

# Hyperbaric oxygen therapy for the management of chronic wounds: patient selection and perspectives

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**Abstract:** The Undersea and Hyperbaric Medical Society includes “select problem wounds” as an accepted indication for the use of hyperbaric oxygen (HBO<sub>2</sub>), however, the treatment of diabetic foot ulcers (DFUs) has dominated any discussions of problem wounds because of the prevalence of DFUs in today’s patient population and the reimbursement available for their treatment. Other wound types (eg, calciphylaxis ulcers, sickle cell ulcers, and pyoderma gangrenosum) that have well-deserved reputations as problem wounds have been infrequently treated with HBO<sub>2</sub>. While there are sound fundamental reasons why additional oxygen may have benefits in the treatment of these wounds, the challenge is finding enough high quality evidence to support routine use of HBO<sub>2</sub>.

**Keywords:** hyperbaric oxygen therapy, HBO<sub>2</sub>, oxygen, problem wounds, chronic wounds, wound healing, diabetic foot ulcers, arterial insufficiency ulcers, sickle cell disease, scleroderma, calciphylaxis, graft versus host disease, pyoderma gangrenosum, venous stasis ulcers

## The role of oxygen in wound healing

Oxygen is involved in nearly every phase of wound healing, acting as a critical co-factor for fibroblast replication, collagen deposition,<sup>1</sup> angiogenesis,<sup>2-5</sup> resistance to infection,<sup>6-8</sup> and intracellular leukocyte bacterial killing.<sup>6</sup> Tissue hypoxia, on the other hand, is the initiator of wound healing and leads to upregulation of hypoxia-inducible factors (HIFs) that play a central role in adapting the body to a hypoxic environment. These adaptations include angiogenesis, anaerobic glycolysis, cellular mobility, growth factor signaling, and erythropoiesis.<sup>9</sup> Wounds become hypoxic as a result of acute or chronic injury.

Hemostasis is the first phase of wound healing. Vasoconstriction, platelet aggregation, and formation of a fibrin clot stop bleeding but also cause local ischemia and hypoxia as vessels thrombose.<sup>10</sup> Wound hypoxia is exacerbated by underlying conditions that result in decreased perfusion to the wound (eg, decreased cardiac output, increased peripheral vascular resistance, and presence of peripheral arterial disease [PAD] or pulmonary dysfunction). Oxygen carrying capacity is determined by the hemoglobin dissociation curve. Although anemia results in decreased overall O<sub>2</sub> carrying capacity, it does not inherently inhibit wound healing.<sup>11</sup> Arterial pO<sub>2</sub> is the key factor in wound healing potential and can be modulated through vasodilation, improved cardiac output, capillary permeability, and increased alveolar pO<sub>2</sub> achieved under hyperbaric conditions.<sup>10</sup>

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The inflammatory phase begins a few days after injury as neutrophils and monocytes begin the process of breaking down and clearing cellular debris.<sup>10</sup> Macrophages take the lead in breaking down devitalized tissue and killing bacteria,<sup>10,12</sup> however, oxidative killing is depressed in patients with local wound hypoxia. A minimum tissue pO<sub>2</sub> of 30 mmHg is required for effective bacterial killing.<sup>7</sup> Neutrophils killed 37% of organisms in 1 hour under anoxic conditions, 58% when pO<sub>2</sub> was raised to 5 mmHg, and 70% at 30 mmHg. There was a minimal increase in killing efficiency when tissue pO<sub>2</sub> was further increased to 150 mmHg.<sup>13</sup> Neutrophil bacterial killing activity depends on an oxygen-dependent respiratory burst where neutrophils convert oxygen to superoxide.<sup>14</sup> This process can result in a 20–100 fold increase in oxygen consumption<sup>15,16</sup> and a decrease in tissue pO<sub>2</sub> from 60 mmHg down to 0–10 mmHg.<sup>17</sup> Superoxide production is at its maximal rate at a tissue pO<sub>2</sub> of 300 mmHg but is cut in half with tissue pO<sub>2</sub> between 80–150 mmHg.<sup>18</sup> There is synergy between antibiotic administration and hyperoxia, as early antibiotic administration combined with hyperoxia resulted in more efficient bacterial clearance than delayed administration of either antibiotics or oxygen.<sup>8</sup> Higher inspired oxygen has also been shown to decrease the spread of infectious necrosis.<sup>6</sup>

