# Hyperbaric oxygen therapy for problem wounds: an update

KEY WORDS
- Adjunctive treatment
- Hyperbaric oxygen therapy
- Wounds

Hyperbaric oxygen therapy (HBOT) has been used as an adjunct for treating wounds for almost sixty years (Brummelkamp et al, 1961). Wound care provision and treatment options have changed significantly during that time. This choice can be beneficial to clinicians and patients but can lead to a lack of knowledge and understanding of the less common treatment modalities, such as hyperbaric oxygen therapy (Atkin et al, 2019). This article seeks to provide information on the use of hyperbaric oxygen to support healthcare professionals in their decision making. The practicalities of the treatment will be discussed, the mechanisms of action explained and clinical recommendations from Europe and the USA will be presented.

ALEXANDRA BISHOP
*Senior Clinical Nurse, Hyperbaric Research Nurse, DDRC Healthcare*

As a treatment modality that has now been used as an adjunct for treating wounds for almost sixty years, hyperbaric oxygen therapy (HBOT) remains controversial and misunderstood in many circles. HBOT is the systemic delivery of oxygen at pressures greater than atmospheric (one atmosphere absolute [ATA]). It was first observed to be of benefit in wounds with clostridial infections in 1961 (Brummelkamp et al, 1961) and then in 1965 in burn wounds in survivors of a mine fire (Clarke, 2008). Those with burns who required HBOT for carbon monoxide poisoning healed quicker and with fewer complications than survivors with burns who did not need HBOT.

People now live longer and with more comorbidities. They develop wounds that are harder to heal and cost the NHS an estimated £5.5 billion annually (Guest et al, 2015). Guest et al (2017) estimated that the prevalence of chronic wounds is increasing annually by 12%. Justifying treatment selection is of the upmost importance in this time of restricted resources and growing need in the UK.

The provision of wound care and treatment options has changed significantly during the last sixty years, with research and developments impacting greatly upon patient and clinician choice. While more choice can be beneficial, it can also lead to a lack of knowledge and understanding of the less common treatment modalities, such as HBOT. The recent Tissue, Inflammation/Infection, Moisture, Edge, Regeneration, Social factors (TIMERS) Consensus Document (Atkin et al, 2019) highlights the importance of considering adjunctive advanced therapies in hard-to-heal wounds, with HBOT being one of those therapies. This article seeks to provide updated information on the use of HBOT for problem wounds to support clinical decision making.

## HYPERBARIC OXYGEN TREATMENT

Hyperbaric oxygen is delivered in chambers that hold one (monoplace) or more (multiplace) people *(Figure 1)*. Monoplace chambers are usually filled and pressurised with 100% oxygen while multiplace chambers are pressurised with air and the patient breathes 100% oxygen through a hood or mask *(Figure 2)*. Patients enter monoplace chambers on a stretcher and the walls are made of clear acrylic, which can reduce claustrophobia since the patient feels they are lying in the room rather than in an enclosed space. Conversely, the multiplace chamber has steel walls but is more spacious within usually allowing patients to walk in for treatment.

Figure 1. Monoplace and multiplace Chambers

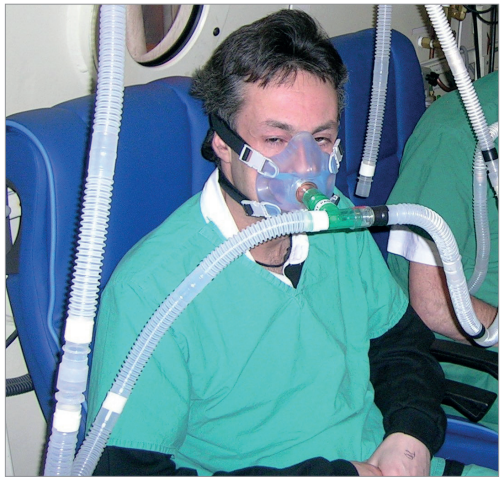

Figure 2. Patients breathe oxygen via a hood or mask

Treatment length varies from 90–150 minutes depending on the wound aetiology and treatment table selected. For example, patients with chronic wounds, such as diabetic foot ulcers (DFUs), would be prescribed 90 minutes of oxygen at 12–14 metres of seawater (2.2–2.4 ATA). With air breaks and a slow pressurisation phase, treatment commonly lasts 140 minutes in total. Patients with chronic wounds receive 20–40 treatments over 4–8 weeks. Those with more acute wounds, such as necrotising fasciitis or a failing flap would usually receive up to 10 treatments with 1–2 treatments a day.

