

RATIONALE, STUDY DESIGN CONSIDERATIONS, AND PROTOCOL RECOMMENDATIONS FOR TREATING COVID-19 PATIENTS WITH HYPERBARIC OXYGEN

Introduction

As SARS-CoV-2 infection accelerated in early 2020, many patients deteriorated rapidly and became ventilator-dependent. The death rate from serious infection was frightening, especially in patients with other chronic diseases. Clinicians and medical researchers began developing strategies to treat and prevent this new worldwide public health threat. They looked to novel interventions because no highly effective therapies existed, and care was mostly supportive. Some recommended hyperbaric oxygen (HBO₂) therapy because of its demonstrated success in providing oxygen and reducing end-organ damage in patients with severe carbon monoxide poisoning or anemia. A publication from China reported dramatic results in five critically ill patients treated with HBO₂ [1]. A second case series published by Thibodeaux, et al. [2]. showed that patients who received hyperbaric oxygen at a critical junction when intubation seemed imminent avoided intubation. Gorenstein and colleagues have now reported in a publication in pre-print form a series of 20 patients treated with hyperbaric oxygen and compared to propensity matched controls. They conclude that HBO₂ is safe and possibly effective. [3] Additional anecdotal reports appeared to show an impressive improvement in sick patients even in the setting of progressive respiratory failure despite delivery of prolonged high FiO₂s (fraction of inspired oxygen). One of our committee members based on her personal experiences in treating a small group of patients has suggested utility in using transcutaneous oxygen in monitoring patients' responses to hyperbaric oxygen, including the continued use of this technology after a hyperbaric treatment and return of the patient to the ICU [4]. Two prior publications had reported experiences in applying transcutaneous oxygen measurements as a monitoring tool to be applied to critically ill patients [5,6].

With these reported successes interest in the possible role of hyperbaric oxygen in COVID-19 treatment increased. The Undersea and Hyperbaric Medical Society (UHMS) was called upon to render an opinion, and a UHMS Policy Statement was developed and released at:

https://www.uhms.org/images/Position-Statements/UHMS_Position_Statement_Hyperbaric_Oxygen_for_COVID-19_Patients_v13_Final_copy_edited.pdf

The Society initially supported treatment only when patients were enrolled in clinical trials approved by an Institutional Review Board (IRB). Subsequent to that initial position statement the UHMS has conducted a webinar reporting likely mechanisms and early clinical experiences. Two prominent hyperbaric experts authored an editorial discussing the major issues of applying hyperbaric oxygen to the treatment of COVID-19 patients [7]. An even more recent paper by Paganini et al. discusses the biological mechanisms of action of hyperbaric oxygen and identifies potential logistic difficulties and toxicities of treatment [8].

The incidence of COVID-19 has increased dramatically, and this unfortunate abundance of patients has led to a significant understanding of what treatments are effective and which are not. Much of this evolution in treatment has been in the utilization of a known technology in a novel application. The UHMS has, therefore, reconsidered its position on the compassionate use of hyperbaric oxygen for COVID patients based on the strong mechanistic evidence and from the impressive results in the patients reported to date. We encourage the enrollment of patients in formal, IRB-approved clinical

trials and would prefer that they be randomized and controlled. Given the dire and widespread implications of the spreading pandemic and the absence of highly effective therapies, we recognize and support single-armed studies and the compassionate application of hyperbaric oxygen when an IRB-approved protocol cannot be reasonably obtained.

We encourage those treating COVID patients to utilize the most recent literature and science to guide clinical decision-making. The following sections will provide guidance for study design and can also serve to guide patient management and clinical assessment standards for all patients receiving hyperbaric oxygen therapy for COVID-19 infections. Regardless of protocol, patient presentation, progress and outcome information should be meticulously documented. The UHMS encourages the involvement of hospital medical staff, administration, and legal counsel in the development and implementation of all innovative therapies.

The UHMS tasked its Research Committee to develop recommendations to the hyperbaric community for study designs simple enough to be used widely by the majority of interested facilities, with a consistent approach so that combined data may be collated for future meta-analyses. This document outlines the committee's efforts. The research committee has been augmented by several additional individuals with special experience, skills, and interests related to COVID-19 who were willing to invest their efforts to develop clinical trial model designs and to provide guidance to those planning to develop their own research protocols. Eight institutional trials are now listed on clinicaltrials.gov; many are international in their scope and are actively recruiting patients.