The proliferative phase of wound healing sees an increase in collagen deposition, angiogenesis, granulation tissue formation, and epithelialization,<sup>10</sup> but all of these are directly related to wound pO<sub>2</sub>.<sup>1,19–21</sup> Fibroblast activity, especially collagen synthesis, is a key component in wound healing. Collagen cannot be synthesized without oxygen.<sup>22</sup> The minimum tissue pO<sub>2</sub> for collagen synthesis is 25 mmHg, so tissue pO<sub>2</sub> below that results in decreased collagen deposition<sup>23</sup> and lower quality collagen as tensile strength increases with high pO<sub>2</sub> and decreases with high pCO<sub>2</sub>.<sup>1</sup> Angiogenesis and vasculogenesis are both increased through hyperoxia.<sup>24,25</sup> Stem progenitor cells (SPCs) have been identified as playing a role in vasculogenesis, and studies suggest that HIF-1 plays an important role in directing circulating SPCs to ischemic tissue.<sup>9</sup> The mitosis rate of squamous cells is oxygen dependent,<sup>26</sup> and epithelialization increases with hyperoxia and decreases with hypoxia.<sup>20,27,28</sup>

Remodeling is the final phase of wound healing and occurs weeks to months after a wound is epithelialized. Immature collagen, which is thinner than mature collagen and deposited parallel to the skin,<sup>29</sup> is reorganized into a more structurally sound lattice. Cross-linking of collagen fibers increases wound strength over the next 4–5 weeks.<sup>10</sup>

Tensile strength of a newly epithelialized wound is only 3% at 1 week, 20% after 3 weeks, and 80% after 3 months. The ultimate strength of the wound depends on both the quality and quantity of the collagen,<sup>10</sup> which is dependent on wound oxygenation.

In summary, acute injury causes wound hypoxia that is magnified if there is pre-existing ischemia and hypoxia in the wound. Wound pO<sub>2</sub> further decreases as vessels thrombose in the hemostasis phase, leukocytes consume oxygen in the inflammatory phase, and fibroblasts consume oxygen in the proliferative phase.<sup>30</sup> Importantly, a healing wound has a higher metabolic demand than when it is in a steady state. This is evidenced by depression of wound-tissue pO<sub>2</sub> in the first few days after a major surgery.<sup>30</sup> Wound pO<sub>2</sub> is the rate limiting step in healing, especially in the acute post-operative phase, as the amount of O<sub>2</sub> extracted rises with increased oxygen breathing.<sup>23</sup>

## Defining the chronic, problem wound

A chronic wound can be defined as a wound that does not heal after an expected period of time. Chronic wounds are often trapped in the inflammatory phase of wound healing, unable to transition into the proliferative phase. Common causes for inflammation include infection, devitalized tissue that has been incompletely debrided, mechanical insults from retained foreign body or external pressure, and hypoxia as a result of wound ischemia. Initial efforts should focus on correcting or ruling out these causes of wound chronicity.

We have enumerated many examples where tissue hypoxia can hinder wound healing.

Local tissue hypoxia may be caused by macrovascular disease with or without concomitant microvascular disease. Macrovascular status can be evaluated using ankle-brachial index, pulse volume recordings, arterial Doppler, computed tomography/magnetic resonance angiogram, and angiography. Presence of macrovascular disease should result in a vascular consultation to determine whether revascularization is possible. Microvascular disease may be evaluated using skin perfusion pressure, transcutaneous oxygen measurement (TCOM), and indocyanine green fluorescence angiography (ICGA).

