality and device best suited to their situation. Patients are frequently pleased to hear that there are efficacious treatment modalities that can be carried out in the privacy of their home or long-term care facility, but the methods require explanation. It is expected that patients will want to know about the probability of improvement, pain and side effects, as well as changes in routine, dosage and stoppage, among other considerations. Responses to common patient concerns are given in *Table 5*. All TOTs are challenging to describe by words alone, thus the use of multimedia technology has allowed health professionals to address this issue.[94] Clinical facilities are increasingly using social media to offer easily accessed and relatable patient experiences via photographs and videos.

Patient experience

There is little qualitative research into the experience of patients undergoing TOT.[95,96] However, specific expert recommendations for impacting the patient experience include the following:

- Suitable patient selection
- Patient preparation
- Appropriate training for TOT application
- Therapy evaluation
- Providing patients with realistic expectations.[96]

Researchers note that TOT is well adopted by patients.[95,96] TOT in the home has been documented to be an easy process,[77] and telemedicine adoption during the COVID-19 pandemic has seen a notable case-report success.[97] Several authors have noted a high level of patient acceptance of topical haemoglobin spray and reported on the ease of product use for the patient.[77,98] A study on HCPO noted a 96% adherence to the prescribed therapy.[12] The panel concluded that:

'TOT is easily self-administered by patients or caregivers at home or long-term care after a brief initial training on appropriate application, thereby facilitating patient activation in their self-care.'

Additionally, a CDO placebo study on DFUs noted that over 99% of patients could manage their therapy without assistance, including dressing changes, between study visits.[56]

The reduction of wound-related pain has support

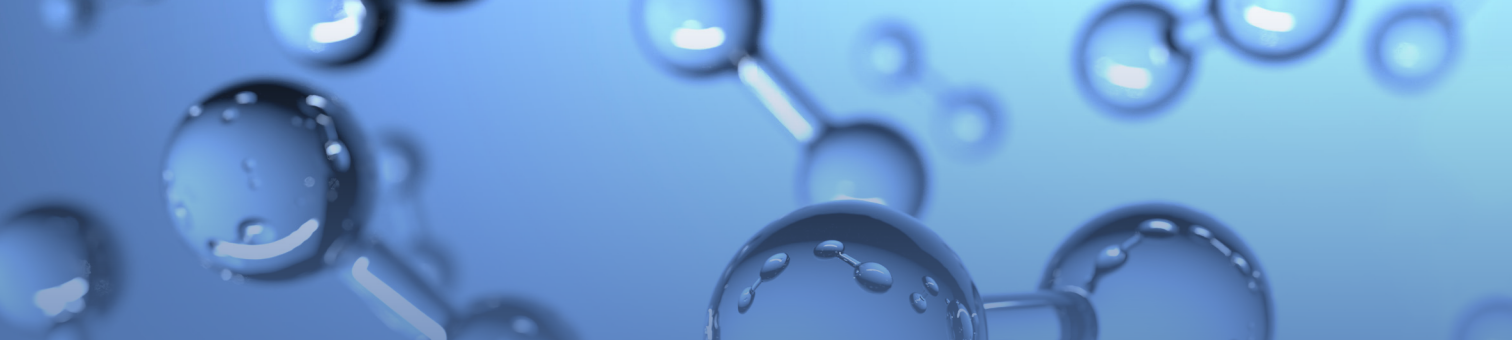


Table 5. Addressing patient concerns about topical oxygen therapy by modality[6]

Modality	Continuous delivery of oxygen	Higher cyclical or low constant pressure oxygen	Haemoglobin spray	Oxygen wound dressings
Pain management	Reported reductions in pain levels	Reported reductions in pain levels	Reported reductions in pain levels	Reported reductions in pain levels
Duration and frequency of treatment	Applied weekly and worn 24 hours a day, 7 days a week	90 minutes each day, 5 days a week, at home	Twice weekly applications of less than 5 seconds	Limited information
Side effects or reactions	None reported	None reported	None reported	None reported
Probability of improvement	Stimulates wound healing when used with good standard care	Stimulates wound healing when used with good standard care	Reduces slough and exudate in the wound bed	Limited evidence of healing; promoted as supplying oxygen directly to wound
Changes to daily routine	Allows full mobility; offloading as required per standard of care	User must be immobile for 90-minute treatment; offloading as required per standard of care	No change to daily routine (can be applied at user's convenience)	No change to daily routine
Risk of sudden cessation	No disadvantages to stopping suddenly	No disadvantages to stopping suddenly	No disadvantages to stopping suddenly	No disadvantages to stopping suddenly
Safety considerations	No safety considerations	Patients must not smoke during treatments	No safety considerations	No safety considerations

from several studies. Patients who used HCPO for VLUs indicated that their pain levels fell from 8/10 to 3/10 on the pain scale shortly after commencement of the therapy. It is believed that the oscillating cyclical nature of the therapy contributes to removing the interstitial oedema in the wounded tissue, relieving pain associated with the extreme tensions and venous stasis of the tissues.[65] Similar results were observed in a CDO study on painful wounds, primarily VLUs. In this study, over half of the patients had a 75% reduction in pain, and over 90% had a noticeable reduction in pain at the first follow-up visit (3–4 days).[60] Additionally, observed reductions in pain have been noted with the use of haemoglobin spray and oxygen wound dressings.[61,75,98]

Key points

- Clinicians should educate patients and address their concerns about topical oxygen therapy (TOT)
- Wound-QoL can measure patient-centred outcomes
- TOT has been shown to reduce wound-related pain
- After initial training, self-administered is easy and facilitates patient activation and engagement in their self-care

Patient-centred recommendations

This review of published data on the patient's perspective on TOT shows a need for large-scale, qualitative research on specific areas, especially:

- Measurement of patient-centred outcomes associated with TOT
- QoL among patients receiving TOT
- Advantages of TOT for patients, from their perspective
- Exploration of health literacy associated with TOT.

Oxygen delivery to wounds to improve wound healing is a dynamic, evolving field. It is increasingly clear that the patient's perspective will impact their usage, experience and perceptions of TOT for wound management. It will likely fall to health professionals to shape, understand and respond to the patient's perspective to corroboratively achieve healing.

Economics of topical oxygen therapy

There is an increasing amount of evidence for the effectiveness of TOT in promoting wound healing, relative to the cost of TOT application, in specific subpopulations of patients.[77] The expectation is that accelerating wound healing will reduce or avoid the costs of ongoing care associated with potential infection, hospitalisation and/or amputation. There is a need for further studies that include economic outcomes to make recommendations on the cost-effectiveness of applying TOT to a broader range of wound-care indications and for various payer systems.

Cost-efficiency principles

A robust understanding of health economics requires well-designed trials, providing measurable outcomes that can be generalised to a broader population. The international health community commonly measures outcomes by quality-adjusted life years (QALYs) and costs measured in local currencies. Wound-treatment analyses should always include the primary costs of treatment and may fairly include secondary cost savings, such as the value of a shorter time to wound healing or reduced risk of hospitalisations, amputations and/or prosthetics.[99,100] Tertiary costs, such as assistance rendered to patients by family, are not typically included, nor are costs of failed treatments.