As with any other treatment modality, a holistic patient assessment is required to confirm suitability. Absolute contraindications include certain chemotherapy drugs and untreated pneumothorax. Respiratory issues, such as chronic obstructive pulmonary disorders and cardiac problems usually need further investigation or a more detailed history before HBOT can be prescribed. Insulin pumps must be disconnected and implanted devices, such as pacemakers, need the manufacturer's advice on whether they can be pressurised. Most are now tested to sufficient pressures to allow treatment to proceed.

Patients may be permitted to eat and drink during treatment and in many chambers can watch a film and/or listen to the radio. Newer models of multiplace chambers may also have running water and built-in toilet facilities. Due to the high levels of oxygen, the risk of fire needs to be considered and reduced by avoiding flammable products and topical applications. Patients are given advise about what they can and cannot wear or take into the chamber. This includes some wound dressings.

In the UK, the British Hyperbaric Association (BHA) support and inspect all

**Table 1. European consensus recommendations on the indications accepted for HBOT (Mathieu et al, 2017)**

| Strongly recommended indications | Recommended indications | Optional indications |
|---|---|---|
| Carbon monoxide poisoning | Diabetic foot lesions | Brain injury in highly selected patients |
| Open fractures with crush injury | Femoral head necrosis | Radio-induced lesions of larynx |
| Prevention of osteoradionecrosis after dental extraction | Compromised skin grafts and musculocutaneous flaps | Radio-induced lesions of the central nervous system |
| Osteoradionecrosis (mandible) | Central retinal artery occlusion | Post-vascular procedure reperfusion syndrome |
| Soft tissue radionecrosis (cystitis, proctitis) | Crush injury without fracture | Limb replantation |
| Decompression illness | Osteoradionecrosis (bones other than mandible) | Selected non-healing wounds secondary to systemic process |
| Gas embolism | Radio-induced lesions of soft tissues (other than cystitis and proctitis) | Sickle cell disease |
| Anaerobic or mixed bacterial infections | Surgery and implant in irradiated tissue | Interstitial cystitis |
| Sudden deafness | Ischaemic ulcers | |
| | Refractory chronic osteomyelitis | |
| | Burns, 2nd degree more than 20% body surface area | |
| | Pneumatosis cystoides intestinalis | |
| | Neuroblastoma, stage IV | |

NHS commissioned hyperbaric centres. They have a five-year internal appraisal system that is closely linked to inspections by the Care Quality Commission (CQC). The BHA accepted indications for HBOT treatment are taken from the European guidance. The list of European consensus recommended indications for HBOT, last reviewed in 2017, can be seen in *Table 1*.

## MECHANISMS OF ACTION

Oxygen is essential for successful wound healing. Hypoxia initiates the healing process as haemostasis occurs and the subsequent gradient encourages the diffusion of oxygen towards the wound centre (LaVan and Hunt, 1990). Large amounts of oxygen are then consumed throughout the inflammatory process as cell metabolism and activity increases. Sufficient levels of oxygen during proliferation will allow successful angiogenesis and epithelialisation. If the tissue surrounding a wound is normally perfused, steep oxygen gradients from the periwound towards the hypoxic wound centre allow normal wound healing to occur and be sustained (Greif et al, 2000; Bishop, 2008). In chronic wounds, oxygen supply to the wound is often affected by the patient's comorbidities and the demands of the wound cannot be met.

Through its systemic delivery, HBOT aims to increase the diffusion gradient of oxygen in subcutaneous tissues by approximately ten to twenty times allowing hyperoxygenation of ischaemic tissue, reduction of inflammatory cytokines and stimulation of growth factor production (Eggleton et al, 2015). HBOT not only fully oxygenates the haemoglobin, but also leads to more oxygen dissolving in the plasma in proportion to the increased pressure (Niinikoski, 2004). This plasma dissolved oxygen can be more readily used than that bound to haemoglobin and passes from the arterial to the venous system (Jain, 2009), which is of particular benefit to patients with ischaemia or vascular disease.

*In vitro* and animal studies have demonstrated the effect of hyperbaric oxygen on a number of mechanisms. Kendall et al (2013) suggested that hyperbaric oxygen could reduce local

inflammation during revascularisation of wounded tissue. They demonstrated a reduction in inflammatory and endothelial cell interaction. Other studies have also demonstrated that HBOT improves white blood cell function as well as reduces oedema, promotes angiogenesis, elevates fibroblast activity, reduces matrix metalloprotease levels, enhances the formation of granulation tissue, accelerates collagen synthesis and induces mobilisation of stem cells from bone marrow (Hunt and Pai, 1972; Knighton et al, 1981; Hopf et al, 2005; Thom et al, 2006; Milovanova et al, 2009; Zhang and Gould, 2014). Oxygen is required to synthesise and organise type I collagen, replacing the type II collagen in the granulation tissue (Eggleton et al, 2015). This enhances the tensile strength of the wound.