TCOM is a non-invasive study that measures the pO<sub>2</sub> of tissue (TcPO<sub>2</sub>) through intact skin.<sup>31</sup> This provides an objective means of assessing local tissue hypoxia and identifying wounds with a high risk of non-healing or amputation. Electrodes are usually placed adjacent to the

ulcer on the peri-wound skin while others may be placed on the contralateral limb for comparison or on the chest wall to measure normal values. TcPO<sub>2</sub> values have been shown to be useful predictors of wound healing and response to hyperbaric oxygen (HBO<sub>2</sub>).<sup>31–34</sup> TcPO<sub>2</sub> measurements while breathing normobaric room air <40 mmHg are considered hypoxic and associated with a reduced likelihood of healing. TcPO<sub>2</sub> values <35 mmHg while breathing 100% normobaric oxygen are associated with a 41% failure rate with HBO<sub>2</sub>.<sup>33</sup> A sea-level oxygen challenge can help predict whether a wound will respond to HBO<sub>2</sub>. A wound that is hypoxic on room air (TcPO<sub>2</sub><40 mmHg) but has a rise in TcPO<sub>2</sub>>35 mmHg and more than double the room air TcPO<sub>2</sub> while breathing 100% normobaric oxygen, is likely to benefit from HBO<sub>2</sub>.<sup>33</sup> The most valuable predictor of response to HBO<sub>2</sub> is the TcPO<sub>2</sub> while breathing 100% O<sub>2</sub> under hyperbaric conditions.<sup>32</sup> An in-chamber TcPO<sub>2</sub>>200–299 mmHg had significantly reduced wound failure rates.<sup>32</sup> In-chamber TcPO<sub>2</sub>>200 mmHg had an 84% likelihood of benefit from HBO<sub>2</sub><sup>33</sup> while in-chamber TcPO<sub>2</sub><100 mmHg had only a 14% likelihood of benefit from HBO<sub>2</sub>.<sup>31</sup>

In-chamber TcPO<sub>2</sub> was used to determine the appropriate treatment pressure for patients undergoing HBO<sub>2</sub> to treat lower extremity wounds.<sup>35</sup> The study used an in-chamber TcPO<sub>2</sub> target of 250 mmHg for decision-making and demonstrated that nearly 80% of patients reached a TcPO<sub>2</sub>>250 mmHg at 2 ATA. For patients with a TcPO<sub>2</sub><250 mmHg at 2 ATA, nearly half (41%) reached a TcPO<sub>2</sub>>250 mmHg when chamber pressure was increased to 2.4 ATA. This monoplace-based HBO<sub>2</sub> protocol allowed objective choice of treatment pressure that maximized benefit while minimizing risk.<sup>35</sup>

ICGA is a newer technology that assesses microvascular skin perfusion using an intravenous injection of ICG followed by imaging with a near-infrared laser camera. It has been used extensively by surgeons in the operating room.<sup>36–40</sup> Recent publications have reported its use for HBO<sub>2</sub> patients with soft tissue radionecrosis,<sup>41,42</sup> and for assessing perfusion in chronic wounds being treated with HBO<sub>2</sub>.<sup>43</sup> While this is a very promising tool, there is more work that needs to be done to determine clinical decision-making parameters surrounding ICGA.<sup>44</sup>

While clinical evidence supports the use of HBO<sub>2</sub> in the treatment of non-healing diabetic foot ulcers (DFUs),<sup>45,46</sup> the variable results seen in actual clinical use suggest that we need to do a better job with patient selection.<sup>47</sup> Patient selection becomes even more critical

when considering HBO<sub>2</sub> for less established problem wound types. Concern for tissue hypoxia or hypoperfusion should be considered before deciding to use adjunctive HBO<sub>2</sub>,<sup>48</sup> but it should not be the sole determinant in deciding to use HBO<sub>2</sub> as some of its systemic effects (eg, endothelial progenitor stem cell mobilization) are not measured by tissue oxygenation.<sup>49,50</sup>