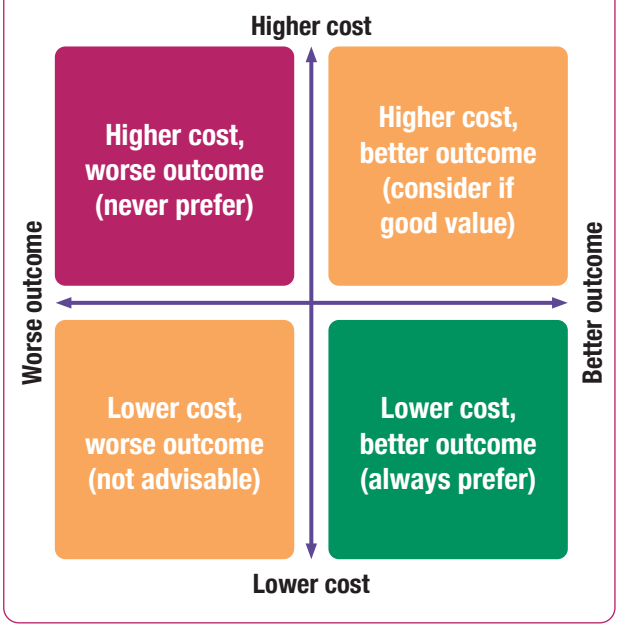
Cost-effectiveness analyses should also include the type of wound, care setting, type of dressing, and patient-related characteristics.[100] In simple terms, this can be illustrated with a cost-effectiveness plane, presenting treatment cost on the vertical axis and treatment effectiveness (in QALYs) on the horizontal axis (*Figure 6*).[101] Commonly, the treatment of interest is compared to SoC. If the unit cost for a QALY is less than the local willingness-to-pay threshold (typically $50 000 or $100 000 per QALY in the US and UK), then adoption of the treatment is deemed incrementally cost-effective. Above the threshold, it is deemed not to be cost-effective. In recent years, the publication of peer-reviewed results from quality RCTs provides the opportunity to calculate increasingly accurate cos-effectiveness analyses. Appropriate cost-effectiveness analysis is an important consideration for most insurers and payers to consider coverage adoption of new technologies.

Cost-effectiveness of topical oxygen therapy

The cost-effectiveness of TOT in wound healing is difficult to estimate, as it is dependent on the TOT modality used; the payment mechanism for the primary medical procedure and service; and secondary costs, such as rehabilitation, sickness benefits and compensation for disablement. Therefore, analyses have country-dependent and payer-dependent components. However, there are an increasing number of reports showing that using TOT as an adjunct to good wound care demonstrates cost-effective principles.[56,102–104]

Hard-to-heal wounds reoccur up to 70% at 1 year and commonly result in hospitalisations and amputations, creating a considerable revolving health-economic burden.[1,3] TOT offers the potential to reduce these costs by providing better-quality and more-durable wound healing. A 2020 RCT on HCPO in DFUs demonstrated significant sustained 12-month healing, reducing recurrence by 83%.[12] A

FIGURE 6. Cost-effectiveness plane



follow-on 2021 real-world study on HCPO showed significant 12-month reductions in hospitalisations and amputations, concluding that this therapy would likely be associated with important QoL and health-economic benefits.[67]

A 2020 cost-effectiveness analysis compared CDO trial results on patients with DFUs[56,58] with results from other therapies.[102] The analysis evaluated multiple outcomes for CDO and NPWT, including wound chronicity, wound size and effect of debridement. A cost-utility analysis was used to calculate savings in year 1, and a six-health-state microsimulation model was used to calculate savings for up to 10 years, all in US dollars, for an episodic cost per wound treatment. Impacts on both cost savings and QALYs were reported. The model predicted that CDO would save $4800 compared with NPWT and increase QALYs by 0.025. Lower cost and improved outcomes were observed in most scenarios, with savings ranging from $1800 to $14 060 versus moist wound therapy, NPWT and HBOT (*Figure 7*). Savings compared with NPWT were particularly notable for larger wounds (up to $5900), frequently debrided wounds ($6100) and hard-to-heal wounds ($6455). Importantly, a probabilistic analysis—based on 5000 repetitions of a simulation, varying parameters within uncertainty—resulted in 87% of the simulations providing a cost savings for CDO and 90% of the simulations resulting in a positive incremental QALY. In 3947 of the simulations (79%), CDO was cost effective and resulted in positive QALYs (*Figure 8*). The results of this economic evaluation demonstrate that CDO therapy reduces healthcare economic burdens, with a modest increase on QALYs.[102] The study is well grounded, but its applicability is limited by being primarily based on Canadian and US healthcare costs.[47]

Preliminary studies have shown that HCPO has the potential for cost savings.[96] Studies have established positive outcomes for wound healing.[12,65,66] One researcher stated that 'The significant differences in treatment outcomes confirm the potential in the benefits of topical pressurised oxygen therapy in the management of difficult to heal DFUs. Clinical efficacy and cost-effectiveness studies are warranted.'[105] Comparing HCPO groups with the controls, researchers identified likely cost savings with the number of physician visits, debridement, dressing, antibiotics and hospitalisations, as well as in reduced amputations, compared with those patients not receiving HCPO therapy.[65,66]

An assessment by the Scottish Health Technologies Group found haemoglobin spray 'to be more effective and less costly than standard care'.[104] The assessment was based on one RCT[75] in VLU and

Figure 7. Cost savings of continuous delivery of oxygen (CDO)[102]

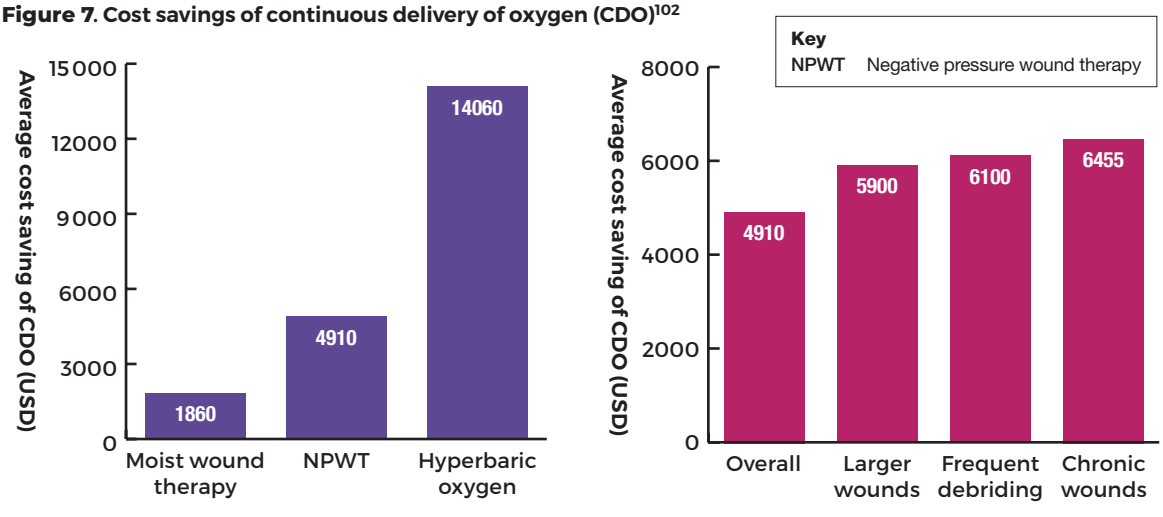
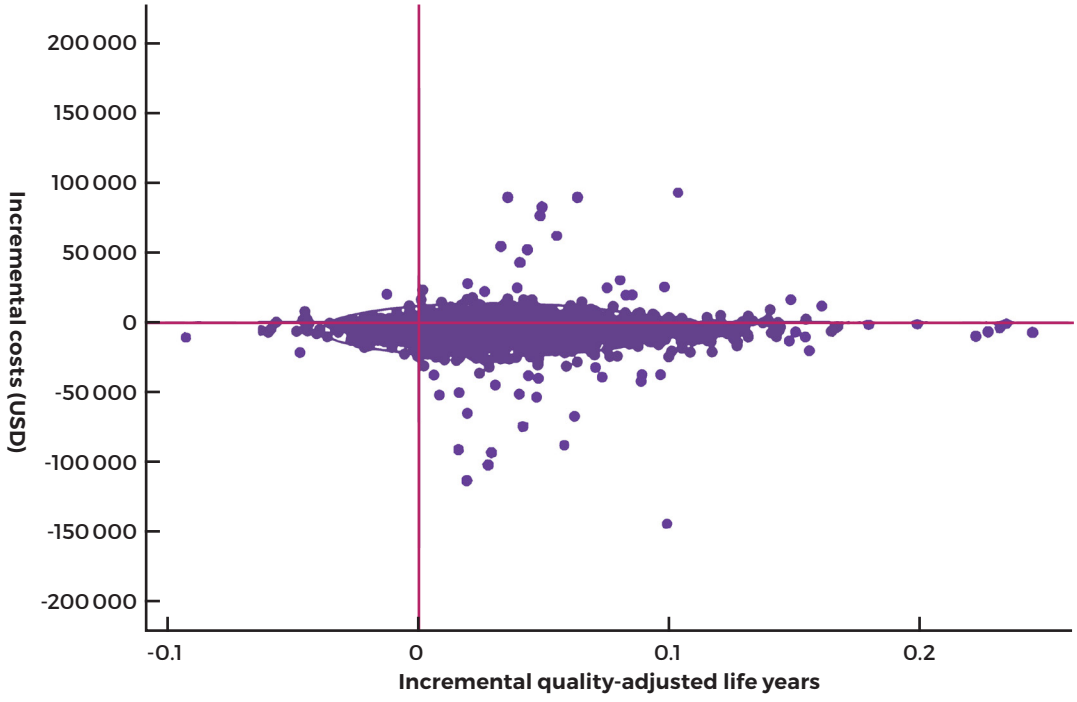


