USE OF OXYGEN THERAPIES IN WOUND HEALING

FOCUS ON TOPICAL AND HYPERBARIC OXYGEN TREATMENT

journal of wound care

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Contents

Abbreviations

- ATA: Absolute atmosphere
- CI: Confidence interval
- CCD: Conventional compression dressings
- CDO: Continuous delivery of non-pressurised oxygen
- CMS: Centers for Medicare & Medicaid Services
- CW: Chronic wound
- DFU: Diabetic foot ulcer
- EWMA: European Wound Management Association
- FGF-2: Fibroblast growth factor-2
- HBOT: Hyperbaric oxygen therapy
- HR: Hazard ratio
- HRQoL: Health-related quality of life
- HTA: Health technology assessment
- IL: Interleukin
- IWGDF: International Working Group on Diabetic Foot
- MRSA: Meticillin-resistant *Staphylococcus aureus*
- NICE: National Institute for Health and Care Excellence
- NOX-2: NADPH oxidase of phagocytes
- NPWT: Negative pressure wounds therapy
- NNT: Number Needed to Treat
- NO: Nitric oxide
- pO_2: partial pressure of O_2
- PAOD: Peripheral arterial occlusive disease
- PVP-1: Povidone iodine
- PU: Pressure ulcer
- QoL: Quality-of-life
- RCTs: Randomised controlled trials
- RR: Relative risk

- ROS: Reactive oxygen species
- RVU: Refractory non-healing venous ulcer
- SR: systematic reviews
- SW: Sloughy wound
- SOS: Super-oxidised solution
- TCOM: Transcutaneous oximetry
- THO: Topical 'hyperbaric' oxygen
- TNF-alpha: Tumour necrosis factor-alpha
- TO: Topical oxygen
- TOT: topical oxygen therapy
- UHMS: Undersea and Hyperbaric Medical Society
- VEGF: Vascular endothelial growth factor
- VLU: Venous leg ulcer

1. Introduction

Among other things wound healing requires restoration of macro- and microcirculation as essential conditions for healing.[1,2] One of the most 'immediate' requirements is oxygen, which is critically important for reconstruction of new vessels and connective tissue and to enable competent resistance to infection.

Sustained oxygen is also vital for the healing of patients with non-healing wounds. This has been proven for wounds associated with peripheral arterial occlusive disease (PAOD) and diabetic foot ulcers (DFUs).[3]

Non-healing wounds are a significant problem in health-care systems worldwide. In the industrialised world almost 1–1.5% of the population will have a non-healing wound at any one time. Furthermore, wound management is expensive; in Europe it is expected that wound management accounts for 2–4% of health-care budgets. These figures will probably rise along with an increase in the elderly and diabetic populations.[4–7]

Oxygen therapy is a general term that covers hyperbaric oxygen therapy (HBOT) and topical oxygen therapy (TOT) among other treatments. HBOT has been known for many years and is well established as essential conditions for healing. Therefore, in this document HBOT is presented as the synopsis of mechanisms of action, clinical evidence and current recommendations of internationally recognised hyperbaric organisations. In recent years new therapeutic approaches based on TOT have been developed to support wound healing. Due to its relative novelty and small number of clinical studies compared with HBOT, the description of several methods classified as TOT are presented in more detail with description of most, including still ongoing, studies. The imbalance in the volume of description between the two treatment methods, we provide, must be carefully judged by the reader with special attention to the grade of evidence and level of recommendations. In future, the relation between TOT and HBOT, with possible synergistic action, must be taken into account when planning further studies.

Aim, objectives and scope

The overall aim of this document is to highlight the present knowledge with regard to the use of oxygen therapies in the care and treatment of wounds of different aetiologies, which fail to progress through an orderly and timely sequence of repair. In this document, these types of wounds are defined as 'non-healing'.[8]

Excluded from this document are animal and cellular models, acute wounds, such as surgical/trauma wounds and burns. The distribution of supplementary systemic oxygen at barometric pressure in connection with surgery is not covered by this document.

We provide an overview of the treatment options, as well as assessments of the best available evidence on their respective results. In addition the document will go into detail with specific aspects and current discussions regarding the use of oxygen in wound healing including:

- The role of oxygen and hypoxia in the wound healing process
- Patient perspectives of oxygen treatment
- Cost-effectiveness aspects of oxygen therapies
- What remains controversial with suggestions for future actions.

In line with other similar documents published by the European Wound Management Association (EWMA) during recent years the document structure is inspired by the different elements that are usually included in the health technology assessment (HTA) approach. Thus, it is not a traditional position document that discusses different treatment strategies, when to use which product, or assesses one product against another, but rather a holistic picture of the current practice and reality of the use of oxygen therapies in wound healing.

Structure and content

The document is presented in nine chapters. Chapters 4–7, which present the main content and analysis, follow the same structure of: introduction, main content including level of evidence, conclusion and recommendations.

- Chapter 1: Introduction to the document including its aim, objectives and scope as well as a short summary of its structure
- Chapter 2: Presents the methodology and terminology used in the document
- Chapter 3: Introduces and discusses the role of molecular oxygen in living tissue in general and in wound healing processes specifically
- Chapter 4: Presents and discusses TOT
- Chapter 5: Presents and discusses HBOT
- Chapter 6: Focuses on patient perspectives of oxygen treatment including health-related quality of life (HRQoL) and patient education
- Chapter 7: Presents considerations regarding economics and cost-efficiency of TOT and HBOT
- Chapter 8: Conclusions of the document
- Chapter 9: Provides a brief look at expected new developments over the next few years in the area of oxygen therapies and wound healing.

2. Methodology and terminology

This document originates from requests and expressions of interest in a document focused on the role and use of oxygen in wound healing by various EWMA stakeholders.

On the basis of a literature search conducted in PubMed by the EWMA secretariat, as well as input from key EWMA stakeholders, a short description of the document aim, objectives and scope was developed during the second quarter of 2015. This basic document outline was then used over the next six months to identify the specialists, who constitute the author group.

In addition to current and former members of the EWMA Council the author group includes a representative of Wounds Australia (www.woundsaustralia.com.au), a representative of the European Underwater and Baromedical Society (http://www.eubs.org/) and the European Committee for Hyperbaric Medicine (http://www.echm.org/), as well as individual and independent specialists from Europe and the US.

Each author has taken responsibility for the elaboration of the first draft of a whole or part of a chapter. It has been the obligation of each author to search and investigate the relevant literature.

The opinions stated in this document have been reached by a consensus of the author group, weighing their professional opinions based on their individual research and that of their peers as well as their own clinical experience.

Assessment of availability and levels of evidence

Throughout this document the GRADE classification of levels of evidence will be used to assess the evidence level of the different oxygen therapies described. An overview of the GRADE classification system is available in Appendix A of this document.

Oxygen therapies are similar to wound care in general in being characterised by the limited existence of high-level evidence regarding the documented effect of most of the therapies used. Many are used because in practice they offer good treatment results. However, high-level evidence is lacking due to the absence of systematic reviews (SR), randomised control trials (RCTs), or other evidence at a higher level than cohort or case-studies.

In spite of the generalised absence of higher level evidence this paper will make recommendations on the basis of the data available.

Table 1 refers to the terminology we have used in this document.[9–13]

Table 1. Terminology

Term	Definition
Biofilm	A coherent cluster of bacterial cells imbedded in a biopolymer matrix, which, compared with planktonic cells, have increased tolerance to antimicrobials and resists the antimicrobial properties of host defence[9]
Colonisation	Microbial multiplication in or on the wound without an overt immunological host reaction[9]
Contamination	Microbial ingress into the wound without growth and division[10]
Endpoint	The occurrence of a disease, symptom, sign, or laboratory abnormality that constitutes the target outcomes of a clinical trial[11]
Hyperbaric oxygen therapy (HBOT)	Exposing the whole body to pressure exceeding 1 absolute atmosphere (ATA) when patient breathes pure oxygen, which is transferred with circulation to all body tissues
Hypoxia	Inappropriately low availability of molecular oxygen
Infection	Invasion and multiplication of microorganisms in body tissues, evoking an inflammatory response (systemic and/or local) and causing local signs of inflammation, tissue destruction, and fever.[12] It is perhaps worth noting that definitions of wound infection vary,[13] but that diagnosis is based on clinical signs and symptoms[9]
Outcome	Documentation of the effectiveness of health-care services and the end results of patient care
Reactive oxygen species (ROS)	Reactive molecules containing oxygen
Resource use	The total amount of resources actually consumed, compared against the amount of resources planned for a specific process[12]
Topical oxygen therapy (TOT)	The administration of oxygen applied topically over injured tissue by either continuous delivery or pressurised systems
Wound cleansing	Removing harmful substances (for example, microorganisms, cell debris, and soiling, from the wound, so that the healing process is not delayed/hindered or to reduce the risk of infection[10]

3. Role of molecular oxygen in wound healing

Sufficient availability of molecular oxygen (O_2) is essential for proper wound healing and it has long been recognised that development of non-healing wounds is more frequent when partial pressure of O_2 (pO_2) in the wound is below a critical hypoxic threshold level. Hypoxia may result when consumption of O_2 supersedes the delivery of O_2. Poor blood perfusion is traditionally associated with reduced supply of O_2 leading to hypoxia in wounds, which can lead to deficient healing, but the depletion of O_2 resulting from the biological activities within the wound may also contribute significantly to the availability of O_2.[1,14]

Oxygen consumption during wound healing

In general, basic need for energy is mainly covered by consumption of O_2 during aerobic respiration. However, a reduction of O_2, due to its role in the production of reactive oxygen species (ROS) during the respiratory burst of activated phagocytes is an essential part of the initial inflammatory response to tissue damage. Furthermore, O_2 is the most immediate requirement for wound healing in order to reestablish new vessels and connective tissue. O_2 consumption by the NADPH oxidase of phagocytes (NOX-2) is necessary for phagocytes to produce adequate amounts of lactate to activate transcription factors that promote the development of angiogenesis factors. The reconstruction of connective tissue is also influenced by the amount of O_2 available for consumption during maturation of collagen fibres and appropriate fibroblast proliferation. Furthermore, O_2 consumption supports a competent host-response to infection due to the requirement of O_2 for generation of suitable amounts of antimicrobial ROS by phagocytes.[1,14]