## Physiological effects of HBO<sub>2</sub>

HBO<sub>2</sub> addresses the fundamental issue of wound hypoxia by providing oxygen to ischemic tissue. The amount of O<sub>2</sub> dissolved in plasma is inconsequential at sea-level atmospheric pressure; however, there is enough oxygen dissolved in plasma when breathing 100% O<sub>2</sub> at 3 ATA to meet the body's metabolic demands without dissociation of any O<sub>2</sub> bound to hemoglobin.<sup>51</sup> Oxygen diffusion from capillary beds increases ten-fold and PaO<sub>2</sub> exceeds 1,500 mmHg with corresponding elevation of soft tissue and muscle PO<sub>2</sub>. Tissue PO<sub>2</sub> increases in a direct linear relationship to the increased PaO<sub>2</sub> present in the circulating plasma,<sup>52</sup> allowing healing to proceed.

As opposed to breathing oxygen at sea-level atmospheric pressure, HBO<sub>2</sub> reduces ischemia-reperfusion (IR) injury, mobilizes circulating SPCs, enhances neutrophil bacterial killing activity, produces both reactive oxygen species (ROS) and reactive nitrogen species (RNS), and stimulates multiple growth factors that promote wound healing.<sup>53</sup> HBO<sub>2</sub> reduces the perivascular edema and inflammation seen with IR injury by inhibiting the adherence of neutrophils to previously ischemic vascular endothelium, but it does not inhibit the normal antimicrobial functions of degranulation, phagocytosis, or the oxidative burst.<sup>54–56</sup> HBO<sub>2</sub> is involved in the recruitment and differentiation of circulating SPCs to form vessels *de novo*.<sup>24,49,53</sup> The knowledge that HIF-1 helps direct circulating SPCs to ischemic tissue<sup>9</sup> suggests that the combination of HIF-1 activity and HBO<sub>2</sub> may be the basis for improved healing seen with HBO<sub>2</sub> therapy.<sup>57</sup> Conversely, HIF-1 has been shown to break down rapidly in non-hypoxic environments<sup>58</sup> and others have shown that HBO<sub>2</sub> improves wound healing by down-regulating HIF-1 $\alpha$ ,<sup>59</sup> highlighting that we have an incomplete understanding of the complex interactions between HIF and HBO<sub>2</sub>.

ROS and RNS are important signaling molecules that are involved in the regulation of various hormones, growth factors, and cytokines involved in wound healing. ROS such as superoxide (O<sub>2</sub><sup>•-</sup>), hydrogen peroxide (H<sub>2</sub>O<sub>2</sub>), hypochlorous acid (HClO), and hydroxyl (HO<sup>•</sup>) are the

natural by-products of normal metabolism, and RNS include nitric oxide (NO) and peroxynitrite (ONOO<sup>-</sup>) – the product of NO and O<sub>2</sub><sup>•-</sup>. NO is synthesized by three NO synthase enzymes: NOS-1 (nNOS), NOS-2 (iNOS), and NOS-3 (eNOS). Bone marrow eNOS activity is required for SPC mobilization – a function that is depressed in diabetic patients – and HBO<sub>2</sub> is able to stimulate eNOS activity, resulting in up-regulation of SPC production.<sup>25,49,53,57</sup> Reactive species may have either positive or negative effects, depending on their concentration and intracellular localization.<sup>60</sup> A complete discussion of the role of ROS and RNS in wound healing is beyond the scope of this review, and readers are directed to Thom's manuscript for more details.<sup>60</sup> The body needs to balance the ROS that are generated as a part of normal metabolism with its natural anti-oxidant defenses. An inability to maintain balance results in oxidative stress, which can be seen where an overproduction of ROS in chronic wounds leads to a prolonged inflammatory state.<sup>61</sup> When speaking about HBO<sub>2</sub>, it is important to realize that oxidative stress and oxygen toxicity are not synonymous,<sup>53</sup> and the body's inherent anti-oxidant defenses are able to manage the oxidative stress seen in the intermittent use of HBO<sub>2</sub>.<sup>62–68</sup> NO, a potent vasodilator, is reduced in non-healing diabetic wounds; however, increased NO levels after a course of HBO<sub>2</sub> treatments correlated with successful healing.<sup>69</sup>