Figure 8. Cost-effectiveness of continuous delivery of oxygen[102]

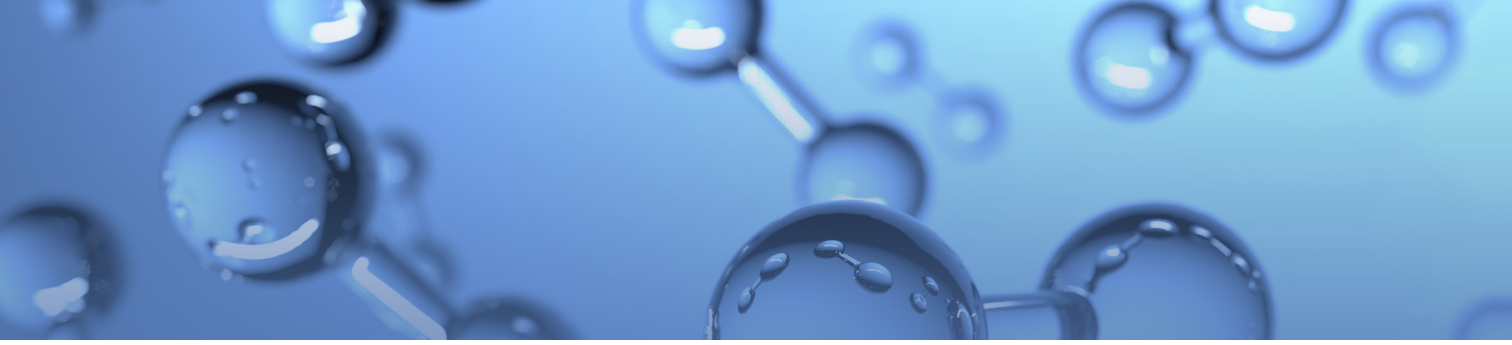


three cohort studies[73,76,77] performed in the UK with fair enrolment numbers. The health-economic impact of adding haemoglobin spray to SoC resulted in an estimated UK healthcare system cost savings of an about £2330 for every DFU patient and £1469 for every hard-to-heal wound patient after 6 months.[104] Limitations of the assessment include the weaknesses of the VLU RCT and retrospective recruitment in the cohort study controls.[106] The impact of haemoglobin spray on treatment costs was also analysed from the perspective of the German statutory health insurance.[103] The group applied a 28-week, six-health-state Markov model to the existing clinical data and calculated approximately 40% lower costs for the treatment of DFUs when adding the haemoglobin spray to the treatment regimen. Savings achieved with adjunctive haemoglobin spray included reductions in nursing care and dressing changes (average of 806 € in savings) and standard wound-care regimen (average of 474 €).[103] Sensitivity analyses confirmed these results, leading to the conclusion that, with adjunctive treatment, a substantial cost reduction could be achieved from the perspective of the German statutory health insurance. Another study evaluated haemoglobin spray on 50 patients over 26 weeks as an adjunct to SoC, compared to a retrospective SoC cohort. The researchers used a micro-costing approach and found reduced healing times and dressing costs in a UK NHS community setting.[107]

Reimbursement and challenges

The following TOT devices have been cleared to market in the US by the FDA:

- EpiFlo (Ogenix)
- NATROX O_2 (Inotec AMD)
- O_2Boot and O_2Sacral (GWR Medical)
- OxyBand (OxyBand Technologies)



- OxyGeni (EO_2 Concepts)
- TWO_2 (AOTI).

The largest US government insurer, Medicare, is managed by the US Centers for Medicare & Medicaid Services (CMS), which allow for coverage of TOT for the treatment of hard-to-heal wounds to be determined by local contractors.[108] Medicaid managed care covers TOT use in New York and various other US states. Other than in the various federal health systems (VA, Department of Defense, Indian Health Service, etc), only a few commercial or government payers in the US currently provide for reimbursement. Across Europe, TOT is typically paid for as part of local wound treatment. Some devices, such as the haemoglobin spray Granulox (Hälsa Diapharm/Mölnlycke), are not available in the US but are reimbursed in EU countries, including the Netherlands, Czechia and Croatia. Cost-effectiveness modelling supports the use of CDO for DFUs in Canada and the US[102] and haemoglobin spray in Germany[103] and the UK.[107]

Cost-efficiency recommendations

There is increasing evidence that using TOT adjunctively to SoC is a cost-effective approach to expediting healing in patients with hard-to-heal wounds. Strong outcomes and good modelling using peer-reviewed costs support the use of TOT, especially for DFUs.[12,67,102] Furthermore, haemoglobin spray as an adjunct treatment has demonstrated improved wound healing and cost reduction in some studies.[103,104] Ultimately, more accurate data on cost-effectiveness for specific indications is going to be necessary before healthcare systems, especially those that are taxpayer-funded, can confidently adopt TOT into their treatment algorithms. The consensus panel states the following:

'Recently published evidence shows inherent cost savings associated with TOT, based on faster healing and fewer hospitalisations (and amputations in DFUs), as well as lower costs for patients, better adherence, greater equity, reduced pain and improved QoL.'

Key points

- Evidence supports the cost-effectiveness of adjunctive TOT in specific patients populations
- By accelerating wound healing, TOT should reduce the costs associated with potential infection, hospitalisation and/or amputation
- Cost-effectiveness likely varies by TOT modality, payment mechanism and secondary costs, such as rehabilitation, sickness benefits and compensation for disablement
- The evidence for the cost-efficacy of TOT is strongest in diabetic foot ulcers
- Further studies are needed on the economic outcomes of TOT in different indications and payer systems

There is growing evidence to support the use of CDO and HCPO for DFUs as cost effective in the US healthcare system, and for haemoglobin spray in the UK NHS and the German statutory health insurance system. Based on current evidence, the consensus panel recommends the following:

- More robust health-economic data, based on large placebo-controlled RCTs, to make recommendations on the cost-effectiveness of TOT in different wound types and in additional countries
- Vascular screening to evaluate if any intervention is indicated before TOT
- The creation of a European or global wound register to further evaluate the benefit of TOT in wound care
- Broad access to therapy with appropriate reimbursement by payers and health systems
- Use of TOT as an adjunctive therapy after 4 weeks of optimal SoC without achieving at least 50% reduction in wound area
- Consideration of TOT earlier rather than later, especially for those with modestly impaired perfusion or complicating comorbidities.

Future developments

Oxygen plays a crucial role in wound healing, including fighting infection, and the clinical and scientific interest in its role is expected to increase in the future.

Diagnostic tools, such as NIRS imaging for measuring local hypoxia, are improving and will further elucidate the role of TOT in wound healing. Regular measurements of oxygenation should be included in clinical trials and may be incorporated into clinical practice. The effort to delineate mechanisms of action of TOT in wound healing, infection prevention and infection resolution continues. Monitoring oxygen levels in response to therapy would inform future studies and aid in the differentiation of which treatment modality is best for a patient. Smart dressings containing oxygen sensors that continuously measure oxygen levels, combined with an oxygen delivery system that can correct oxygen deficits, are on the horizon.

The future of healthcare is moving towards telehealth, and TOT is suited for ambulatory and home care. The panel consensus is that:

'After a brief initial training on appropriate application, TOT is easily self-administered by patients or caregivers at home or in long-term care setting, thereby facilitating patient activation in their care'.