Oxygen supply in wounds

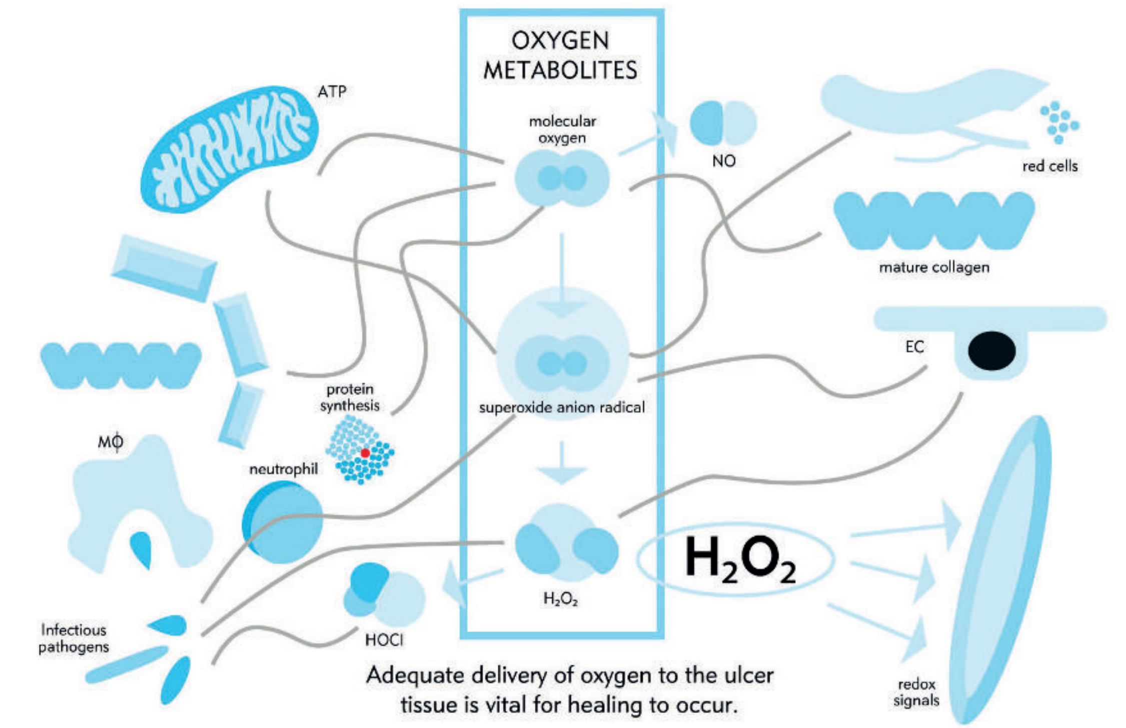
O_2 delivery in wounds predominately depends on pO_2 in the adjacent tissue and the circulating blood.[15] Thus, oedema, the injured microcirculation and contraction of the vessels in traumatised tissue may prevent an adequate supply of O_2. In addition, poor blood circulation may also inhibit the distribution of O_2 in to the wound. Other barriers to appropriate O_2 supply include diffusive constraints due to oedema and O_2 consumption by bacterial biofilm. Also of note, the high metabolic activity present in healing wounds will reduce overall levels of tissue oxygen content.

Extra oxygen consumption in wounds with a chronic infection

Neutrophils are the predominating phagocytes in humans and increased O_2 consumption is a typical response to a vast variety of stimuli including infectious Gram-negative or Gram-positive bacteria, fungi, and even sterile tissue damages.[16–19] The main reason for the extra O_2 consumption is the activation of the phagocytic NADPH-oxidase in order to produce ROS and the ability of NOX-2 to reduce O_2 has been subject to several studies demonstrating the ability to deplete O_2 even when levels are already low.

If the attracted neutrophils manage to successfully

Fig 1. The role of oxygen in wound healing



Adapted from C.K. Sen. Wound healing essentials: let there be oxygen. Wound Repair & Regeneration 2009; 17:1–18

clear the tissue of microbial intruders and pro-inflammatory debris, their work ceases, resulting in reduced accumulation and decreased consumption of O_2, with progression towards resolution and healing of the injury. However, if the bacteria are able to resist the attacking neutrophils, as seen when bacteria are organised in biofilm, a situation occurs where the bacterial biofilm attracts activated neutrophils that deplete the microenvironment of O_2 for ROS formation without eradication of the bacteria. Likewise, failure to resolve the tissue damage and clear debris in the wound may cause an accumulation of neutrophils that advance the consumption of O_2 to an extent where proper wound healing is delayed and even prevented.

In chronic wounds evidence for bacterial existence in biofilm is increasing and infiltration of

Table 2. Methods for measuring levels of O_2 in wounds

Method	Reference
Near-infrared spectroscopy	31–33
Pulse oximetry	34
Tissue oxygen tension	35
Transcutaneous oxygen tension measurement	36

neutrophils surrounding *Pseudomonas aeruginosa* and *Staphylococcus aureus* organised in biofilm may occur.[20,21] In addition, experimental infection with *Pseudomonas aeruginosa* biofilm has demonstrated increased accumulation of neutrophils in mouse wounds.[22] However, an actual demonstration of accelerated hypoxia caused by the activity of the summoned neutrophils in chronic wounds infected with biofilm remains to be done, but indirect observation points to a possible significant contribution to hypoxia by activated neutrophils. These observations include steep gradients of O_2 down to levels of hypoxia in wounds of diabetic mice with wounds infected with *Pseudomonas aeruginosa* biofilm.[23] Such steep oxygen gradients have also been demonstrated in fresh debridement specimens from infected human wounds.[23]

Furthermore, among the bacterial genes that were expressed during the biofilm infection of the wound were genes associated with low levels of O_2 and the hypoxia-stress response, indicating that the host response restricts the availability of O_2.[23] The ability of neutrophils to significantly restrict the availability of O_2 is known from other biofilm-associated infections with hypoxia.[18] In particular, the accelerated O_2 depletion by neutrophils is the predominating mechanism of the O_2 consumption in freshly expectorated sputum samples from patients with biofilm-associated chronic pneumonia.[18,24] Likewise, neutrophils are the major consumer of O_2 when exposed to *Pseudomonas aeruginosa* biofilm *in vitro*.[16] This further indicates that O_2 depletion is a general response by neutrophils to biofilm. As in infected wounds, the freshly expectorated sputum from patients with pneumonia contains steep gradients of O_2[18,25] and bacterial gene expression from chronic pneumonia corresponds to microenvironments where the neutrophils are restricting the availability of O_2. Further evidence for O_2 depletion by neutrophils during infection, comes from the upregulation of genes related to hypoxia in *Staphylococcus aureus* from the synovial fluid of patients with prosthetic joint infection,[26] which is typically characterised by intense accumulation of activated neutrophils.[27]

Examination of the ecology in chronic wounds may also reveal the existence of zones with O_2 depletion. Accordingly, the very high frequency of facultative aerobic and strictly anaerobic bacterial species from chronic wounds[28,29] may be regarded as surrogate biomarkers for sustained hypoxia in chronic wounds. Similarly, the biochemical composition of wound fluid may contain information about the physiology of the wound. In this way, the higher concentration of lactate in wound fluid than in serum[30] indicates ongoing anaerobic glycolysis, which is linked to neutrophil activity and metabolism at hypoxic conditions.

Thus, activated neutrophils may contribute to hypoxia and if the source of activation persists the neutrophils may prolong hypoxia, which may prevent the wound in the inflammatory phase entering the resolving and regenerating phase. In this respect, monitoring levels of wound O_2 may provide guidance to whether wounds with poor healing are associated with a lack of O_2 and if supplemental O_2 may result in re-oxygenation and improved healing of wounds. Several methods for measuring levels of O_2 in wounds have been successfully applied and should be used to estimate level of oxygenation and efficacy of the therapeutic effect (Table 2).[31–36] It should be pointed out that these methods measure local hypoxia but do not allow us to estimate the effect on the level of neutrophils.

Conclusion

Even though hypoxia acts as an initial physiological signal to promote wound healing, prolonged hypoxia may maintain pro-inflammatory conditions and prevent resolution and restoration of wounds. Thus, ongoing hypoxia induced by chronic infections, including enhanced O_2 consumption by activated neutrophils, may impede proper healing of the wound.

Recommendation

Measurement of local tissue oxygenation before and during hyperbaric oxygenation may assist health professionals in identification of patients likely to benefit from HBOT. However, all O_2 therapies, including local O_2 supply or delivery enhancement by haemoglobin, will benefit from the knowledge of the O_2 levels in the proximity of the wound. Measurement of pO_2 near the wound, so called transcutaneous oximetry (TCOM), is currently approved as the best surrogate for oxygenation of the wound bed. This measurement strongly depends on several factors, including local perfusion, temperature reactivity, and O_2 outflow through the skin layers.[37]

The predictive value of TCOM has been mathematically validated for diabetic extremity ulcers with good prediction of the failure rate when taking a TCOM measurement while breathing oxygen at pressure.

4. Topical oxygen therapies

Despite almost 50 years of clinical use, the subject of TOT for non-healing wounds remains controversial.[38–42] TOT can be defined as the administration of oxygen applied topically over injured tissue by either continuous delivery or pressurised systems. The availability to the wound tissue of topically applied higher pO_2 reverses localised hypoxia.[43] This causes both the direct killing of anaerobic bacteria and an enhancement of leukocyte function to address all other pathogens.[44,45] Once the inflammatory cascade subsides, the high availability of oxygen molecules in the wound tissue helps to upregulate angiogenic growth factors like vascular endothelial growth factor (VEGF) and fibroblast growth factor-2 (FGF-2).[45] This results in the prolific structured growth of new blood vessels and the stimulation of collagen synthesis by enhancing fibroblast activity.[46–48] These factors combined result in better wound bed granulation, strong collagen tissue formation, and wound closure.[46,47,49]