The report's authors realize that the ideal scientific design for such clinical trials is a randomized controlled trial (RCT). We recommend that design if possible and recognize that ultimate acceptance of HBO₂ therapy in this setting should be supported by reproducible RCTs. In this time of urgent need, however, we feel additional single-arm Phase I/II trials are more likely to be proposed and conducted. With this in mind, we propose a model that defines our preferred protocol for hyperbaric treatment, including oxygen dosage and treatment frequency. In our suggested model, those receiving hyperbaric oxygen can serve as the study arm; the control arm could be composed of case-controls or propensity-score matched controls who receive "standard treatment." We do not discuss randomization techniques. We believe that given the frequency of cases, investigators will likely be able to identify a well-matched historical control group at their institution. Local investigators are obviously limited by both human and financial resources and may not be able to adhere to every aspect of our recommendations. In selecting our suggested diagnostic studies we highlighted those studies/tests we feel are of high value and cost-effective. Individual investigators will need to obtain and follow diagnostics that are available at their institutions.

The Committee considered how to address the issue of hyperbaric-induced oxygen toxicity. Most clinical measures of oxygen toxicity are non-specific (e.g., cough, chest tightness) and are likely already present in patients with COVID-19. Also, patients with COVID-19 are already receiving high levels of normobaric oxygen, which can also produce oxygen toxicity. The cases that have been treated to date with HBO₂ have not shown evidence of acute oxygen toxicity and have not shown acute worsening due to hyperbaric oxygen treatment. The presentations of Drs. Thibodeaux, Lee and Gorenstein at the webinar sponsored by the UHMS on July 20, 2020 were consistent in this observation. The Committee feels that if there is an adverse effect due to oxygen toxicity this might be seen in worse outcomes for the

hyperbaric group, but there were no specific measures identified that could be used to distinguish oxygen HBO₂ toxicity from lung damage due to standard care or the underlying disease. The overriding concern and reality are that this patient population needs effective supplemental oxygen, and anecdotal experience demonstrates that HBO₂ therapy accomplishes this exceptionally well.

This discussion will offer the following sections:

1. Proposed rationale and mechanisms of action for HBO₂ therapy
2. Recommended study design
3. Recommended diagnostics and outcome parameters

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MECHANISMS LIKELY UNDERLYING HBO₂ THERAPY'S EFFECTS IN COVID-19 PATIENTS

Background

SARS-CoV-2, which produces COVID-19 infection, is a single-stranded RNA-enveloped virus that causes severe respiratory disease in humans [9]. The most common symptoms include fever, cough, muscle aches/fatigue, and dyspnea. Non-pulmonary symptoms such as anosmia, abdominal pain, nausea, and diarrhea can also be seen. Abnormalities characteristically present on chest imaging of infected patients include opacities and bilateral infiltrates. Limited COVID-19 post-mortem data show prominent alveolar edema, proinflammatory concentrates, fibrin deposition within pneumocytes, and indications of early phase acute respiratory distress syndrome (ARDS) [10]. The leading causes of death from COVID-19 are respiratory failure from acute respiratory distress syndrome (ARDS) and multiorgan failure (MOF). In vitro cell experiments show a delayed release of cytokines in respiratory epithelial cells and macrophages in the early stages of infection. Later, the cells secrete high levels of proinflammatory cytokines including interleukin-1 beta (IL-1 β), interleukin-6 (IL-6), tumor necrosis factor (TNF) and chemokines CCL-2, CCL-3, and CCL-5 [11-22] (Figure 1).

This upregulation of the cytokine and chemokine response causes apoptosis of endothelial cells that damages the pulmonary microvascular and alveolar epithelial cell barriers. In return, this causes vascular leakage and alveolar edema, eventually leading to hypoxia and a cytokine storm [23-26]. This cytokine storm, defined as an excessive immune response to an external triggering event, is thought to be one of the major contributors to the development of ARDS and MOF. The rapid increase in cytokines and chemokines attracts large numbers of neutrophils and monocytes, which results in excessive

inflammatory infiltration and resultant lung injury. In patients with COVID-19 there are high levels of expression of IL-1 β , interferon (IFN), and tumor necrosis factor alpha (TNF- α), as well as IL-2R and IL-6, which positively correlate with disease severity and mortality [27]. All of these cytokines are known to be mediators of the inflammatory response and may be affected by HBO₂ therapy.