HBO<sub>2</sub> increases synthesis of a laundry list of growth factors: VEGF,<sup>70</sup> TGF-β<sub>1</sub>,<sup>71</sup> bFGF,<sup>71</sup> angiopoietin-2,<sup>72</sup> MMP-2 and MMP-9, TIMP-1,<sup>73</sup> and PDGF receptors.<sup>74</sup> Collagen synthesis, which is very sensitive to PO<sub>2</sub>, is augmented by HBO<sub>2</sub>.<sup>2</sup> Epithelialization is increased by approximately 30%,<sup>27</sup> but wound contraction is unaffected by ambient pO<sub>2</sub>.<sup>20</sup> HBO<sub>2</sub> has been shown in cell cultures to up- or down-regulate over 8,000 different genes at the molecular and cellular level with large responses only when exposed to HBO<sub>2</sub> and not sea-level 100% oxygen.<sup>75</sup>

If oxygen availability is the rate limiting step in wound healing and O<sub>2</sub> consumption increases as O<sub>2</sub> availability increases,<sup>23</sup> it stands to reason that further increases in available pO<sub>2</sub> during HBO<sub>2</sub> would enhance wound healing. In addition to the effects of hyperoxia, alternating periods of hypoxia or relative hypoxia (compared to HBO<sub>2</sub>) may stabilize HIF, which primes the wound for a more robust response during the next period of.<sup>76</sup> This push-pull relationship may explain how HBO<sub>2</sub> plays a role in enhanced healing of chronic, problem wounds.

## Patient selection for HBO<sub>2</sub>

Although there are sound fundamental principles supporting the use of HBO<sub>2</sub> for chronic wounds,<sup>77</sup> the evidence for some of these conditions is limited to case reports and case series. There are very few randomized controlled trials, and the variability in scientific rigor has led many to question their conclusions.<sup>78</sup>

## DFUs

The largest body of evidence in support of HBO<sub>2</sub> is found in the treatment of DFUs. Patients with diabetes mellitus commonly have sensory, motor, and autonomic neuropathy as well as macrovascular and microvascular angiopathy, leading to ischemic and hypoxic wounds that are prone to ulceration and infection.<sup>79</sup> There is decreased mobilization of circulating SPCs<sup>80</sup> and suppression of NO, reducing healing potential. As detailed previously, HBO<sub>2</sub> reverses local tissue hypoxia, stimulates vasculogenesis, directs SPCs to ischemic tissue, and stimulates multiple growth factors that enhance wound healing and vasculogenesis.<sup>49,53,69–71,74,81–83</sup>

A thorough summary and analysis of the hyperbaric literature regarding DFUs was published in 2017<sup>84</sup> and updated in 2019.<sup>85</sup> Readers are referred to these publications for a more in-depth discussion. Early studies showed that the use of HBO<sub>2</sub> was able to reduce the incidence of lower extremity amputation. Amputation rates decreased from 30%–40% without HBO<sub>2</sub> to only 5% with adjunctive HBO<sub>2</sub>.<sup>86–89</sup> Randomized controlled trials demonstrated that HBO<sub>2</sub> reduced the number of positive wound cultures,<sup>90</sup> reduced major amputation rates,<sup>88,90</sup> and increased the rate of wound healing.<sup>91–94</sup> Transcutaneous oximetry was shown to be a predictor of wound healing potential, but only when looking at TCOM values while breathing HBO<sub>2</sub>.<sup>31–33,48,95</sup> A fundamental tenet for the consideration of adjunctive HBO<sub>2</sub> is whether or not basic wound care principles have been followed prior to instituting HBO<sub>2</sub>.<sup>96,97</sup> Criteria for the use of HBO<sub>2</sub> were established in the United States by the Centers for Medicare and Medicaid Services (CMS) based on the result of a pivotal trial that utilized the Wagner Grading system<sup>88</sup> even though there are other grading systems that are more sophisticated and arguably more clinically relevant.<sup>98</sup>