The toxic effect of HBOT on anaerobic bacteria, particularly *Clostridium perfringens*, has long been known (Brummelkamp et al, 1961; Hung et al, 2016) but more recent work suggests wider bactericidal and bacteriostatic effects without hindering healing further. Almazaiel et al (2013) demonstrated the importance of pressure and hyperoxia to the interaction between bacteria and neutrophil-like cells. Antimicrobial effects can lead to further harm to the wound with the induction of a pro-inflammatory environment. However, enhanced apoptosis, as is seen with HBOT can shorten inflammation and support continued wound healing (Almazaiel et al, 2013).

## CLINICAL RECOMMENDATIONS

The Undersea and Hyperbaric Medical Society (UHMS) publish a list of accepted indications for HBOT as listed in *Box 1*. These are used across the world and are considered to have sufficient evidence to support their use in practice.

The most recent European consensus discussing the indications for HBOT was in 2016 (Mathieu et al, 2017). The findings of this discussion are in *Table 1*. The indications are split into three levels: strongly recommended, recommended and optional indications. The strongly recommended indications are deemed to have robust evidence for use along with general agreement of their acceptability between experienced practitioners attending the consensus meeting.

**Box 1. UHMS accepted indications (Weaver, 2014)**

- Arterial insufficiencies
  - a. Central retinal arterial occlusion
  - b. Enhancement of healing in selected problem wounds
- Carbon monoxide poisoning
- Clostridial myonecrosis (gas gangrene)
- Compromised grafts and flaps
- Crush injuries and skeletal muscle-compartment syndromes
- Decompression sickness
- Delayed radiation injuries (soft tissue and bony necrosis)
- Idiopathic sudden sensorineural healing loss
- Intracranial abscess
- Necrotising soft tissue infections
- Refractory osteomyelitis
- Severe anaemia
- Thermal burns

Enhancement of healing in selected problem wounds is an indication that encompasses a number of wound types. HBOT is an adjunctive therapy and as such is used alongside standard therapy when the wound is not healing as expected. The greatest evidence within this indication exists for DFUs. A number of clinical trials have been conducted demonstrating strong evidence that adjunctive HBOT is beneficial for DFUs of Wagner grades 3 and 4 that are not healing despite standard care (Worth et al, 2014; Mathieu et al, 2017).

Locally, we have developed a clinical pathway to support referral from the foot clinic. This ensures the patient meets the suggested criteria for referral and meets the recommendations of the TIMERS framework for appropriate intervention to support repair and regeneration (Atkin et al, 2019). It also meets with the recommendations from Mathieu et al (2017), including a minimum period of four weeks of standard care and vascular screening before the consideration of HBOT.

HBOT is recommended as an adjunctive treatment for clostridial myonecrosis (gas gangrene) alongside surgery and antibiotics. Clostridial myonecrosis is caused either by contamination from a clostridial focus in the body or occurs in patients with compound and/or complicated fractures with extensive soft tissue injuries following traumatic incidents (Bakker, 2012). This is an indication for which the European consensus group agreed a strong recommendation for use, alongside necrotising soft tissue infections (Mathieu et al, 2017). Indeed, clostridial myonecrosis is treated routinely with HBOT in some European countries, although used less frequently in the UK. Necrotising soft tissue infections are also considered an accepted indication for HBOT, alongside surgery, antibiotics and critical care support, due to the development of hypoxia in such cases (Weaver, 2014).

The European consensus (Mathieu et al, 2017) recommends using HBOT for compromised grafts and flaps and to use it both pre- and post-operatively in cases where there is an increased risk of a graft or flap becoming compromised (for example, infection or previous radiotherapy to the area). Weaver (2014) suggests that HBOT can help maximise the viability of the compromised

tissue. This will reduce the need for re-grafting or repeat flap procedures. However, patients should be carefully selected with consideration of the underlying cause of the problem.

Crush injuries and compartment syndrome can lead to tissue death, the need for debridement and sometimes amputation (Kerrigan and Stotland, 1993). HBOT can support the delivery of oxygen to hypoxic tissues during the early stages following injury (Weaver, 2014). This means that it can support healing and reduce the adhesion of neutrophils to the endothelium and decrease the subsequent release of reactive oxygen species that cause irreversible damage to the tissues (Weaver, 2014). Mathieu et al (2017) strongly recommend HBOT for the treatment of open fractures with crush injury as it can reduce complications such as tissue necrosis. They recommend its use in crush injuries with open wounds but without fracture, where there is significant infection risk or tissue viability is threatened.