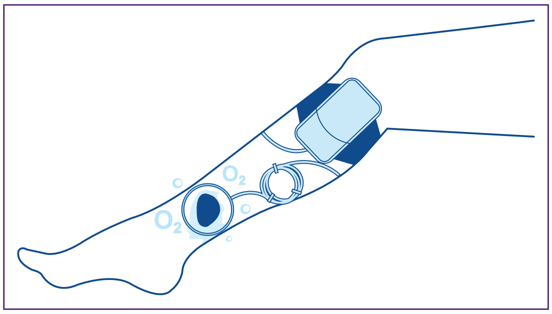
Background

The first report of TOT was published in 1969[41] wherein this therapy was called 'topical hyperbaric oxygen'. However, the term 'hyperbaric' as used in that paper was misleading and incorrect as currently used. Using specially constructed topical chambers on 52 patients with wounds of varying aetiologies, pure humidified oxygen was delivered under a constant pressure of 22mmHg; oxygen was applied continuously for 4–12 hours a day. Although uncontrolled by current standards, success was noted in the majority of cases with only six reported failures with an average healing time of three weeks in those treated with pressurised oxygen. It was found that wounds subjected to O_2 therapy at ambient pressures improved, but more slowly than those under pressure.[41] In the first RCT of topical 'hyperbaric' oxygen (THO) treatment, a total of only 28 patients were allocated to THO (n=12) and control (n=16) groups. All patients were admitted to the hospital for debridement, local dressings, intravenous antibiotics, and bedrest. The intervention group received THO in only four daily 90 minute sessions using a leg chamber providing humidified 100% oxygen under cycled pressures between 0 and 30mmHg. During the 14-day study period both groups experienced progressive reductions in the size of their DFUs. Not surprisingly, there were no significant differences in wound area reduction between the two groups. The obvious (and fatal) flaws in this study were the small numbers of patients treated and the very limited time period under study. There was simply insufficient power to detect any differences in treatments should any exist at only two weeks. The standard time frames that are currently employed for such DFU wound healing studies are 12-week treatment periods. Nonetheless, this study is often quoted as 'evidence' that THO is ineffective in promoting healing of foot ulcers.[50] In the following years there were inconsistent results in case series and reviews suggesting the putative benefits of administering oxygen topically to chronic wounds.[45,47,51–54]

A subsequent non-randomised study sought to evaluate the healing benefits of both HBO and topical oxygen (TO) in a group of 57 patients with a variety of chronic wounds.[45] Using standardised protocols for both therapies, healing outcomes were assessed at 14 weeks. Although they found no statistically significant change in wound volume reduction in the HBO group after this treatment period, the 25 wounds subjected to TOT showed a significant 57% reduction after 14 weeks of treatment (4 days each week). Additionally, wound edge tissue biopsies were taken to assess VEGF gene expression at baseline and at treatment end. Comparing VEGF expression at the final time point to the baseline measurement, those wounds treated with TO achieved a significant induction of VEGF expression, higher in those wounds where wound healing/ volume reduction occurred. The overall difference in VEGF gene expression for HBO treated patients was not found to be statistically significant, although there was indeed an increase noted for most patients.[45] This study provides further evidence that treatment with topical oxygen can have a beneficial effect towards the healing of chronic wounds

Continuous delivery of non-pressurised oxygen

This category of devices apply topical continuous delivery of non-pressurised (normobaric) oxygen (CDO) through small cannulas or thin tubes to essentially occlusive wound dressings. Small portable battery-powered oxygen generators (extraction units) supply a continuous flow of pure oxygen to the wounds 24 hours a day.[3] The wound dressings are typically changed weekly and the oxygen generators are generally replaced after one to two weeks of continuous use.



Continuous delivery of non-pressurised oxygen

The interim results of the RCT of the TransCuO_2 CDO device showed that wound closure at 12 weeks was not significantly associated with treatment per the protocol, active 11 (52.3%), sham 8 (38.1%), [relative risk (RR) 1.38; 95% confidence interval (CI): 0.7, 2.7), p=0.54].[55] However, in the recently published results of the completed RCT a significantly higher proportion of people healed in the active arm compared with the sham arm (46% versus 22%, p=0.02). This relative effect became greater in more chronic wounds (42.5% versus 13.5%, p=0.006). Patients randomised to the active device also experienced

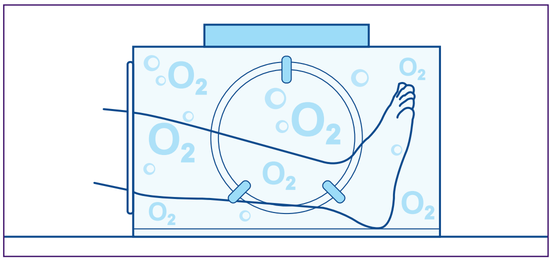
Table 3: Technologies available for distribution of topical oxygen in wound healing

Technologies available for distribution of topical oxygen in wound healing
Continuous delivery of non-pressurised oxygen (CDO)
Low constant pressure oxygen in a contained chamber
Higher cyclical pressure oxygen
Oxygen release through dressing or gel
Oxygen transfer
Application of oxygen species

significantly faster rates of closure relative to the sham ($p<0.001$). Unfortunately, this was only a per protocol analysis of the first 50 patients in each arm to complete the 12-week trial.[56]

Despite several small case studies indicating beneficial healing for chronic wounds,[57,58] results for the Epiflo device multicentre RCT have yet to be published in any journal. Nonetheless, information available on clinicaltrials.gov indicates that wound closure at 12 weeks was not statistically significantly associated with treatment per the protocol active 55.7%, sham 50.8% with 61 patients in each group.[59] A prior single centre randomised study of 17 DFU patients followed for four weeks indicated that the TO group achieved an average wound size reduction of 87% compared with 46% in the standard of care group ($p<0.05$).[60] While tissue and wound sample cellular and cytokine level changes were noted, these patients were not followed to complete healing and the sample size was too small to be widely generalisable.

The Natrox CDO device has been marketed for several years with posters and presentations indicating positive results in a variety of wounds. A small published case series on the treatment of venous leg ulcers (VLUs) indicated positive results towards healing and a reduction in pain scores during the treatment periods.[61] A recent small, single-centre, randomised non-placebo controlled trial of 20 patients with chronic DFUs compared this device with standard care alone over 8 weeks.[62] They found a significantly increased healing rate (wound area reduction) in those treated with the topical oxygen device compared with baseline at week 8 ($p<0.001$), but no such increased difference was noted in the control group ($p<0.262$). While all superficial ulcers healed in both groups, the TOT group seemed to show a more beneficial effect in more advanced ulcers. While published data is not yet available, a large RCT using this device is currently in progress to further determine its efficacy in healing chronic DFUs.



Oxygen delivery in a contained chamber

Low constant pressure oxygen in a contained chamber

The lower constant pressure devices include such devices as the O_2 Boot or OxyCare. In this approach oxygen is provided in a simple plastic chamber/boot that is placed around the extremity with the ulcer. Constant pressure is then maintained within the chamber up to 35mmHg. There are numerous studies that have been conducted on these types of devices over the last four decades that have ostensibly shown good clinical efficacy. However, the majority of these studies have consisted of case series or uncontrolled trials.[45] The one very poorly conducted RCT that used a similar device has been previously discussed.[50] Unfortunately, this study is often cited as evidence of the ineffectiveness of TO despite its being underpowered and of too short of a duration. This outcome is not surprising considering the fact that the therapy arm only received two treatments each week (four total treatments) with the O_2 therapy devices used.

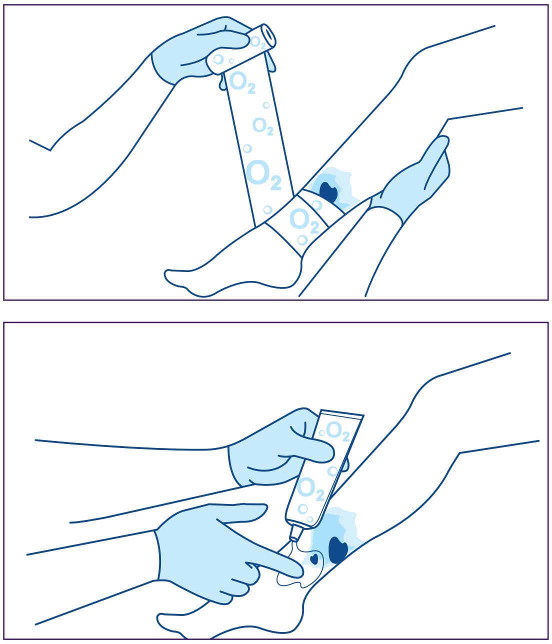
Higher cyclical pressure oxygen

The Topical Wound Oxygen (TWO_2) system differs from other devices in that it applies a higher topical O_2 pressure between 5mmHg and 50mmHg, in a cyclical pressure waveform, combined with humidification. The benefit of this approach is that the higher pressure gradient results in O_2 molecules diffusing deeper into the hypoxic wound tissue and enhances multiple molecular and enzymatic functions.[46,63] The cyclical pressure applied with TWO_2 of between 5mmHg and 50mmHg creates sequential non-contact compression of the limb that helps to reduce peripheral oedema and stimulates wound site perfusion further.[48,64] Several prospective clinical studies have been conducted using this device on both VLUs and DFUs. One non-randomised parallel arm study of 83 patients was conducted on VLUs to measure the effect of TWO_2 compared with conventional compression dressings (CCD) on wound healing using the primary endpoint of the proportion of ulcers healed at 12 weeks.[48] At 12 weeks, 80% of TWO_2 managed ulcers were completely healed compared with 35% of the CCD-managed ulcers. Median time to full healing was 45 days in the TWO_2 arm and 182 days in CCD arm. Unfortunately, there was a good deal of selection bias pertaining to treatment allocation in this study. These same authors later conducted another comparative study that similarly investigated the efficacy of TWO_2 versus CCD in the management of refractory non-healing venous ulcers (RVUs) with a duration of at least two years.[64] This study was also non-randomised and allotment to treatment arm was primarily based on patient preference. A total of 132 patients were enrolled with 67 patients (mean age: 69 years) using TWO_2 and 65 patients (mean age: 68 years) with CCDs for 12 weeks or until full healing. At 12 weeks 76% of the TWO_2 managed ulcers had completely healed, compared with 46% of the CCD-managed ulcers with a median time to full healing of 57 days and 107 days, respectively. Interestingly, in those patients with meticillin-resistant *Staphylococcus aureus* (MRSA) colonised ulcers, MRSA elimination occurred in 46% of patients managed with TWO_2 and 0% of patients managed with CCD. Another prospective non-blinded, non-randomised study was conducted to examine the clinical efficacy of TWO_2 therapy in healing patients with severe DFUs referred to a community wound care clinic in Canada.[65] Patients were simply allocated to the TO if a unit was available or were otherwise treated with advanced moist wound therapy. At 12 weeks 82.4% of the ulcers in the TWO_2 therapy arm and 45.5% in the standard care arm (control) healed completely. Median time to complete healing was of 56 days in the TWO_2 therapy arm and 93 days in the control standard care arm. An ongoing study is currently enrolling subjects into a 220 patient multinational, multicentre, prospective, randomised, double blinded, placebo-controlled trial to evaluate the efficacy of TWO_2 in the treatment of chronic DFUs. The study's inclusion criterion allows for non-healing DFUs up to Stage 2D in the University of Texas Classification of Diabetic Foot Ulcers, defined as wounds penetrating to tendon or capsule with infection and ischaemia. It includes a two-week run-in period with best standard of care to flush out wounds that would heal with this alone and a 12-month follow-up to assess recurrence. With a standardised primary outcome of the incidence of complete wound closure at 12 weeks, this trial should not only address the need for TOT, but it should also make its results comparable with other advanced wound care therapies including systemic HBOT.[66]

Oxygen release through dressings or gels

Different kinds of products are available, either using the release of pure O_2 embedded in the dressing or releasing O_2 generated by a biochemical reaction in a hydrogel. In the O_2 containing dressings, pure O_2 is embedded, such as in vesicles, and released after the dressing is liquefied by the wound exudate. Continuous O_2 release dressings can be used as secondary dressing and release O_2 for up to six days. In order to optimise conditions for delivery at the wound, debridement and cleansing should be carried out at regular intervals before the dressings are applied.