Smart dressings and supportive software for tracking oxygen levels and wound healing should allow health providers to monitor their patients and identify when a visit is needed. This can help achieve individualised wound therapy by providing the right treatment at the right time for the right patient.

There remains a need for additional well-designed prospective RCTs using intention to treat analyses to critically evaluate the efficacy and effectiveness of TOT for the management of different types of hard-to-heal wounds. This should include the study of the important gaps identified in *Box 3*.

Box 3. Evidentiary gaps regarding topical oxygen therapy

- Other types of hard-to-heal wounds, such as pressure ulcers,[63] pyoderma gangrenosum, surgical wound dehiscence, soft tissue radiation injuries and surgical site infections
- Better differentiation between modalities for different wound aetiologies
- Technologies to identify wounds most at risk of failure to heal due to tissue hypoxia and thus most likely to benefit from topical oxygen
- Patients with peripheral artery disease and ischaemic ulcers
- Impact in patients with renal failure
- The cost-effectiveness of various indications and each modality
- Mechanisms of pain reduction
- The impact of early vs late implementation
- Adjunctive use with other treatment modalities, such as cellular, acellular and matrix-like products (CAMPS),[68] vascular intervention or skin grafting

Key points

- **There is increasing clinical and scientific interest in the crucial role of oxygen in wound healing**
- **Regular oxygenation measurements should be included in trials and may be incorporated into practice**
- **Intention to treat analysis should be used to evaluate the efficacy of topical oxygen therapy (TOT) in different wound types**
- **Smart dressings and software for tracking oxygen levels and wound healing should allow providers to monitor patients and identify if a visit is needed**
- **Monitoring oxygen levels in response to therapy would help determine which TOT modality is best for a patient**
- **There are evidentiary gaps in knowledge on TOT that require further research**

Conclusion

On the principle that sufficient availability of oxygen is essential for wound healing, the various modalities of TOT aim to improve the local wound oxygen environment in hard-to-heal wounds. The clinical evidence for the efficacy of TOT is heterogeneous, ranging from uncontrolled case reports to RCTs and meta-analyses, some with notable limitations. Meanwhile, important questions about adjunctive use of TOT with other therapeutic procedures remain unanswered.

In spite of this, the increasing amount of clinical evidence evaluated in this consensus document shows TOT to be safe and clinically effective. Accordingly, TOT received the highest-level evidence rating for the first time in the ADA's 2023 Standards of Care ADA Standards of Care; use of TOT in ischaemic, diabetic and leg ulcers was broadly recommended in Delphi consensus guidelines published in 2022;[82] and the IWGDF made its first-time recommendation to consider adjunctive TOT for hard-to-heal DFUs in 2023.[46] Likewise, there is growing evidence that TOT is cost-efficient in specific subpopulations and clinical settings.[109] Moreover, TOT has the important added benefit of patient empowerment, since most TOT modalities can be easily carried out in everyday clinical or home-based practice. This relative accessibility could allow TOT to help address growing concerns about disparities in healthcare access in rural or primarily minority localities.

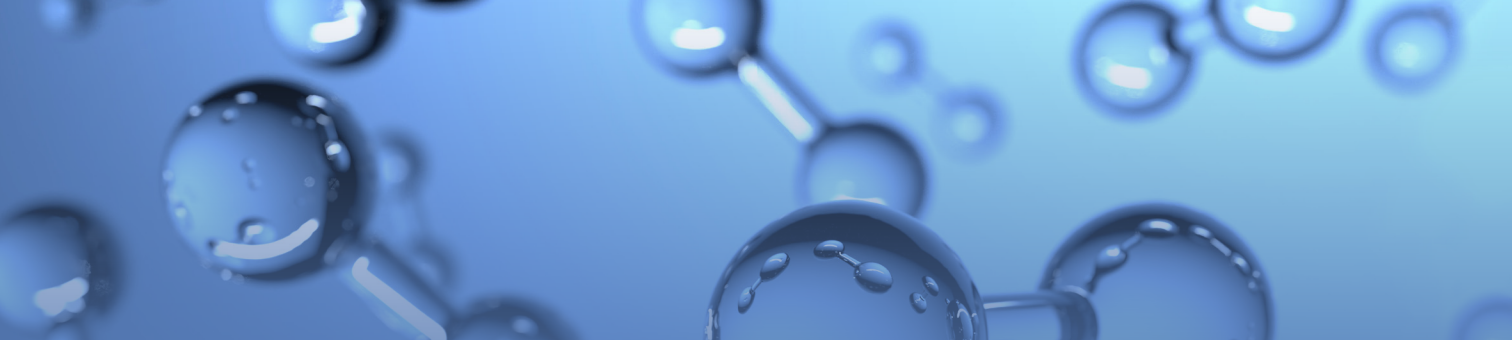
It is hoped that this document will inform readers of the important advances in TOT, increase access to these therapies for the management of hard-to-heal wounds and thus improve patient outcomes. In this, it is important to consider the patient's perspective, which will likely have an impact on their uptake, experience and perceptions. The panel also hopes that it will assist with education of wound care providers, insurers and payers who are evaluating the cost efficacy of TOT. Lastly, by highlighting some developing technologies, the panel hopes to demonstrate the great potential of future treatment strategies.

Consensus panel recommendations

1. Consideration in hard-to-heal wounds (those that have failed to achieve a 50% size reduction after 4 weeks of standard of care)
2. Applicability to most kinds of non-neoplastic hard-to-heal wounds
3. Contraindication in untreated infection, malignancy or necrosis
4. Avoidance in critical limb ischaemia while there is insufficient evidence
5. Earlier rather than later consideration
6. Initial vascular assessment and possible vascular intervention
7. Frequent and adequate debridement
8. Adjunctive use alongside standard of care
9. Treatment of underlying aetiology, such as offloading, compression or glucose control
10. Management of any pain, infection or comorbidities
11. Avoidance of wound dressings that might impede oxygen diffusion
12. Multidisciplinary approach to treatment
13. Appropriate training to facilitate self-administration by patients or caregivers
14. Broad access, with appropriate reimbursement by payers and healthcare systems
15. Education of providers, insurers and payers on cost-efficacy of treatment
16. Collection of health-economic data on cost-effectiveness in different wound types
17. Creation of a European or global wound register to further evaluate benefits
18. Development of assessment tools to identify regional ischaemia
19. Research into potential as a first-line therapy