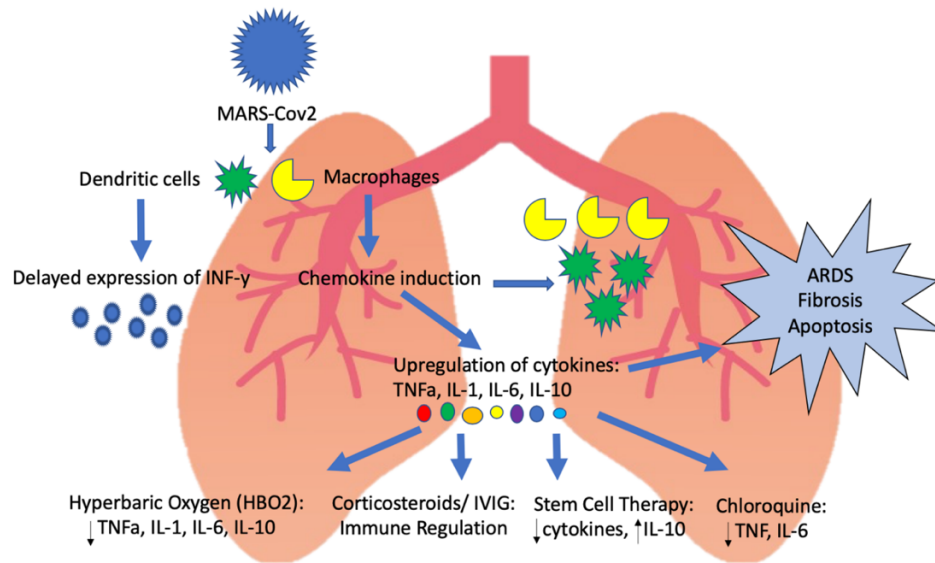


Figure 1: Mechanism of cytokine storm in COVID-19 and potential therapies [22].

At present, effective antiviral medications and vaccines are in early stages of development, so considering novel therapeutic interventions is imperative. HBO₂ therapy increases dissolved oxygen in plasma and tissues. HBO₂ ameliorates hypoxia and inflammatory processes in a variety of conditions, including ischemia/reperfusion injury, inflammatory bowel disease, and acute arterial insufficiencies including crush injury and compartment syndrome. These same mechanisms will likely be operative in the treatment of COVID-19 patients.

The following sections discuss additional putative mechanisms that likely contribute to the therapeutic application of HBO₂ in the COVID-19 patient.

Reactive oxygen and nitrogen species

HBO₂ increases production of reactive oxygen species (ROS) and reactive nitrogen species (RNS), both of which serve as signaling molecules for multiple intracellular cascades. These agents are widely recognized for their beneficial, as well as harmful, effects. The role played by ROS in the pathogenesis and progression of viral infections remains partially understood. HBO₂ therapy is unlikely to have direct effects on viral reproduction, although studies have reported mixed effects. At least one study, also of RNA viruses, suggests a virus-static effect of hyperbaric oxygen therapy.

Viral infections likely do not trigger oxidative stress (OS). Instead, the host defense responses induce ROS, and some reactive oxygen species may counter viral effects. On the other hand, OS may contribute to increased viral replication, transcription and/or reactivation of latent infection. Some studies have suggested that OS may play a role in HIV infection because HIV-infected patients are under chronic OS that results in perturbations in their antioxidant defense system. In this regard, data showing induction of antioxidant defenses by hyperbaric oxygen may yield benefits by mitigating damage caused by free radicals. Speit and colleagues [28] have demonstrated that the expression of heme oxygenase-1 increases 24 hours after HBO₂ exposure. HBO₂ can also increase activity of inducible nitric oxide synthase (iNOS) in leukocytes and endothelial nitric oxide synthase (eNOS) in platelets. The platelet activity of eNOS (at least in diabetics) yielding nitric oxide and related species may have benefits to blunt platelet aggregation, but whether HBO₂ prevents platelet aggregation in patients with COVID-19 is currently unknown.

OS and reactive species of oxygen and nitrogen have complex effects on cell signaling mediators such as hypoxia-inducible factor-1 (HIF-1) and nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB). There are competing pathways that influence levels of these agents in cells, and some evidence for a beneficial influence of HBO₂ therapy in certain situations. HBO₂ can increase HIF-1 via an oxidative stress response mediated in part by thioredoxin. HIF-1 and NF-κB crosstalk regulates essential inflammatory functions in myeloid cells. HIF-1 in myeloid cells increases the transcription of key glycolytic enzymes, resulting in increased glucose uptake and glycolytic rate. It also increases macrophage aggregation, invasion and motility. HIF-1 enhances intracellular bacterial killing by macrophages and promotes granule protease production and release of nitric oxide. HIF-1 has a mixed impact on host inflammatory response. Whereas HIF-1 drives the expression of proinflammatory cytokines, its impact on pathogen clearance acts to reduce production of inflammatory mediators.