In hydrogel dressings an increased concentration of dissolved O_2 is obtained via a chemical or biochemical reaction. These occlusive dressings make use of the reactivity of 0.3% hydrogen peroxide, which is converted to water and dissolved O_2. This can diffuse via a permeable separator to the wound bed. In contrast, another product consists of two separate components must be applied together to activate the biochemical process. One component contains a hydrogel sheet containing glucose and a low-concentration gel matrix with less than 0.04% of iodide ions, and a second component sheet containing glucose oxidase. The glucose oxidase incorporated in the second gel sheet catalyses the oxidation of (beta)-D-glucose to D-gluconic acid and hydrogen peroxide in the presence of O_2. The hydrogen peroxide released as a result is thought to diffuse through the dressing and either oxidises iodide ions to free iodine and O_2 or, if it reaches the wound surface, is metabolised to water and O_2. Iodine has a beneficial antimicrobial effect within the gel and should help to prevent the proliferation of microorganisms at the wound–dressing interface,



Oxygen release through dressings or gels

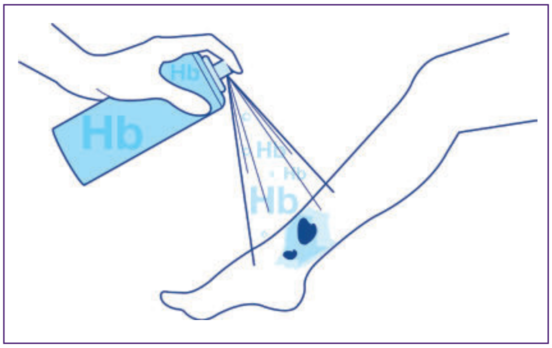
while the dissolved O_2 is believed to create beneficial effects within the wound.[3]

Several case study reports demonstrate improvements in the healing of different wound types.[67,68] As an example, in a non-controlled multicentre case series of 51 patients the dressing was tested over a six-week period in wounds with various aetiologies and a mean duration of 25.8 months. The results showed six wounds healed fully, 37 were judged to have improved, seven remained static and one deteriorated.[69] *In vitro* experiments have shown that such dressings are capable of significantly increasing O_2 levels in wounds.[70] Further evidence of its beneficial impacts on wound healing was generated by using these dressings on burn patients treating larger donor site wounds in comparison with standard care.[71] Moreover the oxygenating hydrogel dressings, which release O_2 and different levels of iodine into the wounds, were tested in different *in vitro* tests against various target organisms. It was shown that the dressings were significantly more effective against a broad spectrum of microorganisms including biofilm than controls.[72,73]

Oxygen transfer

Haemoglobin as an O_2 carrier is another approach to topical wound treatment. Haemoglobin augments transport of O_2 by means of facilitated delivery.[74] The mode of action of this approach is based solely on the physical effect of facilitated delivery, and not on a pharmacological or metabolic effect. In wound treatment, the haemoglobin spray should be applied in addition to standard therapy. The spray can be used concomitantly with most existing treatment regimens.[3] In a pilot study the O_2 saturation of ulcer tissue was measured in five patients with chronic leg ulcers before application and 5 and 20 minutes after application using photoacoustic tomography. The average O_2 saturation showed a significant increase up to 5mm depth from 56.4% before to 69% after 5 minutes and 78.8% after 20 minutes following a single application of haemoglobin spray. The authors conclude that the application of topical haemoglobin spray leads to an increase in O_2 saturation *in vivo* in patients with chronic leg ulcers.[75]

The authors of an RCT compared the application of the haemoglobin spray versus a sham product as add-on to best practice wound care over 13 weeks. In each treatment group there were 36 patients. In contrast with the control group, where no wound size reductions were observed, the patients treated with the complementary haemoglobin spray demonstrated a significant wound size reduction of 53%.[76] The clinical effects of a haemoglobin spray were also observed in a multicentre observational evaluation of 17 patients with 20 chronic DFUs. In 14 of the 18 wounds that completed the evaluation over a four-week period a mean reduction in wound size of 53.8% was observed. After 12 weeks 20% had healed, 53% were progressing towards healing, 20% increased in size and 7% were slow to heal.[77] In a case series of 11 patients with pressure ulcers (PUs) who were treated with haemoglobin spray for three months, nine wounds healed and two demonstrated reduced wound-size. From ten patients with pain at baseline, nine were pain-free by week 8. A rapid elimination of slough was observed in all patients.[78] In another set of recently collected data cohorts, sequential patients were recruited prospectively from patients with DFUs, chronic wounds (CWs), and sloughy wounds (SWs). The number of patients recruited to each cohort was 20, 50 and 100 respectively. As 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 CW/SW 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 four weeks. In the DFU cohort the mean wound size reduction was greater in the haemoglobin spray group at week 4 (–63% versus –21%), week 16 (–91% versus –43%) and week 28 (–95% versus –63%). At week 28 follow-up, 15/20 patients in the haemoglobin spray cohort had complete healing compared with 8/20 in the control cohort. The CW 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% versus –14%) and the final 26 week follow-up (–89% versus –75%). Altogether 45/50 patients had complete healing at the final 26-week follow-up compared with 19/50 in the control group. The SW cohort results were reported in a more limited fashion. At week 8 follow-up there was a mean wound size reduction of –93% in the haemoglobin spray group compared with –32% in the control group. At week six complete wound closure was observed for 65/100 patients in the haemoglobin spray group and 37/100 patients in the control group.[79,80]



Oxygen transfer

Based on the published evidence and positive clinical outcomes regarding the efficacy of haemoglobin spray practical-oriented clinical algorithms have been established for this kind of treatment both by the German-speaking D.A.CH.-(Germany, Austria, Switzerland) region[81] and in England.[82]

Application of oxygen species

Another therapeutic approach using topically applied O_2 in wound treatment is based on the fact that ROS can be used in antimicrobial treatment and perhaps as a signalling molecule that support wound healing processes.[79,80] ROS are effective in destroying a broad range of pathogens and also biofilms. Their mode of action is typically the physical destruction of the pathogen's cell-wall integrity and hence they are not linked to the problems of antibiotic resistance, which are related to a range of pharmacological effects. There is an increasing spectrum of products using ROS for antimicrobial and cleansing wound therapy available. A product containing hyperosmotic ionised seawater, ROS, triplet oxygen $^3O_2$ and a high pH-value is thought to reduce wound swelling, inflammation, microbial contamination and to stimulate cellular signalling transduction pathways. It is available as a rinsing solution and a wound gel. The antimicrobial effects are mediated primarily by the singlet O_2.

These effects are regulated by the basic pH value which supports a high concentration of hydroxyl ions, which act as an antioxidant.

In a cohort study conducted in four wound clinics, the clinical efficacy of singlet O_2 solution was

Table 4. Types of topical oxygen devices and therapies currently available

TOT type	Medical devices	Treatment details				
	Company, Product			Treatment location	Moist wound environment	GRADE
Higher cyclical pressure oxygen	Aoti Inc., TWO_2	50mbar to 5mbar cycles;	Pressure low, >1bar Flow rate high Treatment time: 60–90 minutes Treatment frequency: 3–7 days	Open wound in chamber or bag	Possible	Grade 18, (RCT, controlled cohort studies, various case series) positive effect shown
Low constant pressure oxygen in a contained chamber	OxyCare GmbH, O_2TopiCare System	2-5 l/min;<50mbar;	Pressure: low, >>1bar Flow rate: high Treatment time: 60–90 minutes Treatment frequency: 3–7 days	Open wound in chamber or bag	Possible	
	GWR Medical, TO_2	2-5 l/min;<50mbar;	Pressure: low, >1bar Flow rate: high Treatment time: 60–90 minutes Treatment frequency: 3–7 days	Open wound in chamber or bag	Possible	
Continuous delivery of non-pressurised oxygen (CDO)	Ogenix Inc., EpiFLO	Continuous, slow flow of pure oxygen of 3 ml/hr for 15 days through a cannula to blanket the wound.	Pressure: low, <1bar Flow rate: low Treatment time: 24 hours Treatment frequency: 7 days	Occlusive wound dressing	yes	Grade 2C, (1 Interim report on RCT showed no advantage versus sham. Cohort studies, various case series) only weak evidence
	Inotec AMD Ltd., Natrox	Continuous, slow flow of pure oxygen of ~12ml/hour for several days via a thin flexible tube to the Oxygen Delivery System which is in direct contact with the wound surface	Pressure: low, <1bar Flow rate: low Treatment time: 24 hours Treatment frequency: 7 days	Occlusive wound dressing	yes	

evaluated. In 73 patients with critically colonised and/or infected, malodorous wounds, covered with slough/fibrin, or wounds showing inflammation of the periwound skin were included. After 42 days 33% of the wounds in the study had healed, 57% had improved and 10% remained stagnant. All wounds had shown clinical signs and symptoms of critical colonisation and/or infection at day 0, at day 42 the infection was completely eradicated and inflammation was reduced in 60%.[83]