References

1. Frykberg RG, Banks J. Challenges in the treatment of chronic wounds. Adv Wound Care. 2015;4(9):560–582. https://doi.org/10.1089/wound.2015.0635
2. Nussbaum SR, Carter MJ, Fife CE et al. An economic evaluation of the impact, cost, and medicare policy implications of chronic nonhealing wounds. Value in Health. 2018;21(1):27–32. https://doi.org/10.1016/j.jval.2017.07.007
3. Guest JF, Fuller GW, Vowden P. Cohort study evaluating the burden of wounds to the UK's National Health Service in 2017/2018: update from 2012/2013. BMJ Open. 2020;10(12). https://doi.org/10.1136/bmjopen-2020-045253
4. Olsson M, Järbrink K, Divakar U et al. The humanistic and economic burden of chronic wounds: a systematic review. Wound Rep Regen. 2019;27(1):114–125. https://doi.org/10.1111/wrr.12683
5. Sen CK, Gordillo GM, Roy S et al. Human skin wounds: a major and snowballing threat to public health and the economy: perspective article. Wound Rep Regen. 2009;17(6):763–771. https://doi.org/10.1111/j.1524-475X.2009.00543.x
6. Gottrup F. Oxygen therapies for wound healing: EWMA findings and recommendations. Wounds International. 2017;8(4):18–22
7. ElSayed NA, Aleppo G, Aroda VR et al. Introduction and methodology: standards of care in diabetes. Diabetes Care. 2023;46(S1):S1–S4. https://doi.org/10.2337/DC23-SINT
8. Gottrup F. Oxygen in wound healing and infection. World J Surg. 2004;28(3):312–315. https://doi.org/10.1007/s00268-003-7398-5
9. Hunt TK, Hopf HW. Wound healing and wound infection: what surgeons and anesthesiologists can do. Surg Clin North Am. 1997;77(3):587–606. https://doi.org/10.1016/S0039-6109(05)70570-3
10. Frykberg RG. Topical wound oxygen therapy in the treatment of chronic diabetic foot ulcers. Medicina (Lithuania). 2021;57(9). https://doi.org/10.3390/medicina57090917
11. Gupta S, Mujawdiya P, Maheshwari G, Sagar S. Dynamic role of oxygen in wound healing: a microbial, immunological, and biochemical perspective. Arch Razi Inst. 2022;77(2):513–523. https://doi.org/10.22092/ARI.2022.357230.2003
12. Frykberg RG, Franks PJ, Edmonds M et al. A multinational, multicenter, randomized, double-blinded, placebo-controlled trial to evaluate the efficacy of cyclical topical wound oxygen (TWO_2) therapy in the treatment of chronic diabetic foot ulcers: the TwO_2 study. Diabetes Care. 2020;43(3):616–624. https://doi.org/10.2337/dc19-0476
13. Fries RB, Wallace WA, Roy S et al. Dermal excisional wound healing in pigs following treatment with topically applied pure oxygen. Mutation Research - Fundamental and Molecular Mechanisms of Mutagenesis. 2005;579(1–2):172–181. https://doi.org/10.1016/j.mrfmmm.2005.02.023
14. Sen CK. Wound healing essentials: let there be oxygen. Wound Rep Regen. 2009;17(1):1–18. https://doi.org/10.1111/j.1524-475X.2008.00436.x
15. Troitzsch D, Vogt S, Abdul-Khaliq H, Moosdorf R. Muscle tissue oxygen tension and oxidative metabolism during ischemia and reperfusion. J Surg Res. 2005;128(1):9–14. https://doi.org/10.1016/j.jss.2004.09.014
16. Alhede M, Bjarnsholt T, Jensen P et al. Pseudomonas aeruginosa recognizes and responds aggressively to the presence of polymorphonuclear leukocytes. Microbiology (N Y). 2009;155(11):3500–3508. https://doi.org/10.1099/mic.0.031443-0
17. Fazli M, Bjarnsholt T, Kirketerp-Møller K et al. Quantitative analysis of the cellular inflammatory response against biofilm bacteria in chronic wounds. Wound Rep Regen. 2011;19(3):387–391. https://doi.org/10.1111/j.1524-475X.2011.00681.x
18. Ciofu O, Moser C, Jensen PØ, Høiby N. Tolerance and resistance of microbial biofilms. Nat Rev Microbiol. 2022;20(10):621–635. https://doi.org/10.1038/s41579-022-00682-4
19. Trøstrup H, Thomsen K, Christophersen LJ et al. Pseudomonas aeruginosa biofilm aggravates skin inflammatory response in BALB/c mice in a novel chronic wound model. Wound Rep Regen. 2013;21(2):292–299. https://doi.org/10.1111/wrr.12016
20. Rani SA, Pitts B, Beyenal H et al. Spatial patterns of DNA replication, protein synthesis, and oxygen concentration within bacterial biofilms reveal diverse physiological states. J Bacteriol. 2007;189(11):4223–4233. https://doi.org/10.1128/JB.00107-07
21. Sønderholm M, Bjarnsholt T, Alhede M et al. The consequences of being in an infectious biofilm: microenvironmental conditions governing antibiotic tolerance. Int J Mol Sci. 2017;18(12). https://doi.org/10.3390/ijms18122688
22. James GA, Ge Zhao A, Usui M et al. Microsensor and transcriptomic signatures of oxygen depletion in biofilms associated with chronic wounds. Wound Rep Regen. 2016;24(2):373–383. https://doi.org/10.1111/wrr.12401
23. Gordillo GM, Sen CK. Revisiting the essential role of oxygen in wound healing. Am J Surg. 2003;186(3):259–263. https://doi.org/10.1016/S0002-9610(03)00211-3
24. Oropallo AR, Serena TE, Armstrong DG, Niederauer MQ. Molecular biomarkers of oxygen therapy in patients with diabetic foot ulcers. Biomolecules. 2021;11(7). https://doi.org/10.3390/BIOM11070925
25. Singer AJ, Clark RAF. Cutaneous wound healing. Epstein FH, ed. N Eng J Med. 1999;341(10):738–746. https://doi.org/10.1056/NEJM199909023411006
26. Oates A, Bowling FL, Boulton AJM, Bowler PG, Metcalf DG, McBain AJ. The visualization of biofilms in chronic diabetic foot wounds using routine diagnostic microscopy methods. J Diabetes Res. 2014;2014. https://doi.org/10.1155/2014/153586
27. Dowd SE, Sun Y, Secor PR et al. Survey of bacterial diversity in chronic wounds using Pyrosequencing, DGGE, and full ribosome shotgun sequencing. BMC Microbiol. 2008;8. https://doi.org/10.1186/1471-2180-8-43
28. Trengove NJ, Langton SR, Stacey MC. Biochemical analysis of wound fluid from nonhealing and healing chronic leg ulcers. Wound Repair Regen. 1996;4(2):234–239. https://doi.org/10.1046/j.1524-475X.1996.40211.x
29. Arnež ZM, Ramella V, Papa G et al. Is the LICOX® PtO_2 system reliable for monitoring of free flaps? Comparison between two cohorts of patients. Microsurgery. 2019;39(5):423–427. https://doi.org/10.1002/micr.30396
30. Bianchi J, Douglas WS, Dawe RS et al. Pulse oximetry: a new tool to assess patients with leg ulcers. J Wound Care. 2000;9(3):109–112. https://doi.org/10.12968/jowc.2000.9.3.26267
31. Serena TE, Yaakov R, Serena L, Mayhugh T, Harrell K. Comparing near infrared spectroscopy and transcutaneous oxygen measurement in hard-to-heal wounds: a pilot study. J Wound Care. 2020;29:S4–S9. https://doi.org/10.12968/jowc.2020.29.sup6.s4
32. Sowa MG, Kuo WC, Ko ACT, Armstrong DG. Review of near-infrared methods for wound assessment. J Biomed Opt. 2016;21(9):091304. https://doi.org/10.1117/1.jbo.21.9.091304
33. Leenstra B, de Kleijn R, Kuppens G, Verhoeven BAN, Hinnen JW, de Borst GJ. Photo-optical transcutaneous oxygen tension measurement is of added value to predict diabetic foot ulcer healing: an observational study. J Clin Med. 2020;9(10):1–9. https://doi.org/10.3390/jcm9103291
34. Fife CE, Buyukcakir C, Otto GH et al. The predictive value of transcutaneous oxygen tension measurement in diabetic lower extremity ulcers treated with hyperbaric oxygen therapy: a retrospective analysis of 1,144 patients. Wound Repair Regen. 2002;10(4):198–207. https://doi.org/10.1046/J.1524-475X.2002.10402.X
35. Bowen R, Ginna Treadwell G, Goodwin M. Correlation of near infrared spectroscopy measurements of tissue oxygen saturation with transcutaneous pO_2 in patients with chronic wounds. SM Vascular Medicine. 2016;1(2):1–3
36. Katsamouris A, Brewster DC, Megerman J, Cina C, Darling RC, Abbott WM. Transcutaneous oxygen tension in selection of amputation level. Am J Surg. 1984;147(4):510–517. https://doi.org/10.1016/0002-9610(84)90014-X
37. Striebel HW, Kretz FJ. Advantages and limitations of pulse oximetry: clinical aspects of O_2 transport and tissue oxygenation. 1989:212–229. https://doi.org/10.1007/978-3-642-83872-9_17
38. Castilla DM, Liu ZJ, Velazquez OC. Oxygen: implications for wound healing. Adv Wound Care. 2012;1(6):225. https://doi.org/10.1089/WOUND.2011.0319
39. Hopf HW, Gibson JJ, Angeles AP et al. Hyperoxia and angiogenesis. Wound Rep Regen. 2005;13(6):558–564. https://doi.org/10.1111/j.1524-475X.2005.00078.x
40. Hunt TK, Linsey M, Grislis H, Sonne M, Jawetz E. The effect of differing ambient oxygen tensions on wound infection. Ann Surg. 1975;181(1):35–39. https://doi.org/10.1097/00000658-197501000-00009
41. Gordillo GM, Roy S, Khanna S et al. Topical oxygen therapy induces vascular endothelial growth factor expression and improves closure of clinically presented chronic wounds. Clin Exp Pharmacol Physiol.