Radiation injuries are considered a well-established indication for HBOT (Weaver, 2014; Mathieu et al, 2017). Soft tissue radionecrosis and osteoradionecrosis of the mandible are strongly recommended by the European consensus group with other bones affected by osteoradionecrosis having a little less evidence supporting their use (Mathieu et al, 2017). HBOT stimulates neovascularisation in hypoxic tissue and increases the vascularity in tissue and bone damaged by radiotherapy as well as reducing fibrosis (Feldmeier, 2012). Surgery may be indicated alongside HBOT, especially in the case of osteoradionecrosis.

Osteomyelitis becomes refractory when it persists or recurs despite appropriate interventions (Strauss, 1987). Systemic antibiotics should be administered alongside HBOT at 2–3 ATA (Hart, 2014) for 20–60 treatments (Weaver, 2014; Mathieu et al, 2017), depending on the response. Surgical intervention, for example debridement, may also be required. HBOT is understood to optimise the inflammatory process, augment the transport of antibiotics across bacterial cell walls and enhance osteogenesis (Hart, 2014).

Thermal burns can cause oedema and are at a high risk of becoming infected. The mechanisms of HBOT can help to address and reduce the risk of these complications (Weaver, 2014). The greatest evidence suggests burns greater than 20% body surface area will benefit, and it is suggested that vulnerable areas like the face, hands and perineum should be treated even if the body surface area affected is less than 20% (Mathieu et al, 2017). However, as treatment should be initiated within 6–8 hours of injury (Mathieu et al, 2017), HBOT is only an option for patients attending a burns unit with a hyperbaric centre close by. Two treatments a day are recommended for a minimum of 3 days alongside other standard burn care (Mathieu et al, 2017).

## ACCESSIBILITY

The availability, accessibility and use of HBOT varies greatly throughout Europe and indeed the world, with some regions seeing HBOT as a relatively routine adjunctive therapy for wounds and others utilising it very rarely. In some countries, such as the USA, insurance companies will support the use of this treatment for the accepted indications.

The commissioning of hyperbaric oxygen treatment in England has seen major changes since April 2019. The number of NHS England (NHSE) approved chambers has reduced by one to eight this year, due to NHSE now commissioning only one chamber for the London area and now only commissioning treatments for diving injuries and gas embolism. At the time of writing, the Welsh Health Specialised Services Committee has also decided to restrict its funding for HBOT, and is currently commissioning treatment only for decompression injury, gas embolism, crush injury and other traumatic ischaemias with compromised circulation and chronic refractory osteomyelitis. However, many chambers in England and some in Scotland are still accepting patients with the full range of generally accepted indications for HBOT.

Nationally, and with NHS support, it is hoped to gather more data on outcomes following treatment with hyperbaric oxygen so that the lack of evidence can be addressed. The process of setting up a national registry is not straightforward and requires ethical approval. This is made more complex as there is the intention to share and

compare the data globally, initially with data collected in the USA and then Australia, to expand the evidence base for HBOT therapy.

## CONCLUSION

Despite its longevity as an adjunctive treatment for wounds, HBOT remains a controversial choice. Guidelines from Europe and the USA seek to support clinicians and commissioners considering the intervention, while auditing and monitoring at a national level ensures standards are maintained.

Research suggests that HBOT has many effects on healing by improving oxygen delivery to the wound, which results in beneficial changes within wounds, such as reduced inflammation, increased angiogenesis, stem cell mobilisation and greater tensile strength. However, further clinical research would be beneficial to demonstrate those effects more clearly in practice. It is essential to remember that HBOT does not replace the accepted standards of care and access to facilities can vary across the country making it less easy for some to access the treatment. This also makes clinical research and outcome monitoring difficult with relatively low numbers of patients. National data collection in the future should help to provide some of this missing information. WUK

## REFERENCES


Almazaiel AJ, Billington R, Smerdon G, Moody AJ (2013) Effects of hyperbaric oxygen treatment on antimicrobial function and apoptosis of differentiated HL-60 (neutrophil-like) cells. *Life Sciences* 93 (2–3): 125-131

Atkin L, Bućko Z, Conde Montero E et al (2019) Implementing TIMERS: the race against hard-to-heal wounds. *J Wound Care* 28 (3 Supp): S1–S49

Bakker DJ (2012) Clostridial myonecrosis (gas gangrene). *Undersea Hyperb Med* 39(3): 731–7

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

Brummelkamp WH, Hogendijk J, Boerma I (1961) Treatment of anaerobic infections (clostridial myositis) by drenching the tissues with oxygen under high atmospheric pressure. *Surgery* 49: 299–302