Table 4. Types of topical oxygen devices and therapies currently available

Oxygen release through dressing or gel	OxyBand Technologies Inc., OxyBand	Oxygen release for up to 5 days after contact with moisture within a simple occlusive wound dressing	Pressure: na Flow rate: na Treatment time: 24 hours Treatment frequency: 7 days	Occlusive wound dressing	yes	Grade 2B, (1RCT, cohort studies, various case series) only weak recommendation for oxyzyme by Nice due to lack of efficacy
	AcryMed/ Kimberly Clark, OxygeneSys Continuous	Use as a foam dressing, Oxygen release for up to 5 days when dressing is moistened	Pressure: na Flow rate: na Treatment time: 24 hours Treatment frequency: 7 days	Occlusive wound dressing	yes	
	AcryMed/ Kimberly Clark, OxygeneSys On Demand	Oxygen release for up to 5 days after contact with moisture within a simple occlusive wound dressing	Pressure: na Flow rate: na Treatment time: 24 hours Treatment frequency: 7 days	Occlusive wound dressing	yes	
	Crawford Healthcare Ltd, Oxyzyme	Use as a primary dressing, in early stage wound treatment. Oxygen release when both layers are attached to each other	Pressure: na Flow rate: na Treatment time: 24 hours Treatment frequency: 7 days	×	yes	
Oxygen transfer	SastoMed GmbH, Granulox	Liquid spray with 10% purified haemoglobin, applied as thin layer to the wound bed, and before wound is covered by a non-occlusive dressing, twice weekly up to once daily application depends on wound status	Pressure: na Flow rate: na Treatment time: 24 hours Treatment frequency: 7 days	×	yes	Grade 1B, (1RCT, 1 controlled open label study 3 controlled cohort studies, various case series) positive effect statistically shown, >50,000 treatments in more than 20 countries with no relevant side effects, clear positive benefit risk value
Application of oxygen species	Buchs· Actimaris	wound rinsing solutions and wound gel	Pressure: n.a. Flow rate: n.a. Treatment time: few minutes to hours Treatment frequency: at dressing change	×	yes	Grade 2C, 1 cohort study

Other products contain super-oxidised solution or gel manufactured through the electrolysis of ultra-pure water and NaCl. The active ingredient as source of ROS is hypochlorous acid (HOCl), a major inorganic bactericidal compound of innate immunity.[84] HOCl has been shown to be effective against a broad range of microorganisms either as stabilised neutral or acidic HOCl-solutions.[85] These solutions are intended for use in the cleansing and debridement phase primarily to decrease the microbial load by eliminating pathogenic microorganisms.

In an RCT, a stabilised super-oxidised solutions at neutral to acidic pH was tested for the treatment of 40 patients with postsurgical lesions larger than 5cm^2 in DFUs. The outcome of the use of the SOS was compared with use of povidone iodine as a local medication. Patients were followed-up weekly for six months. The authors were able to demonstrate that the healing rates, time taken for cultures to become negative and duration of antibiotic therapy were significantly shorter in the group treated with super-oxidised solution.[86] The authors claim that the cost of the super-oxidised solutions is lower than standard treatment with a saving of 40% on the total expenditure, especially due to less antibiotic therapy and following surgical procedures. Results are in accordance with findings of other clinical trials performed. Recently, a safety, effectiveness and cost-effectiveness evaluation of stabilised super-oxidised solutions in comparison with povidone iodine (PVP-I) treatments was published.[87] The authors concluded that such solutions are a safe, effective and cost-effective irrigation and cleansing agents and can provide an economical alternative to the other available antimicrobial agents.

Conclusion

The clinical results achieved with these methods indicate possible benefits over standard care alone. As for many other products used in wound care management, the clinical evidence for the efficacy of topical oxygen-based treatment is not homogeneous and ranges from uncontrolled case reports to RCTs with some limitations. Although most of the published data does not meet the highest standards of evidence, it suggests that such adjunctive therapies are easy to handle, safe and may be potentially effective modalities for use in modern strategies of wound care in specific subpopulations. Interesting question about the concomitant action of TOT with other therapeutic procedures, including HBOT, vascular interventions or skin transplantation, still remains unanswered.

Recommendations

There is a limited but expanding evidence base for successful healing after treatment with TO products, especially in a subset of non-healing patients who failed to achieve an adequate healing response in standard treatment settings. Although the authors endorse the adjunctive administration of TO therapies for non-healing chronic wounds, more robust data from multi-centre prospective placebo-controlled trials affirming their clinical efficacy will be required before this promising therapy can be given a stronger recommendation.

5. Hyperbaric oxygen therapy

Beyond the most superficial cell layers, there is supposedly no significant topical absorption of O_2.[47,88] Therefore, for additional O_2 to be delivered to hypoxic tissues, it must be administered systemically—it must be breathed. HBOT involves exposing the whole body to pressure exceeding 1 ATA when a patient breathes pure O_2, which is transferred with circulation to all body tissues. If given at sufficiently high pressure, typically 2.2–2.5ATA, O_2 dissolved in blood plasma diffuses from microcirculation to wound tissues and reverses local hypoxia, which usually exists in the centre of chronic non-healing wounds.[89] Generally speaking, there are two types of hyperbaric chambers used worldwide: mono-place, where patients stay alone within small pressurised vessels filled with O_2, and multi-place, where several patients can be treated at the same time with medical attendant, either nurse or physician, present inside the vessel for direct assistance and support. In Europe, most hyperbaric facilities use multi-place chambers and in the US rates of multi-place and mono-place chambers are approximately the same. While there is an on-going discussion about the differences between those two types of devices, the final dose of treatment, which is pO_2 breathed by the patient, is exactly the same in those two treatment modalities. In chronic wounds treatment HBOT sessions are normally repeated once or twice daily over several weeks. Such intermittent reversion of local hypoxia restores the optimal conditions for regeneration, but in those patients in whom hyperoxic conditions can be created locally during the HBOT the unique effects of hyperoxia per se or regular stimulation with anoxia–hyperoxia status can be observed.

HBOT and wound healing

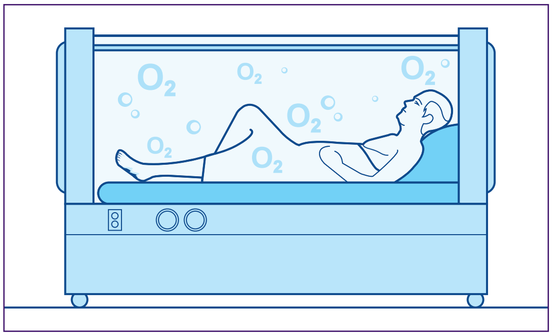
The positive effects of HBOT stem from increasing the tissue O_2 tension and/or pressure within the wound site and have been studied and published in dozens of papers reporting research on humans. The most important actions include:[90]

- Alteration of ischaemic effect
- Reduction of oedema
- Modulation of nitric oxide production
- Modification of growth factors and cytokines effect
- Promotion of cellular proliferation
- Acceleration of collagen deposition
- Stimulation of capillary budding
- Accelerated microbial oxidative killing
- Interference with bacterial proliferation
- Modulation of the immune system response
- Enhancement of O_2 radical scavengers, thereby reducing ischemia reperfusion injury.

An excellent review of use of HBOT in chronic wounds was published by Thackham et al.[92]

HBOT and bacteria

If pO_2 within the wound exceeds the limits for survival of obligate, facultative anaerobes



Mono-place hyperbaric oxygen therapy

and microaerophilic aerobes, the HBOT has a bacteriostatic activity.[93] During *in vitro* experiments, direct bactericidal effect of high enough pO_2 on anaerobic bacteria, i.e. *Clostridium perfringens*, *Bacteroides fragilis*, or *Enterococcus faecalis*, can be observed.[94] But raising the wound O_2 tension increases the capability of leukocytes to kill bacteria and this mechanism explains the indirect antibacterial effect of HBOT on both anaerobic and aerobic strains.[95] Moreover, there is a strong synergistic effect of HBOT with at least some antibiotics, including linezolid, vancomycin, teicoplanin, ciprofloxacin and imipenem.[96–98] We recommend reading the excellent review on HBOT as an anti-infective agent by Cimşit.[99]

HBOT and inflammatory reactions

The anti-inflammatory effects of HBOT have been shown to be mediated by a decrease tumour necrosis factor (TNF)-alpha, interleukin (IL) IL-1beta and IL-8.[100,101] This effect is relatively weak and short acting, which means that it cannot replace the potential use of pharmacological agents to attenuate inflammatory reactions if necessary and that HBOT sessions should be repeated in order to keep that effect.

HBOT and stem cells

Stem cells are mobilised by the HBOT and this effect is observed after a single HBOT session gradually increasing until approximately 20 sessions.[102]

HBOT and genetics

Interestingly, HBOT modifies gene expressions, this has been noted for genes encoding the IL-8 and ANG expression.[101,103] This effect is seen after ending the series of HBOT sessions, when one can observe that healing processes are still persistent for at least several weeks after completing the HBOT.

Monitoring of local oxygenation

The clear TCOM cut-offs for different types of wounds have been established identifying that failure of HBOT is highly probable if TCOM measured at pressure of 2.5ATA while breathing O_2 near the session is lower than 20, 50, 50 or 100mmHg for arterial trauma, musculocutaneous flaps, arterial ulcers or diabetic foot lesion, respectively.[104,105] Other measurement, including near-infrared reflectance spectroscopy or laser Doppler flowmetry and imaging give additional data on oxygenation or microcirculation, but until now they have not been part of routine clinical measurement.

Clinical evidence

There is clinical evidence that HBOT used as the adjunct therapy in selected cases of different types of non-healing wounds can prevent amputations or enhance wound healing. In fact, in the intention-to-treat analysis during one RCT study, complete healing of the index ulcer was achieved in 52% of patients at 1-year follow-up in the HBOT group versus 29% in the placebo group ($p=0.03$).[106] Moreover, the addition of HBOT to conventional therapy reduces the average healing time in the short term (up to six weeks) when compared with conventional therapy alone in DFUs [Peto Odds Ratio: 14.25; 95% CI: 7.08–28.68],[107] VLUs [mean difference 33.00%, 95% CI: 18.97–47.03, $p<0.00001$],[108] mixed arterial and venous wounds [mean difference 61.88%, 95%CI: 41.91–81.85, $p<0.00001$][108] and recurrent non-healing vasculitic wounds not responding to immunosuppressive therapy.[109] Treatment with HBOT is also associated with a significant reduction in the risk of major amputations, defined as amputations above the ankle joint [RR: 0.29; 95% CI: 0.19–0.44].[110]

Contraindications, side-effects and safety

There are few contraindications known, but—excepting undrained pneumothorax, which is considered an absolute contraindication unless treated—all of them are relative and temporal, including inability to equilibrate pressure within middle ear, fever, claustrophobia, pregnancy, severe heart insufficiency, uncontrolled asthma or concurrent chemotherapy, which could increase O_2 toxicity.[111] HBOT is generally recognised as a safe procedure and the most often observed side-effects include middle ear barotrauma.[112] Other side-effects, including central nervous system or pulmonary oxygen toxicity, are rare.