A large longitudinal cohort study of 6,259 patients with a plantar DFU questioned the effectiveness of HBO<sub>2</sub>, showing that patients receiving HBO<sub>2</sub> had a lower healing rate (42.3% vs 49.6%), higher overall amputation rate (6.7% vs 2.1%), and higher major amputation rate (3.3% vs 1.3%) than patients who did not receive HBO<sub>2</sub>.<sup>47</sup> This study

highlighted the difference between the efficacy of HBO<sub>2</sub> as shown in tightly controlled clinical trials vs how patients were treated in a real-world scenario, but it was criticized for its reliance on propensity scoring to account for the lack of randomization between treatment groups.<sup>91,99</sup> Two recent randomized controlled trials also failed to show a benefit for HBO<sub>2</sub> in healing DFUs or reducing amputations,<sup>100,101</sup> but one was hampered by the use of photographs to adjudicate whether a wound met pre-determined criteria for amputation rather than amputation itself,<sup>102–104</sup> and the other showed that a high percentage of patients did not start or could not complete the prescribed treatment protocol.<sup>105,106</sup> When considering patients who did complete the protocol, however, HBO<sub>2</sub> was able to show significantly fewer amputations than standard care alone.<sup>101</sup> This is consistent with several other studies that showed that patients who underwent a longer course of therapy had successful wound healing, while those with shorter courses did not.<sup>31,107,108</sup>

The UHMS developed a set of clinical practice guidelines to help the hyperbaric provider judiciously use HBO<sub>2</sub> as part of the treatment plan. Even though CMS guidelines restrict HBO<sub>2</sub> for Wagner Grade 3 DFUs or higher, over 45% of patients in multiple studies had only Wagner Grade 2 DFUs.<sup>47,100,101</sup> The UHMS found insufficient high-quality evidence to suggest using HBO<sub>2</sub> in the treatment of Wagner Grade 2 DFUs. It did find enough evidence to suggest treating Wagner Grade 3 or higher DFUs that were either refractory to wound healing and had been present for 30 days, or for acutely infected Wagner Grade 3 or higher DFUs that required urgent surgical intervention.<sup>46</sup> HBO<sub>2</sub> was shown to be more effective than standard therapy when restricted to only Wagner Grade 3 and 4 DFUs.<sup>108</sup> Cost effectiveness studies comparing HBO<sub>2</sub> with the cost of an amputation with subsequent rehabilitation and physical therapy have been uniformly favorable toward HBO<sub>2</sub>,<sup>109–113</sup> and the integration of HBO<sub>2</sub> into a comprehensive limb salvage protocol has been advocated.<sup>87,113</sup>

DFUs remain the most common chronic wound type being treated with HBO<sub>2</sub>, but tightening requirements for reimbursement are constraining the frequency of its use. This may be wholly appropriate, given the rapid rise in outpatient wound and hyperbaric centers,<sup>114</sup> but there is a risk of denying limb-saving therapy to a patient who truly requires it.