Clarke D (2008) History of hyperbaric therapy. In: Neuman TS and Thom SR eds. *Physiology and Medicine of Hyperbaric Oxygen Therapy*. Saunders Elsevier, Philadelphia: 3–23

Eggleton P, Bishop AJ, Smerdon GR (2015) Safety and efficacy of hyperbaric oxygen therapy in chronic wound management: current evidence. *Chronic Wound Care Management and Research*. 2: 81–93

Feldmeier JJ (2012) Hyperbaric oxygen therapy and delayed radiation injuries (soft tissue and bony necrosis): 2012 update. *Undersea Hyperb Med* 39 (6): 1121–39

Greif R, Akça O, Horn EP, Kurz A & Sessler DI (2000) Supplemental perioperative oxygen to reduce the incidence of surgical-wound infection. *N Engl J Med* 342 (3): 161–67

Guest J, Ayoub N, Mcllwraith T et al (2015) Health economic burden that wounds impose on the National Health Service in the UK. *BMJ Open*. 5: e009283

Guest JF, Vowden K , Vowden P (2017) The health economic burden that acute and chronic wounds impose on an average clinical commissioning group health board in the UK. *J Wound Care* 26(6): 292–303

Hart BB (2014) Refractory osteomyelitis. In: Weaver LK ed. *Undersea and Hyperbaric Medical Society. Hyperbaric Oxygen Therapy Indications.* 13th edn. Best Publishing, Florida: 179–208

Hopf HW et al (2005) Hyperoxia and angiogenesis. *Wound Repair and Regeneration* 13 (6): 558–64

Hung MC, Chou CL, Cheng LC et al (2016) The role of hyperbaric oxygen therapy in treating extensive Fournier's gangrene. *Urological Science.* 27(3): 148–53

Hunt TK, Pai MP (1972) The effect of varying ambient oxygen tensions on wound metabolism and collagen synthesis. *Surg Gynecol Obstet* 135 (4): 561–7

Jain KK (2009) *Textbook of Hyperbaric Medicine.* 5th ed. Hogrefe , Göttingen

Kendall AC, Whatmore JL, Winyard PG et al (2013) Hyperbaric oxygen treatment reduces neutrophil-endothelial adhesion in chronic wound conditions through S-nitrosation. *Wound Repair Regen* 21 (6): 860–68

Kerrigan CL, Stotland MA (1993) Ischemia reperfusion injury: a review. *Microsurgery* 14 (3): 165–75

Knighton DR, Silver IA, Hunt TK (1981) Regulation of wound healing angiogenesis – effect of oxygen gradients and inspired oxygen concentration. *Surgery* 90 (2): 262–70

LaVan FB, Hunt TK (1990) Oxygen and wound healing. *Clin Plast Surg* 17(3): 463–72

Mathieu D, Marroni A, Kot J (2017) Tenth European consensus conference on hyperbaric medicine: recommendations for accepted and non-accepted clinical indications and practice of hyperbaric oxygen treatment. *Diving Hyperb Med* 47 (1): 24–32

Milovanova TN, Bhopale VM, Sorokina EM et al (2009) Hyperbaric oxygen stimulates vasculogenic stem cell growth and differentiation in vivo. *J Appl Physiol (1985)* 106 (2): 711–28

Niinikoski JHA (2004) Clinical hyperbaric oxygen therapy, wound perfusion, and transcutaneous oximetry. *World J Surg* 28(3): 307–11

Strauss MB (1987) Refractory osteomyelitis. *J Hyperbaric Med* 2: 147–59

Thom SR, Bhopale VM, Velazquez OC et al (2006) Stem cell mobilization by hyperbaric oxygen. *Am J Physiol Heart Circ Physiol* 290 (4): H1378–86

Weaver LK (2014) *Undersea and Hyperbaric Medical Society. Hyperbaric Oxygen Therapy Indications. 13th edn.* Available at: https://www.uhms.org/images/indications/UHMS_HBO2_Indications_13th_Ed._Front_Matter__References.pdf (accessed 21.08.2019)

Worth ER, Tettelbach WH, Hopf HW (2014) Arterial insufficiences: enhancement of healing in selected problem wounds. In: Weaver LK. ed, *Undersea and Hyperbaric Medical Society. Hyperbaric Oxygen Therapy Indications.* 13th edn. Best Publishing, Florida: 25–46

Zhang Q and Gould LJ (2014) Hyperbaric oxygen reduces matrix metalloproteinases in ischemic wounds through a redox-dependent mechanism. *J Invest Dermatol* 134(1): 237–46