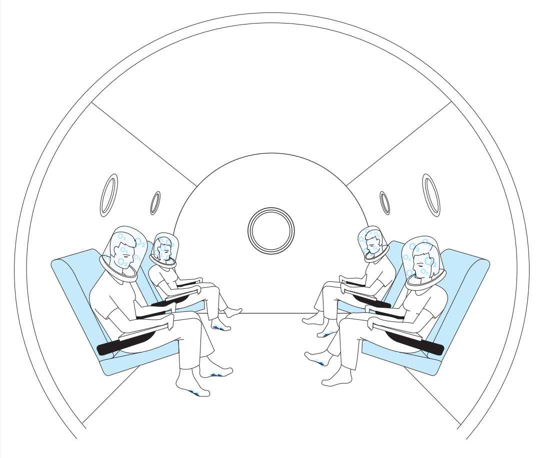
Conclusions

There is evidence that HBOT improves healing by restoration of local hypoxia, exerting an anti-infective effect on both aerobes and anaerobes, decreasing inflammation and oedema, stimulation of angiogenesis and vasculogenesis as well as stem-cells. It should be considered in those cases of non-healing wounds where there is a possibility to restore local hypoxia or induce hyperoxia. Monitoring of the efficacy should be implemented, preferably with TCOM measurements.

Evidence-based recommendations

Based on all available clinical evidence and consensus agreements within the group of internationally recognised experts, the recent tenth European Consensus Conference[113] has issued specific recommendations ranging from 1A–2C for non-healing wounds in different types of wounds (DFUs, VLUs, ischaemic ulcers and systemic inflammatory ulcers) and different populations of patients. An excerpt of these recommendations is included below.

- HBOT is suggested in the treatment of diabetic foot lesion (GRADE 2B)
- We suggest using HBOT in the treatment of ischaemic ulcers (GRADE 2C)
- It would be reasonable to use HBOT in the treatment of selected non-healing wounds secondary to systemic processes (GRADE 2C)
- HBOT is recommended in ischaemic lesions (ulcers or gangrene) without surgically treatable arterial lesions or after vascular surgery:
  - In patients with diabetes, the use of HBOT is recommended in the presence of a chronic critical ischaemia as defined by the European Consensus Conference on Critical Ischemia (see note below), if transcutaneous oxygen pressure readings under hyperbaric conditions (2.5ATA, 100% O_2) are higher than 100mmHg (GRADE 1A)
  - In the arteriosclerotic patient the use of HBOT is recommended in case of a chronic



Multi-place hyperbaric oxygen therapy

critical ischaemia (see note below), if transcutaneous oxygen pressure readings under hyperbaric conditions (2.5ATA, 100% O_2) are higher than 50mmHg (GRADE 2B)

- Note: the chronic critical ischaemia can be recognised when there is: periodical pain, persistent at rest, needing regular analgesic treatment for more than two weeks, or ulceration or gangrene of foot or toes with ankle systolic pressure <50mmHg in the non-diabetic or toe systolic pressure <30mmHg in patients with diabetes[114]

- However, despite the strong agreement on the validity of the criteria listed above to properly select patients for HBOT, the jury acknowledges the fact that not all hyperbaric centres are able to measure transcutaneous oxygen pressure under hyperbaric conditions (2.5 ATA, 100% O_2). Therefore, due to this limitation, we suggest HBOT in DFUs (grade 3 and above of Wagner classification, stage B, grade 3 and above of University of Texas classification) that have failed to respond to adequate basic wound care after 4 weeks (GRADE 2B)

- For the same reason as above, it would be reasonable to use HBOT in delayed healing (chronic), non-diabetic wounds and in recurrent multiple non-healing wounds due to vasculitis (especially those that have not responded to immunosuppressive therapy) (GRADE 2C)

- It is recommended, as the standard of care, that HBOT should always be used as part of a multidisciplinary treatment plan with ongoing wound care on a regular basis and not as a stand-alone therapy (GRADE 1B)

- It is recommended that, before the application of HBOT, standard wound care has been provided during at least a four-week period (including appropriate debridement, vascular screening for significant peripheral arterial disease and/or local wound hypoxia, adequate offloading and infection management) (GRADE 1C)

- It is recommended that, before the application of HBOT, vascular screening including imaging technique is performed in order to evaluate if any revascularisation procedure is indicated (GRADE 1C)

- The use of TCOM is recommended as the best technique to monitor the local pressure of oxygen and to select patients for HBOT (GRADE 1C)

- It is suggested that therapeutic dose of HBOT (pressure, time and length of treatment course) should be adapted to patient, type of chronic wound and evolution (GRADE 2C)

- It would be reasonable to consider HBOT as part of a multiinterventional approach in the treatment of calciphylaxis (GRADE 2C).

6. Patient perspective of oxygen treatment

This chapter explores the patient's perspective of oxygen therapies. Many patients view O_2 as curative,[115] it is a product they are familiar with and many seek out methods to increase their intake of O_2 with the intent of assisting in their wound healing. The patient's impression of an O_2 delivery method may be influenced by the information and education they receive from health professionals, their own experience of O_2 treatment and the progress of their condition as it impacts on their quality of life. However, there is a paucity of published evidence concerning the patient's perspective in the fields of HBOT, TOT and wound management O_2 introducing products (such as haemoglobin spray). Therefore much of the discussion presented is grounded in and extrapolated from low levels of evidence.

Patient/clinical outcome

Soon and Chen[116] described HRQoL tools as an attempt to capture 'patient important outcomes', although they are designed and used by health professionals. At this time there is no HRQoL tool specific to O_2 therapy for patients with wounds.[117] However, data from a range of currently used HRQoL scores may yield information on the efficacy of O_2 therapies from the patients' subjective perspective.

Prospective outcome data collected from patients with a chronic wound and receiving HBOT[118–120,121] have demonstrated an increase in HRQoL and more specifically a reduction in the level of pain experienced in patients with chronic wounds.[122] Pain has also been noted to be reduced with the use of a topical haemoglobin spray.[76,78]

Wounds caused by the effects of external beam radiation therapy and treated with HBOT[123–130] have offered positive, conclusive outcome data using a 'condition-specific'[8] radiotherapy validated clinical outcome score. These patients generally demonstrate an increase in both their HRQoL and clinical outcome score. This is particularly evident in patients receiving HBOT for recovery from the effects of primary treatment (radiotherapy) of head, neck, bladder or bowel cancer.

There is limited HRQoL data associated with TO.[131] It is advocated that further detailed work should be considered and that endpoints identifying the patient's perspective are needed to show improved quality of life.

Comprehensive reviews from several authors[82,131,132] have reported that careful patient selection is essential in providing the best outcome for the patient. Health professionals are responsible for ensuring the patient is matched to the treatment to provide a positive, synergistic result.

Patient education

Information and education shape a patient's perspective about the treatment they are about to choose or undertake. It is therefore essential that comprehensive, easily understood information and education is offered to the patient[133] before any collaborative health-care decision being made. Sykes and FitzGerald[134] offered the four 'rights' of health literacy; right information, right literacy level,

Table 5 Frequently asked questions

	HBOT (hyperbaric chamber)	Topical oxygen therapy		
		Oxygen-releasing wound dressings	Oxygen diffusion enhancer	Topical oxygen perfusor / chamber
Pain Increase or decrease? Management of pain during treatment	Pain medication can be administered while inside the multi-place chamber.	No evidence	Demonstrate reduction in pain scores	No information available
Recommended therapeutic dose How many treatments do I need? How often do I need them?	Daily treatment sessions Often 2 hours in length 5 days per week (normally Monday—Friday) Number of treatments is dependent on condition. Ranges from 2 or 3 to over 40	Little information regarding generic dosage, length of time and use etc.	Twice per week application to coincide with routine dressing change. Standard container has 30 average wound size applications. Number of treatment depends upon wound healing stage. Takes 5 seconds to apply actual product following wound bed preparation	Topical oxygen chamber: Number of treatments is dependent on condition. Ranges from 2 or 3 to over 40, from 3 times per week up to daily treatment sessions. Up to two hours a treatment Topical oxygen perfusor: treatment 7 days a week for 24 hours
Side effects What I might experience	Visual changes—myopia (short sightedness) can occur after approximately 20 treatments. Vision usually returns to normal over time	No known detrimental effects to the wound bed	No side effects, reactions or allergies to product	No side effects, reactions or allergies to products
Probability of improvement What can I expect with the process of healing	Does not immediately heal the wound HBOT provides highly oxygenated blood and creates a physiologically improved environment for healing	Limited evidence to healing potential. Promoted as supplying unobtrusive oxygen directly to the wound	Positive impact upon slough elimination and exudate reduction Granulox works to increase oxyhaemoglobin to the wound bed cells	Topical oxygen chamber: limited evidence of healing potential Topical oxygen perfusor: provide continuously pure oxygen to wound surface to stimulate wound healing
Changes in routine How does this treatment affect my routine?	It is time consuming, may need to travel to the hyperbaric chamber and daily treatment will most likely take about 2 hours	Device has to be worn close to the body and may thus interrupt patients activities of daily living	No change to patients daily routine. Patients can apply the product at their convenience	Topical oxygen chamber: Yes—may need to travel to the chamber and daily treatment will most likely take about 2 hours Topical oxygen perfusor: has to be worn close to the body, but no change to patients daily routine

Can I stop without disadvantage? To my health, wound etc.	Yes—can cease HBOT or take a break. However break in treatment is discouraged, evidence supports continuity	There are no disadvantages to stopping the product suddenly	There are no disadvantages to stopping the product suddenly	There are no disadvantages to stopping the product suddenly
Complications Is there anything that I should consider that I will need to change in my life so I can have this treatment safely?	Patients with diabetes are likely to experience changes in blood glucose metabolism that will necessitate adjustment in diet and medication supervised by the doctor	Suitability of wearing device depending on location of wound	There are no considerations in regards to treatment safety	There are no considerations in regards to treatment safety
Table elaborated by Carol Baines and Sharon Hunt (Lead Advanced Nurse Practitioner, Independent specialist in wound care, Wellway Medical Group)				

right modality and right time, with 'due respect for any cultural, language and socioeconomic barriers'. O_2 therapy education is based on these essential components and allows the choice to commence O_2 therapy and which type/method of treatment/ O_2 delivery is most suited to their situation to be made in a supported patient focused manner.

All O_2 therapies are challenging to describe by words alone thus the use of multimedia technology has allowed health professionals to improve and transcend this gap.

Before admission to a HBOT service, patients are offered information (in all formats) that details what to expect and how to behave in a hyperbaric chamber. Frequently asked questions such as, 'Who will be responsible for my dressing?' and 'How long is treatment? and 'What type of entertainment can I expect during treatment'? are addressed. There are online virtual tours of hyperbaric facilities while other HBOT services offer 'dry runs' (where patients can sit in a chamber for the experience) and open days to increase public awareness.