## Arterial insufficiency ulcers (AIUs)

Between 8–12 million people in the United States over 40 years of age are affected by PAD<sup>115</sup> and suffer tissue ischemia due to atherosclerosis.<sup>116</sup> AIUs are closely

related to DFUs as the majority of patients with DFU also have PAD. These patients are often unable to be revascularized, leaving an above-ankle amputation as their only alternative. Healing rates with revascularization are reported between 50%–90% with amputation rates of <20%.<sup>117,118</sup> Outcomes change dramatically without revascularization, however, with healing rates of 40%–50% and amputation rates between 25%–40%.<sup>117,118</sup>

HBO<sub>2</sub> reverses local tissue hypoxia and stimulates vasculogenesis, however it is less effective in the face of severe macrovascular disease. Inability to revascularize the lower extremity is not a reason to exclude HBO<sub>2</sub> from the treatment plan. A commonly overlooked aspect of the DFU studies previously mentioned is whether or not they include patients with underlying, uncorrectable vascular disease. While many wound healing studies excluded patients with significant PAD, the Faglia study included patients who had persistent tissue hypoxia and still showed increased healing and decreased amputation rates.<sup>88</sup>

There are very few studies to guide patient selection for HBO<sub>2</sub>, but a case series of 82 patients with AIUs in the absence of diabetes mellitus showed a significant clinical response to HBO<sub>2</sub>.<sup>119</sup> The Wound Healing Society recommends consideration of HBO<sub>2</sub> if patients have an AIU refractory to revascularization or if they are not a candidate for revascularization.<sup>120</sup> Any decision to use HBO<sub>2</sub> for an AIU should be done after a thorough arterial insufficiency workup, although it may be considered as a bridging therapy to preserve ischemic tissue until definitive revascularization can occur. Objective measurements of tissue ischemia and hypoxia should be used to guide patient selection and monitor response to therapy, although there are no clear-cut criteria in the literature.

## Calciphylaxis

Calciphylaxis is a rare condition that causes small vessel calcification of unknown etiology. This can present as painful skin lesions and chronic, non-healing ulcers with gangrene. Calciphylaxis is reported to have a prevalence of 1%–4% in end-stage renal disease patients on dialysis.<sup>121,122</sup> Vascular calcification results in hypovascular tissue, fibrosis, and dermal necrosis, most often in the lower extremities.<sup>123</sup> A mortality rate of 60%–80% is reported and is most often the result of septic complications of calciphylaxis wounds.<sup>124</sup>

HBO<sub>2</sub> has been used for calciphylaxis wounds based on the rationale of hyperoxygenating ischemic tissue. Multiple case studies and case series have reported healing in previously refractory calciphylaxis wounds after a

course of HBO<sub>2</sub>,<sup>122,125–132</sup> and concomitant use of HBO<sub>2</sub> and thiosulfate has been advocated.<sup>131,132</sup> Despite the fact that there are no high-quality studies that compare HBO<sub>2</sub> to a control group, it has been used as a treatment of last resort after other standard therapies have failed. Logic dictates that earlier use of HBO<sub>2</sub> would be more successful than later use of HBO<sub>2</sub>.

## Scleroderma

Scleroderma is an autoimmune connective tissue disease that affects the hands, feet, and face. Abnormal thickening of the skin is caused by overproduction of collagen and subsequent damage to smaller arteries, resulting in local tissue hypoxia.<sup>133</sup> HBO<sub>2</sub> is thought to improve healing by overcoming tissue hypoxia,<sup>32,134,135</sup> although the effects of collagen modulation with HBO<sub>2</sub> are unclear. Systemic scleroderma is an autoimmune disease, and HBO<sub>2</sub> has been shown to play a role in minimizing the proliferation of damaging lymphocytes and modulating the biology of cytokines and inflammatory mediators.<sup>136,137</sup>

The evidence for the use of HBO<sub>2</sub> in the treatment of scleroderma relies on case reports of refractive scleroderma wounds that have healed with HBO<sub>2</sub>.<sup>138–145</sup> Patient selection should rely on clinical judgement as to the likelihood that HBO<sub>2</sub> can alter the trajectory of the scleroderma ulcer.