2008;35(8):957–964. https://doi.org/10.1111/j.1440-1681.2008.04934.x
42. Sibbald RG, Woo KY, Queen D. Wound bed preparation and oxygen balance - a new component? Int Wound J. 2007;4(S3):9–17. https://doi.org/10.1111/j.1742-481X.2007.00388.x
43. Lavery LA, Killeen AL, Farrar D et al. The effect of continuous diffusion of oxygen treatment on cytokines, perfusion, bacterial load, and healing in patients with diabetic foot ulcers. Int Wound J. 2020;17(6):1986–1995. https://doi.org/10.1111/iwj.13490
44. Gottrup F. Controversies in wound healing. Int J Low Extrem Wounds. 2010;9(1):9. https://doi.org/10.1177/1534734610362738
45. Elsayed NA, Aleppo G, Aroda VR et al. Retinopathy, neuropathy, and foot care: standards of care in diabetes. Diabetes Care. 2023;46:S203–S215. https://doi.org/10.2337/dc23-S012
46. Chen P, Vilorio NC, Dhatariya K et al. Guidelines on interventions to enhance healing of foot ulcers in people with diabetes (IWGDF 2023 update). Diabetes Metab Res Rev. 2023. https://doi.org/10.1002/DMRR.3644
47. Sethi A, Khambhayta Y, Vas P. Topical oxygen therapy for healing diabetic foot ulcers: A systematic review and meta-analysis of randomised control trials. Health Sciences Review. 2022;3
48. Wen Q, Liu D, Wang X et al. A systematic review of ozone therapy for treating chronically refractory wounds and ulcers. Int Wound J. 2022;19(4):853–870. https://doi.org/10.1111/iwj.13687
49. Elg F, Hunt S. 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. 2018;6. https://doi.org/10.1177/2050312118784313
50. Nataraj M, Maiya AG, Karkada G et al. Application of topical oxygen therapy in healing dynamics of diabetic foot ulcers-a systematic review. Rev Diabetic Stud. 2019;15(1):74–82. https://doi.org/10.1900/RDS.2019.15.74
51. Thanigaimani S, Singh T, Golledge J. Topical oxygen therapy for diabetes-related foot ulcers: a systematic review and meta-analysis. Diabetic Med. 2021;38(8). https://doi.org/10.1111/dme.14585
52. Connaghan F, Avsar P, Patton D, O'Connor T, Moore Z. Impact of topical oxygen therapy on diabetic foot ulcer healing rates: a systematic review. J Wound Care. 2021;30(10):823–829. https://doi.org/10.12968/jowc.2021.30.10.823
53. Sun XK, Li R, Yang XL, Yuan L. Efficacy and safety of topical oxygen therapy for diabetic foot ulcers: an updated systematic review and meta-analysis. Int Wound J. 2022;19(8):2200–2209. https://doi.org/10.1111/iwj.13830
54. Carter MJ, Frykberg RG, Oropallo A et al. Efficacy of topical wound oxygen therapy in healing chronic diabetic foot ulcers: systematic review and meta-analysis. Adv Wound Care. 2023;12(4):177–186. https://doi.org/10.1089/wound.2022.0041
55. Frykberg RG. Number eight in the service of diabetic foot ulcer healing. Diabetes Care. 2020;43(9):e116–e117. https://doi.org/10.2337/dc20-0729
56. Niederauer MQ, Michalek JE, Liu Q, Papas KK, Lavery LA, Armstrong DG. Continuous diffusion of oxygen improves diabetic foot ulcer healing when compared with a placebo control: a randomised, double-blind, multicentre study. J Wound Care. 2018;27:S30–S45. https://doi.org/10.12968/jowc.2018.27.Sup9.S30
57. Niederauer MQ, Michalek JE, Armstrong DG. A prospective, randomized, double-blind multicenter study comparing continuous diffusion of oxygen therapy to sham therapy in the treatment of diabetic foot ulcers. J Diabetes Sci Technol. 2017;11(5):883–891. https://doi.org/10.1177/1932296817695574
58. Lavery LA, Niederauer MQ, Papas KK, Armstrong DG. Does debridement improve clinical outcomes in people with diabetic foot ulcers treated with continuous diffusion of oxygen? Wounds. 2019;31(10):246–251
59. Serena TE, Bullock NM, Cole W et al. Topical oxygen therapy in the treatment of diabetic foot ulcers: a multicentre, open, randomised controlled clinical trial. J Wound Care. 2021;30:S7–S14. https://doi.org/10.12968/jowc.2021.30.sup5.s7
60. Bowen J, Ingersoll M, Carlson R. Effect of continuous oxygen diffusion on pain in treatment of chronic wounds. Wound Central. 2018;2(4):186–195
61. Jebril W, Nowak M, Palin L, Nordgren M, Bachar-Wikstrom E, Wikstrom JD. Topical oxygen treatment relieves pain from hard-to-heal leg ulcers and improves healing: a case series. J Wound Care. 2022;31(1):4–11. https://doi.org/10.12968/jowc.2022.31.1.4
62. Driver VR, Reyzelman A, Kawalec J, French M. A prospective, randomized, blinded, controlled trial comparing transdermal continuous oxygen delivery to moist wound therapy for the treatment of diabetic foot ulcers. Ostomy Wound Manage. 2017;63(4):12–28
63. Azimian J, Dehghan Nayeri N, Pourkhaleghi E, Ansari M. Transdermal wound oxygen therapy on pressure ulcer healing: a single-blind multi-center randomized controlled trial. Iran Red Crescent Med J. 2015;17(11):e20211. https://doi.org/10.5812/ircmj.20211
64. Ladizinsky D, Roe D. New insights into oxygen therapy for wound healing. Wounds. 2010;22(12):294–300
65. Tawfick W, Sultan S. Does topical wound oxygen (TWO_2) offer an improved outcome over conventional compression dressings (ccd) in the management of Refractory Venous Ulcers (RVU)? A parallel observational comparative study. Eur J Vasc Endovasc Surg. 2009;38(1):125–132. https://doi.org/10.1016/j.ejvs.2009.03.027
66. Tawfick WA, Sultan S. Technical and clinical outcome of topical wound oxygen in comparison to conventional compression dressings in the management of refractory nonhealing venous ulcers. Vasc Endovascular Surg. 2013;47(1):30–37. https://doi.org/10.1177/1538574412467684
67. Yellin JI, Gaebler JA, Zhou FF et al. Reduced hospitalizations and amputations in patients with diabetic foot ulcers treated with cyclical pressurized topical wound oxygen therapy: real-world outcomes. Adv Wound Care. 2022;11(12):657–665. https://doi.org/10.1089/wound.2021.0118
68. Wu S, Carter M, Cole W, Crombie R, Kapp D, Kim P. Best practice for use of biomaterials: a new definition and categorisation – CAMPs. J Wound Care. 2023;32(4Suppl. 4a):S1–S32
69. Scholander PF. Oxygen transport through hemoglobin solutions. Science (1979). 1960;131(3400):585–590. https://doi.org/10.1126/science.131.3400.585
70. Dissemond J, Kröger K, Storck M, Risse A, Engels P. Topical oxygen wound therapies for chronic wounds: a review. J Wound Care. 2015;24(2):53–63. https://doi.org/10.12968/jowc.2015.24.2.53
71. Petri M, Stoffels I, Griewank K et al. Oxygenation status in chronic leg ulcer after topical hemoglobin application may act as a surrogate marker to find the best treatment strategy and to avoid ineffective conservative long-term therapy. Mol Imaging Biol. 2018;20(1):124–130. https://doi.org/10.1007/s11307-017-1103-9
72. Petri M, Stoffels I, Jose J et al. Photoacoustic imaging of real-time oxygen changes in chronic leg ulcers after topical application of a haemoglobin spray: a pilot study. J Wound Care. 2016;25(2):87–91. https://doi.org/10.12968/jowc.2016.25.2.87
73. Hunt S, Elg F. The clinical effectiveness of haemoglobin spray as adjunctive therapy in the treatment of chronic wounds. J Wound Care. 2017;26(9):558–568. https://doi.org/10.12968/jowc.2017.26.9.558
74. Healthcare Improvement Scotland. Innovative medical technology overview: Granulox® haemoglobin spray. 2016. https://shtg.scot/our-advice/granulox-haemoglobin-spray (accessed 12 March 2023)
75. Arenbergerova M, Engels P, Gkalpakiotis S, Dubská Z, Arenberger P. Einfluss von topischem Hämoglobin auf die Heilung von Patienten mit Ulcus cruris venosum. Hautarzt. 2013;64(3):180–186. https://doi.org/10.1007/s00105-012-2528-3
76. Haycocks S, McCardle J, Findlow AH, Guttormsen K. Evaluating the effect of a haemoglobin spray on size reduction in chronic DFUs. Br J Nurs. 2016;25(6):S54–S62. https://doi.org/10.12968/bjon.2016.25.6.S54
77. Bateman SD. Topical haemoglobin spray for diabetic foot ulceration. Br J Nurs. 2015;24:S24–S29. https://doi.org/10.12968/bjon.2015.24.Sup12.S24
78. Lo JF, Brennan M, Merchant Z et al. Microfluidic wound bandage: localized oxygen modulation of collagen maturation. Wound Rep Regen. 2013;21(2):226–234. https://doi.org/10.1111/wrr.12021
79. Lairet KF, Baer D, Leas ML, Renz EM, Cancio LC. Evaluation of an oxygen-diffusion dressing for accelerated healing of donor-site wounds. J Burn Care Res. 2014;35(3):214–218. https://doi.org/10.1097/BCR.0b013e31829b3338
80. Ivins N, Simmonds W, Turner A, Harding K. The use of an oxygenating hydrogel dressing in VLU. Wounds UK 2007. 2007;3:77–81
81. Davis P, Wood L, Wood Z, Eaton A, Wilkins J. Clinical experience with a