Clinical facilities are also engaging with social media and in doing so they offer humanistic patient experiences via contemporary photographs and videos. It is noted that some of the larger hyperbaric services in the US maintain online support groups and peer-to-peer education.

The application of topical O_2 in the home has been documented to be an easy process.[135,136] DVDs, leaflets and peer education has been made available for patients that explain the process, which encourages independence and personal autonomy.

Patient experience

There is little published qualitative research into the 'lived experience' of patients undergoing hyperbaric treatment in a mono-place (single occupancy chamber) or multi-place/patient (several patients being treated at the same time in one chamber) chamber, topical O_2 treatment or O_2 enhancing product (haemoglobin spray).

In research undertaken in old 'deck style' multi-place, cylindrical hyperbaric chambers[137,138] patients reported cold noisy air, feeling uncomfortable sitting, and felt only slightly reassured when they watched 'desensitisation' videos before treatment. Knight[139] wrote of his personal experience that 'treatment is dull' while another study[140] found that patients felt that their 'life was on hold' while they committed to a daily treatment schedule for 30 treatments. However, these types of chambers are no longer appropriate for use in a clinical medical setting. Hyperbaric chambers are now built to resemble large square rooms, furnished in a familiar 'clinical' style with television monitors and air conditioning. Patients are able to sit or lie comfortably and watch a movie to while away the treatment time. Additionally, the mono-place chamber has added to the hyperbaric suite of options and has certain logistical benefits over multi-place chambers[140] such as fitting treatment time in around work schedules.

Surveys and focus groups conclude that patients' 'lived experience' of hyperbaric therapy in a multi-place chamber is a generally pleasant experience, is person centred,[121,130,140] can be sociable and companionable, and allows/encourages strong peer support situations. However, it was also noted that it can be physically and mentally demanding, time consuming and sometimes burdensome. Katarina et al.[121] presented evidence offered by patients that the continuity of care and consistent clinical message provided by a HBOT team was of great value.

The patient experience of TOT has been explored in a limited context. Gordillo[53] and Orsted[131] provided evidence-based recommendations for practice and comment that the use of this therapy is well adopted by patients.

Several authors[78,135,136,141] have noted a high level of patient acceptance of a haemoglobin treatment, specifically the spray method and have reported on the ease of product use for the patient

Conclusion

This chapter reviews available published data to offer details of the patient's perspective on care with either HBOT, TOT or haemoglobin-enhancing products. The ability to increase O_2 delivery and consequently improve wound healing is a dynamic, evolving field. Despite the paucity of evidence, it seems likely that the patient's perspective will impact on their uptake, experience and the perceived success of O_2 therapy for wound management. This highlights the opportunity and responsibility of the health professional to shape, research, understand and respond to the patient's perspective in order to corroboratively achieve healing.

Recommendations

Large scale, qualitative research is required to focus on specific areas of the patient perspective of oxygen treatment, especially:

- Measurement of patient outcomes associated with O_2 treatment
- HRQoL of patients receiving O_2 treatment
- Advantages of O_2 therapy for the patient from their perspective.
- Exploration and expansion of research into health literacy associated with O_2 treatment. Research to explore the use of HBOT in the treatment of specific skin/wound conditions.

7. Economics

There is some direct evidence on the cost-effectiveness of HBOT in the treatment of acute and chronic wounds.[125,142] A position statement for TOT for chronic wounds by the Undersea and Hyperbaric Medical Society (UHMS) dated 2005 stated that application of TOT should not be recommended before having scientific evidence of its effectiveness.[38] Also, the International Working Group on Diabetic Foot (IWGDF) published in 2015 guidance on the use of interventions to enhance the healing of chronic ulcers of the foot of patients with diabetes giving a strong recommendation, even though based on low-level evidence, that:

'[medical practitioners should] not select agents reported to improve wound healing by altering the biology of the wound, including growth factors, bioengineered skin products and gases, in preference to accepted standards of good quality care'.[143]

There is an increasing amount of evidence for the effectiveness of TOT, at least in specific subpopulations of patients, which is promising due to the relatively low cost of application of TOT.[135,144] In general there is a need for further studies that include economic outcomes in order to make recommendations on the cost-effectiveness of applying HBOT or TOT or both in wound care.

Cost efficiency of individual treatment principles

A limited number of studies have used a double-blind approach to evaluate the efficacy of HBOT in the treatment of DFUs. Gomez-Castillo reported 2003–2004 Australian data that the average cost for wound care and HBOT was AUD14,928 for each amputation prevented, and that HBOT might decrease the overall cost of health care when the costs of amputation and rehabilitation were considered.[145] In Italy the economic indicators for using HBOT in DFUs showed potential saving of €19,000 per patient, which represents about 35% savings.[146] Chuck used 2008 Canadian data on DFU prevalence and HBOT efficacy data to create a computer model that estimated the 12-year cost for patients receiving HBOT was CAD40,695, compared with CAD49,786 for standard care alone.[147] One prospective RCT evaluated the cost of ulcer dressings per visit per patient for one year in both the treatment and control groups and found an average savings of UK£2,960 per patient treated with HBOT.[148]

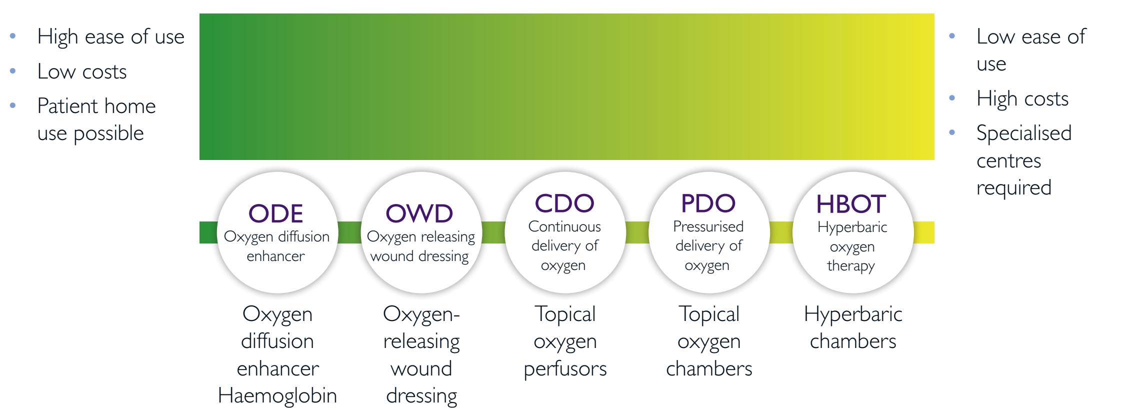
The value of the HBOT for the money spent has been estimated in several countries considering the number needed to treat (NNT).[149] In order to have a homogenous value for money spent, the cost of amputation was standardised for the NHS-UK value.[150] The considered NNT for patients with DFUs is four for up to 35 HBOT sessions and three for more than 35 HBOT sessions.[106,151] In all the Countries evaluated, the HBOT cost is from neutral to likely saving (except Norway and the US due to the high cost of HBOT sessions). However, the cost-effectiveness of HBOT could not be considered as established so long as robust health economic data based on evaluation of large placebo-controlled RCTs evaluating the effect of HBOT as adjunctive treatment in DFUs patients is lacking.[152]

An RCT, which analysed costs in a group treated with O_2-releasing dressings compared with standard of care, failed to show significance. The mean cost per patient treated with the O_2 releasing dressings was £436.33, compared with £525.54 per patient for standard care. Mean cost per ulcer healed at 12 weeks or earlier was £976.54 compared with £1071.29 per patient for standard care only. The cost saving is based on a reduction in the mean number of nurse visits from 14.8 visits for standard care patients to 10.04 visits for patients obtaining the O_2-releasing dressing.[144] UK-based clinical studies have shown that, when added to standard care, haemoglobin spray could save the UK health-care system an average of £2,330 for every patient with a DFU and £1,469 for every chronic wound patient after six months.[135] Thus, there is an increasing clinical evidence that such adjunctive treatment has a positive impact on wound healing and cost reduction.

Where are we today regarding reimbursement in Europe?

The situation is very heterogeneous. In some countries HBOT is paid for by the health system, in other countries it is not. In the US for HBOT to be reimbursed, a facility must ensure the provider supervising the treatment meets Centers for Medicare & Medicaid Services (CMS) requirements. Physicians who supervise HBOT should be certified in UHMS or must have completed a 40-hour, in-person training programme by an approved entity. In addition, if HBOT is performed off-site from a hospital campus or in a physician's office, Advanced Cardiac Life Support training and certification of the supervising physician are required. CMS also requires appropriate direct physician supervision for coverage, meaning that the physician must be present on the premises and immediately available to furnish assistance and direction throughout the performance of the procedure.

Fig 2. General considerations for use of oxygen therapies



This figure does not imply any specific sequential use of different oxygen therapies. Decision on choice of appropriate therapy or concomitant use of different therapies belongs to the physician and depends on clinical status of the patient and the wound as well as availability of the resources.

TOT is not burdened by such requirements and is paid as part of local wound treatment. As they are less expensive than HBOT any prevented amputation should be cost-effective.

This figure does not imply any specific sequential use of different oxygen therapies. Decision on the appropriate choice of therapy or concomitant use of different therapies belongs to the physician and depends on clinical status of the patient and the wound as well as availability of the resources.

Cost-effectiveness

The cost-effectiveness of HBOT and TOT in wound healing is difficult to estimate as it strongly depends on type of payment for both medical procedures and services as well as for general health-related costs (such as rehabilitation, sickness benefits, compensation for disablement etc.). Therefore such analysis is a country-dependent process. However, there are some reports showing that using HBOT or TOT or both as an adjunct for general medical approach might be a cost-effective procedure.

Conclusion

Using HBOT or TOT or both as an adjunct for general medical approach might be cost-effective.

Currently, there is some direct evidence on the cost-effectiveness of HBOT in the treatment of acute and chronic wounds. In DFUs HBOT might decrease the overall cost of health care when the costs of amputation and rehabilitation were considered. Considering the NNT in DFUs, the HBOT value for money spent is from neutral to likely saving for the health system.

In the past, some position statements maintained that the application of TOT should not be recommended before having scientific evidence of its effectiveness but, recently there is increasing evidence on the effectiveness of TOT due to its relatively low cost of application, at least in specific subpopulations of patients. The cost saving of O_2-releasing dressings is especially based on a reduction in the mean number of nurse visits. Furthermore, haemoglobin spray as an adjunct treatment seems to have a positive impact on wound healing and cost reduction.