## Graft-versus-host disease (GvHD)

Allogeneic stem cell transplantation in the treatment of hematopoietic and lymphatic malignancies may result in cutaneous complications of GvHD. The most common manifestations of GvHD are skin ulcers resulting from dermal/subcutaneous endothelial damage and microangiopathy.<sup>146–148</sup> HBO<sub>2</sub> results in neovascularization and collagen deposition at the site of hypoxic tissue such as those in GvHD.<sup>24,53</sup> HBO<sub>2</sub> may also play a role in immune modulation.<sup>136,137</sup>

The evidence for use of HBO<sub>2</sub> in GvHD relies on animal studies and case report data.<sup>149,150</sup> Patient selection should rely on clinical judgement and may benefit from objective assessments of tissue perfusion and hypoxia to determine whether treatment is appropriate for individual patients.

## Pyoderma gangrenosum (PG)

PG is a rare neutrophilic dermatosis that affects the skin and subcutaneous tissues. Histopathologic characteristics include edema and neutrophil infiltrates of small and medium-sized vessels. Thrombosis of these vessels results in

surrounding hemorrhage. The neutrophil infiltration and inflammation can result in abscess formation with resultant liquefaction of the tissue.<sup>151</sup>

HBO<sub>2</sub> has been utilized for decades for the treatment of PG,<sup>152–154</sup> overcoming hypoxia and providing an anti-inflammatory effect. A 2007 review provided a comprehensive listing of positive and negative case studies and concluded that HBO<sub>2</sub> was an effective treatment option for cutaneous ulcers related to PG, resulting in decreased pain and increased quality of life.<sup>153</sup> HBO<sub>2</sub> may be considered for PG ulcers refractive to conventional therapies.

## Sickle cell disease (SCD)

SCD is characterized by red blood cells that deform and take a sickled shape, impairing binding of oxygen, compromising circulation, producing ischemia, and causing anemia.<sup>155</sup> Approximately 2.5% of patients with SCD will develop a lower extremity ulcer.<sup>156</sup> HBO<sub>2</sub> has been shown to reduce the percentage of circulating sickled cells after a hyperbaric exposure to 2 ATA.<sup>157,158</sup>

There is a single case report describing the use of HBO<sub>2</sub> for two patients with SCD-related cutaneous wounds with a 50% response rate.<sup>159</sup> There are both positive and negative case reports for the use of HBO<sub>2</sub> in the treatment of pain crises,<sup>158,160,161</sup> priapism,<sup>162</sup> and central retinal artery occlusion<sup>163</sup> complicated by SCD. There is insufficient evidence to support the routine use of HBO<sub>2</sub> in the treatment of SCD ulcers, although it may be useful for non-cutaneous manifestations of SCD.

## Venous stasis ulcers (VLUs)

VLUs account for 90% of ulcers of the lower extremity and are the result of uncontrolled leg edema. Edema decreases perfusion as intra-compartment pressures rise and compromise capillary flow. Compression therapy is the mainstay of therapy, reducing edema through augmentation of the calf pump and directly increasing extraluminal pressure. With uncontrolled edema, oxygen diffusion from capillary beds is reduced as the distance between capillaries increases as a result of cellular tumescence.

HBO<sub>2</sub> has been found to reduce wound surface area following therapy in two randomized, sham controlled trials, but neither showed an improvement in healing rates.<sup>164,165</sup> A third study did show statistically significant wound healing with HBO<sub>2</sub>.<sup>166</sup> There is insufficient evidence to support the routine use of HBO<sub>2</sub> in the treatment of VLUs.

## Conclusion

The use of HBO<sub>2</sub> for chronic, problem wounds is best defined for DFUs, but there is a sound fundamental basis for its use for some other chronic wound types. There is a lack of high-quality clinical evidence for non-DFU indications however, and providers must utilize clinical judgement to decide whether the reason for wound healing failure can be overcome with HBO<sub>2</sub>. Large clinical trials are unlikely to be successful given the rarity of these conditions, but participation in a research registry may allow pooled data to demonstrate efficacy of HBO<sub>2</sub>.

## Disclosure

The authors report no conflicts of interest in this work.

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