glucose oxidase-containing dressing on recalcitrant wounds. J Wound Care. 2009;18(3). https://doi.org/10.12968/jowc.2009.18.3.39812
82. Serena TE, Andersen C, Cole W, Garoufalis M, Frykberg R, Simman R. Guidelines for the use of topical oxygen therapy in the treatment of hard-to-heal wounds based on a Delphi consensus. J Wound Care. 2022;31:S20–S24. https://doi.org/10.12968/jowc.2022.31.Sup3.S20
83. Tettelbach WH, Cazzell SM, Hubbs B, De Jong JL, Forsyth RA, Reyzelman AM. The influence of adequate debridement and placental-derived allografts on diabetic foot ulcers. J Wound Care. 2022;31(9):16–26. https://doi.org/10.12968/jowc.2022.31.sup9.s16
84. Kennon B, Leese GP, Cochrane L et al. Reduced incidence of lower-extremity amputations in people with diabetes in Scotland: a nationwide study. Diabetes Care. 2012;35(12):2588–2590. https://doi.org/10.2337/dc12-0511
85. Kalliainen LK, Gordillo GM, Schlanger R, Sen CK. Topical oxygen as an adjunct to wound healing: a clinical case series. Pathophysiology. 2003;9(2):81–87. https://doi.org/10.1016/S0928-4680(02)00079-2
86. Kelly CA, Lynes D, O'Brien MR, Shaw B. A wolf in sheep's clothing? Patients' and healthcare professionals' perceptions of oxygen therapy: an interpretative phenomenological analysis. Clinical Respiratory Journal. 2018;12(2):616–632. https://doi.org/10.1111/crj.12571
87. Kelly CA, Maden M. How do respiratory patients perceive oxygen therapy? A critical interpretative synthesis of the literature. Chron Respir Dis. 2014;11(4):209–228. https://doi.org/10.1177/1479972314551561
88. McDonald CF. Home oxygen therapy. Aust Prescr. 2022;45(1):21–24. https://doi.org/10.18773/austprescr.2022.007
89. Kelly CA, Maden M. How do health-care professionals perceive oxygen therapy? A critical interpretive synthesis of the literature. Chron Respir Dis. 2015;12(1):11–23. https://doi.org/10.1177/1479972314562408
90. Augustin M, Conde Montero E, Zander N et al. Validity and feasibility of the wound-QoL questionnaire on health-related quality of life in chronic wounds. Wound Rep Regen. 2017;25(5):852–857. https://doi.org/10.1111/wrr.12583
91. Amesz SF, Klein TM, Meulendijks AM et al. A translation and preliminary validation of the Dutch Wound-QoL questionnaire. BMC Dermatol. 2020;20(1). https://doi.org/10.1186/s12895-020-00101-2
92. Blome C, Baade K, Sebastian Debus E, Price P, Augustin M. The "Wound-QoL": a short questionnaire measuring quality of life in patients with chronic wounds based on three established disease-specific instruments. Wound Rep Regen. 2014;22(4):504–514. https://doi.org/10.1111/wrr.12193
93. Ferguson L, Pawlak R. Health literacy: the road to improved health outcomes. J Nurs Pract. 2011;7(2):123–129
94. Sykes PK, FitzGerald M. Consumer engagement in the development of a video to inform health service clients about the risks and prevention of venous thromboembolism. Eur J Pers Cent Healthc. 2015;3(3).
95. Gordillo GM, Sen CK. Evidence-based recommendations for the use of topical oxygen therapy in the treatment of lower extremity wounds. Int J Lower Extremity Wound. 2009;8(2):105–111. https://doi.org/10.1177/1534734609335149
96. Orsted HL, Poulson R, Baum J et al. Evidence-based practice standards for the use of topical pressurised oxygen therapy. Int Wound J. 2012;9(3):271–284. https://doi.org/10.1111/j.1742-481X.2012.00956.x
97. Cole W, Yoder CM, Coe S. The use of topical oxygen therapy to treat a calciphylaxis wound during a global pandemic: a case report. Wounds. 2020;32(11):294–298
98. Tickle J. A topical haemoglobin spray for oxygenating pressure ulcers: a pilot study. Br J Community Nurs. 2015;20:S12–S18. https://doi.org/10.12968/bjcn.2015.20.Sup3.S12
99. Tettelbach WH, Armstrong DG, Chang TJ et al. Cost-effectiveness of dehydrated human amnion/chorion membrane allografts in lower extremity diabetic ulcer treatment. J Wound Care. 2022;31(Sup2):S10–S31. https://doi.org/10.12968/JOWC.2022.31.SUP2.S10
100. Al-Gharibi KA, Sharstha S, Al-Faras MA. Cost-effectiveness of wound care a concept analysis. Sultan Qaboos Univ Med J. 2018;18(4):e433–e439. https://doi.org/10.18295/squmj.2018.18.04.002
101. Cohen DJ, Reynolds MR. Interpreting the results of cost-effectiveness studies. J Am Coll Cardiol. 2008;52(25):2119–2126. https://doi.org/10.1016/j.jacc.2008.09.018
102. Chan BCF, Campbell KE. An economic evaluation examining the cost-effectiveness of continuous diffusion of oxygen therapy for individuals with diabetic foot ulcers. Int Wound J. 2020;17(6):1791–1808. https://doi.org/10.1111/iwj.13468
103. Brüggenjürgen B, Hunt SD, Eberlein T. Wundversorgung des diabetischen Fuß-Ulkus (DFU) – inkrementelle Kostenanalyse der mit einem Hämoglobinspray erweiterten Therapie der diabetischneuropathischen Fußläsion in Deutschland. Gesundh Ökon Qual Manag. 2018;23(6):320–327. https://doi.org/10.1055/s-0043-120204
104. Scottish Health Technologies Group. Innovative medical technology overview: number 006/2016. Granulox® haemoglobin spray. 2016. https://shtg.scot/our-advice/granulox-haemoglobin-spray/ (accessed 6 February 2023)
105. Blackman E, Moore C, Hyatt J, Railton R, Frye C. Topical wound oxygen therapy in the treatment of severe diabetic foot ulcers: a prospective controlled study. Ostomy Wound Manage. 2010;56(6):24–31
106. Kröger K, Gäbel G, Juntermanns B. Assessment of acceptability and ease of use of haemoglobin spray (Granulox®) in the management of chronic wounds. Chron Wound Care Manage Res. 2020;7:1–10. https://doi.org/10.2147/CWCMR.S212108
107. Elg F, Bothma G. Cost-effectiveness of adjunct haemoglobin spray in the treatment of hard-to-heal wounds in a UK NHS primary care setting. J Wound Care. 2019;28(12):844–849. https://doi.org/10.12968/jowc.2019.28.12.844
108. Centers for Medicare & Medicaid Services. Topical oxygen therapy (L37873). 2023. www.cms.gov/medicare-coverage-database/view/lcd.aspx?lcdid=37873 (accessed 8 February 2023)
109. Loh C, Tan QY, Eng DLK, Walsh SR, Chong TT, Tang TY. Granulox—the use of topical hemoglobin to aid wound healing: a literature review and case series from Singapore. Int J Lower Extremity Wound. 2021;20(2):88–97. https://doi.org/10.1177/1534734620910318
110. Marotz J, Kulcke A, Siemers F et al. Extended perfusion parameter estimation from hyperspectral imaging data for bedside diagnostic in medicine. Molecules. 2019;24(22). https://doi.org/10.3390/MOLECULES24224164
111. Fedorko L, Bowen JM, Jones W et al. Hyperbaric oxygen therapy does not reduce indications for amputation in patients with diabetes with nonhealing ulcers of the lower limb: a prospective, double-blind, randomized controlled clinical trial. Diabetes Care. 2016;39(3):392–399. https://doi.org/10.2337/dc15-2001
112. Santema KTB, Stoekenbroek RM, Koelemay MJW et al. Hyperbaric oxygen therapy in the treatment of ischemic lower-extremity ulcers in patients with diabetes: results of the DAMO2CLES multicenter randomized clinical trial. Diabetes Care. 2018;41(1):112–119. https://doi.org/10.2337/dc17-0654
113. Margolis DJ, Gupta J, Hoffstad O et al. Lack of effectiveness of hyperbaric oxygen therapy for the treatment of diabetic foot ulcer and the prevention of amputation a cohort study. Diabetes Care. 2013;36(7):1961–1966. https://doi.org/10.2337/dc12-2160
114. Kranke P, Bennett MH, Martyn-St James M, Schnabel A, Debus SE, Weibel S. Hyperbaric oxygen therapy for chronic wounds. Cochrane Dat Syst Rev. 2015;2015(6). https://doi.org/10.1002/14651858.CD004123.pub4
115. Centers for Medicare & Medicaid Services. Hyperbaric oxygen therapy. 2023. www.cms.gov/medicare-coverage-database/view/ncd.aspx?ncdid=12 (accessed 14 March 2023)
116. Hammarlund C, Sundberg T. Hyperbaric oxygen reduced size of chronic leg ulcers: a randomized double-blind study. Plast Reconstr Surg. 1994;93(4):829
117. Thistlethwaite KR, Finlayson KJ, Cooper PD et al. The effectiveness of hyperbaric oxygen therapy for healing chronic venous leg ulcers: a randomized, double-blind, placebo-controlled trial. J Vasc Surg. 2019;7(3):466. https://doi.org/10.1016/j.jvsv.2019.02.008
118. Hunt SD, Elg F. Clinical effectiveness of hemoglobin spray (Granulox®) as adjunctive therapy in the treatment of chronic diabetic foot ulcers. Diabet Foot Ankle. 2016;7:33101. https://doi.org/10.3402/dfa.v7.33101
119. Hunt SD, Elg F, Percival SL. Assessment of clinical effectiveness of haemoglobin spray as adjunctive therapy in the treatment of sloughy wounds. J Wound Care. 2018;27(4):210–219. https://doi.org/10.12968/jowc.2018.27.4.210