The reimbursement is very heterogeneous. In some countries HBOT is paid by the health system, in other countries not. TOT is mostly paid as part of local wound treatment and any prevented amputation should be cost-effective.

Recommendations

- In general there is a need for robust health-economic data based on evaluation of large placebo-controlled RCTs in order to make recommendations on the cost-effectiveness of applying HBOT or TOT or both in wound care (GRADE 1)

- As standard of care HBOT should always be used as part of a multidisciplinary treatment plan with ongoing wound care on a regular basis and not as a stand-alone therapy (GRADE 1B)

- It is recommended to provide standard wound care during at least a four-week period before the application of HBOT (GRADE 1C)

- Vascular screening is recommended in order to evaluate if any revascularisation procedure is indicated before HBOT and TOT or both. (GRADE 1 C (HBOT))

- The creation of a European Wound Register to further evaluate the benefit of HBOT and TOT or both in wound care is recommended (GRADE 1 C).

8. Conclusion

Sufficient availability of molecular O_2 is essential for healing of all kind of wounds. O_2 therapies is a general term that includes among other treatments HBOT and TOT. HBOT has been known for many years and is well-established. This paper presented a synopsis of mechanisms of action, clinical evidence and current recommendations of internationally recognised organisations. Due to its relative novelty and the small number of clinical studies of TOT compared with HBOT, the description of several methods classified as TOT were described in more details.

The document provided an overview of treatment options available, as well as an assessment of the best available evidence on their respective results. In addition, it details specific aspects and current discussions regarding the use of O_2 in wound healing, the role of O_2 and hypoxia in the wound healing process, patient perspectives of these treatments, the cost-effectiveness of O_2 therapies as well as discussions of what remains controversial and suggestions for future actions.

The clinical evidence for the efficacy of TOT is not homogeneous and ranges from uncontrolled case reports to RCTs with some limitations. In spite of this adjunct therapies are easy to handle, safe and may be potentially effective modalities for use in modern strategies of wound care in specific subpopulations.

There is evidence that HBOT improves healing by reoxygenation of tissues, exerting an anti-infective effect on both aerobes and anaerobes, decreasing inflammation and oedema, stimulation of angiogenesis and vasculogenesis as well as stem cells in specific subpopulations.

The important question about the concomitant action of TOT with other therapeutic procedures, including HBOT, vascular interventions or skin transplantation, is still unanswered. However, there is an increasing amount of clinical data available on the efficacy of TOT. The patient's perspective seems likely to have an impact on their uptake, experience and the perceived success of O_2 therapy for wound management. Relating to this most TOT procedures can be easily carried out in everyday clinical or home-based practice. Moreover there is some evidence that HBOT and TOT had been used economically in specific clinical settings.

Overall the authors feel that this document helps to clarify the present status in the important treatment modalities dealing with O_2 especially to the patient with non-healing wounds. This information may help the current planning and show the great potential for future treatment strategies.

9. Future perspectives

Oxygen is a pivotal substance in wound healing including infection, and the clinical and scientific interest on its role will improve in the future.

To date, diagnostic tools for measuring local hypoxia have not been adequately used. For further clinical decisions it would therefore be meaningful to use the available measurements regularly, and to improve such techniques. Further studies should demonstrate which treatment modality would be the best for the patient. Yet another point concerns smart dressings, which could incorporate specific sensors and actively modify environmental conditions within the wound.

Thus, targeted patient selection could be performed. This would be a first step towards individualised wound therapy in the near future. Also, there is a distinct need for well-designed prospective and controlled studies to critically evaluate the efficacy and effectiveness of O_2 treatment for the management of non-healing wounds.

In particular with increasing antibiotic resistance the antimicrobial effects of O_2 should be part of future strategies.

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Appendix A

GRADE recommendation explanation

The committee used the GRADE approach (Grades of Recommendation Assessment, Development and Evaluation) system[153] to rate the quality of evidence (confidence in the estimates) and grade the strength of recommendations. This system, adopted by more than 70 other organisations, categorises recommendations as strong GRADE 1 or weak GRADE 2, based on the quality of evidence, the balance be-tween desirable effects and undesirable ones, the values and preferences, and the resources and costs.

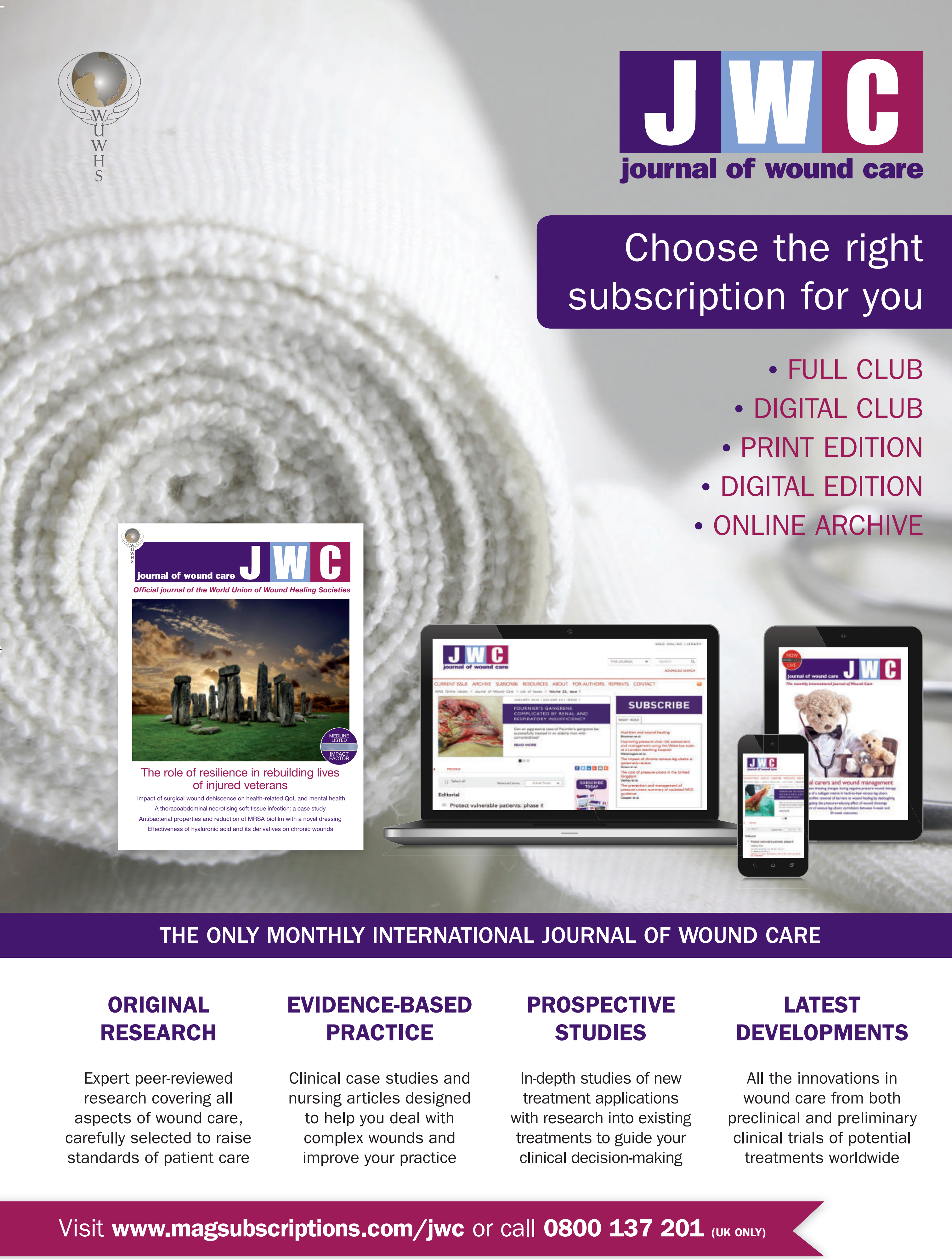
GRADE 1 recommendations are meant to identify practices where benefit clearly outweighs risk. These recommendations can be made by clinicians and accepted by patients with a high degree of confidence. GRADE 2 recommendations are made when the benefits and risks are more closely matched and are more dependent on specific clinical scenarios. In general, physician and patient preferences play a more important role in the decision-making process in these latter circumstances.

In GRADE, the level of evidence to support the recommendation is divided into 3 categories: A (high quality), B (moderate quality), and C (low quality). Conclusions based on high-quality evidence are unlikely to change with further investigation; whereas those based on moderate-quality evidence are more likely to be affected by further scrutiny. Those based on low-quality evidence are the least supported by current data and the most likely to be subject to change in the future.

It is important to recognize that a GRADE 1 recommendation can be made based on low-quality (C) evidence by the effect on patient outcome. A full explanation of the GRADE system has been presented to the vascular surgery community.[153,154] A consensus of the recommendations and level of evidence to support it was attained and every recommendation in this guideline represents the unanimous opinion of the task force. Although some recommendations are GRADE 2 with Level 3 data, the task force deemed it appropriate to present these as the unanimous opinion of its members regarding optimal current management. This was done with the understanding that these recommendations could change in the future but that it was unlikely that new data would emerge soon. These guidelines are likely to be a 'living document' that will be modified as techniques are further refined, technology develops, medical therapy improves, and new data emerge. The Committee monitored the literature for new evidence emerging after the search of the 5 commissioned systematic reviews and the group periodically updated guidelines as new data became available.

Table 6 GRADE approach to treatment recommendations

Recommendation	Benefit vs risk	Quality of evidence	Comment
1A	Clear	High: Consistent results from RCTs or observational studies with large effects	Strong recommendation, generaliseable
1B	Clear	Moderate: RCTs with limitations and very strong observational studies	Strong recommendation; May change with further research
1C	Clear	Low: Observational studies Very Low: Case series, descriptive re-ports, expert opinion	Intermediate recommendation; Likely to change with further re-search
2A	Balanced or Unclear	High: Consistent results from RCTs or observational studies with large effects	Intermediate recommendation: May vary with patient values
2B	Balanced or Unclear	Moderate: RCTs with limitations and very strong observational studies	Weak recommendation; May vary with patient values
2C	Balanced or Unclear	Low: Observational studies Very Low: Case series, descriptive re-ports, expert opinion	Weak recommendation; Alternative treatments may be equally valid
Adapted from Guyatt G, Schunemann HJ, Cook D, Jaeschke R, and Pauker S. Applying the grades of recommendation for antithrombotic and thrombolytic therapy. Chest 2004; 126; 179S-187S.			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