Clearly, there are many potential ways that reactive oxygen and nitrogen species from HBO₂ therapy could have an effect in COVID-19, but the exact mechanisms and ultimate result remain to be determined.

Inflammatory mediation

A possible mechanism of HBO₂ therapy is the attenuation of the production of proinflammatory cytokines in response to an inflammatory stimulus such as surgery [29-32]. A critical role in ischemia-reperfusion injury is played by TNF-α, IL-1α and IL-1β. An increase in TNF-α occurs in the early phase of inflammation whereas elevation of IL-1β levels occurs in the later phase, suggesting that this cytokine sustains the inflammatory process. Previous studies have proven that TNF-α enters the systemic circulation and upregulates macrophages in the liver and lungs, promoting the inflammation process in other organs. Additionally, studies have demonstrated that HBO₂ inhibits TNF-α production during intestinal ischemic reperfusion and decreases production of both TNF-α and IL-1β on indomethacin-induced enteropathy [32,33]. A randomized pilot study found that a single preoperative HBO₂ session the day before pancreatic surgery modulated the inflammatory response for cytokines IL-6 and IL-10 and showed a decrease in postoperative pneumonia [34]. Caution should be taken in equating the impact of HBO₂ in preventing inflammation with the impact of hyperbaric oxygen in reducing already established inflammatory conditions.

Bosco and colleagues have demonstrated a persistent reduction in TNF- α and IL-6 and reduced inflammation in patients with avascular necrosis of the hip after receiving hyperbaric oxygen [35]. In an animal model of traumatic brain injury Qian and associates have reported reductions in IL-1 β and the inflammasome NLRP-3 after HBO₂ therapy [36]. If these effects occur in COVID-19 patients, these cytokine reductions could also work to mitigate the damage caused by an overactive immune response.

Evidence that hyperbaric oxygen may be useful in acute inflammation also comes from studies with acute pancreatitis, sepsis, and inflammatory bowel disease. In acute pancreatitis, animal studies show HBO₂ therapy reduces inflammation and improves outcomes [37-39]. Similarly, HBO₂ improved sepsis outcomes in mice, perhaps by an effect on interleukin-10 [40]. In a randomized trial of HBO₂ in patients with moderately severe ulcerative colitis, which like COVID-19 is characterized by uncontrolled inflammation, HBO₂ seemed to improve outcomes [41]. Taken together, the data suggest that HBO₂ can improve outcomes in settings of acute inflammation.

Hypercoagulopathy

Since the very first cases in the COVID-19 pandemic, hypercoagulability has been recognized as one of the hallmarks of its clinical presentation and consequences. It has been a significant cause of death in patients with severe disease. This hypercoagulable state can lead to deep vein thrombosis (DVT), pulmonary embolism, myocardial infarction, and strokes [42]. It is also frequently associated with disseminated intravascular coagulation (DIC), though as yet the characteristic multifocal bleeding that results after the consumption of coagulation factors and platelets typical of DIC has not yet been described in COVID patients [43]. The presence of widespread thrombosis and microangiopathy in pulmonary vessels and microthrombi in alveolar capillaries is a consistent finding in a post-mortem study of seven deceased COVID-19 patients. This effect likely contributes significantly to the respiratory failure pathognomonic of COVID-19 [44].

A retrospective analysis of 99 patients from China demonstrated several abnormalities in coagulation studies [45]. Of the 99, 36% percent of patients had elevated D-dimer; 16% showed a reduced activated partial thromboplastin time (APTT); 6% had an increased APTT; 30% had a shortened prothrombin time (PT) while 30% had an extended PT. In contrast, there has been a recent article reviewing the etiology, detection, and clinical implications of COVID-19 coagulopathy that demonstrated an elevation in D-dimer and fibrinogen but no significant differences in APTT, PT, and platelet counts. In both reports, a higher D-dimer was associated with an increased mortality rate [46].