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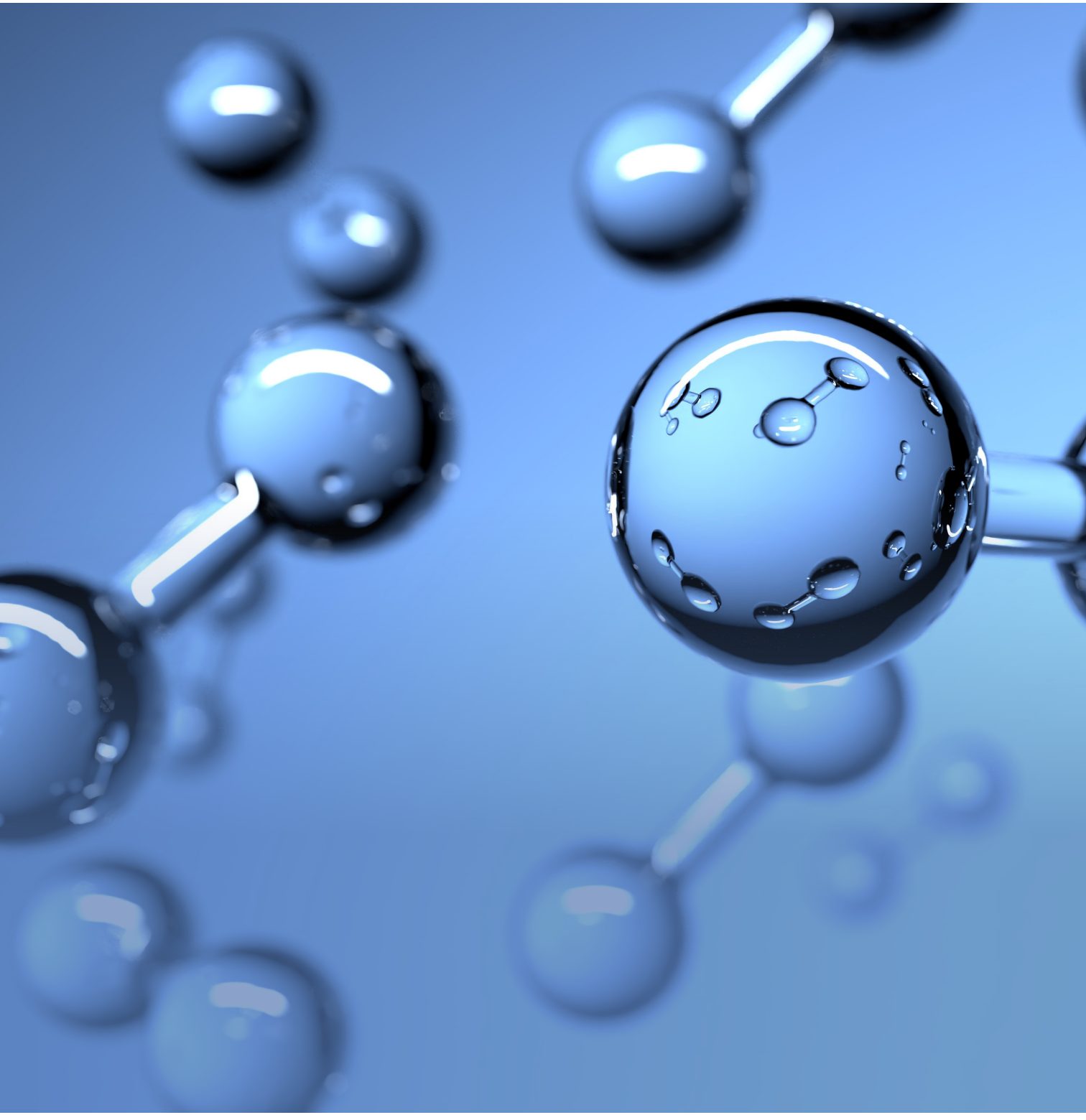

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