A commentary by Connors and Levy discusses thromboinflammation, the interaction between inflammation and coagulation [43]. The inflammatory reaction characterizing the hyperactive immune response of the host patient appears to be the primary source of the hypercoagulative state and is mediated by cytokines – notably IL-6. As the understanding of SARS-CoV-2 has increased it has become apparent that much of its pathologic effect is attributable to the overexuberant host immune response moderated by inflammatory and proinflammatory cytokines. Mukund and associates have observed that the microvascular events, including activation of the coagulation cascade, are in part driven by complement activation [46]. They also state that plasmin is a crucial mediator that serves to “prime” interactions between complement and the platelet-activating systems involving the pulmonary

epithelium. They suggest that recognition of this interaction may offer opportunities for therapeutic intervention.

In the clinical series of COVID patients receiving HBO₂ reported to date there is no clear indication that hyperbaric oxygen interrupts or diminishes the hypercoagulable state of advanced stage SARS-CoV-2 infections, although one case from the Thibodeaux, et al. series had a significant diminution in elevated D-dimer [47]. In a webinar sponsored by the UHMS Dr. Thibodeaux presented a larger group of 12 patients who had consistent decreases in D-dimer. Of note, these patients were routinely treated with heparin drips.

Oxygen debt

On average, body tissues extract 5 to 6 mL of oxygen for every 100 mL of blood flow. The brain, heart and retina have even higher oxygen requirements. In those who are acutely anemic, reductions of hemoglobin to 6 gm/dL reach a common threshold for critical oxygen debt. Oxygen debt can be thought of as the minimum requirement for tissue/organ consumption minus the oxygen supply available. This oxygen debt continues to accumulate with time as long as the inadequacy of supply exists. It is typically expressed in liters of oxygen undersupplied per meters squared of body surface area. Van Meter states that survival is not possible if the oxygen debt exceeds 33 L/m². Multiorgan failure occurs at a debt of 22L/m², whereas those whose debt is no more than 9L/m² typically survive without residual organ dysfunction or injury [48].

In a review article from 2005 Rixen and Siegel discuss the importance of oxygen debt in determining the severity of hemorrhage and post-traumatic shock. They state that oxygen debt may actually be a more important determinant of the severity of hemorrhagic shock than estimates of blood loss, volume replacement, blood pressure or heart rate [49].

Intermittent hyperbaric oxygen may satisfy this “debt” in the setting of severe anemia until hemoglobin levels can be restored to resume their normal function of transporting oxygen to the tissues to meet their minimal needs. Oxygen debt has also been described as an initiating factor of disease exacerbation in sepsis and ARDS [50]. Though not demonstrated specifically as yet in COVID-19 patients, an oxygen debt primarily due to prolonged periods of hypoxemia may benefit from HBO₂. The additional oxygen delivered under hyperbaric conditions is driven across the pulmonary membranes and dissolved in plasma to be transported to organ systems and tissues whose supply has been inadequate. The ability to restore or “pay back” this oxygen debt may represent an important effect of HBO₂ in the management of these patients with tissue oxygen insufficiencies.

On the other hand, tissue hypoxia is an uncommon cause of elevated blood lactate levels (a potential marker of “oxygen debt”) in sepsis, particularly after adequate initial resuscitation [51,52]. Other sepsis-related reasons for elevated lactate include impaired oxygen use due to mitochondrial dysfunction, which would not be ameliorated by an increase in oxygen delivery [48] and stress-related increase in glucose metabolism and impaired lactate clearance [51-53], neither of which are likely to respond to hyperoxemia. Further studies are needed to assess whether the payment of “oxygen debt” is a key mechanism for HBO₂ in COVID-19

Mobilization of stem cells

Hyperbaric oxygen has also been shown to increase the mobilization of stem cells [54]. Mesenchymal stem cells (MSC) have strong anti-inflammatory and immune regulatory functions. In addition, they can inhibit the abnormal activation of T lymphocytes and macrophages and induce their differentiation into regulatory T cell subsets and anti-inflammatory macrophages. They are known to inhibit the secretion of proinflammatory cytokines such as IL1, TNF- α , IL-6, IL-12, and IFN- γ , thereby reducing the occurrence of cytokine storms [55].

SUMMARY OF POTENTIAL MECHANISMS UNDERLYING COVID-19

PATIENT RESPONSES TO HBO₂

Patients with COVID-19 experience hypoxia, a profound inflammatory response, hypercoagulability, and may incur an oxygen debt. Hyperbaric oxygen may have an influence on all of these.

A prominent feature of COVID-19 is hypoxia due to lung dysfunction. These patients are subject to severe hypoxemia and resultant tissue hypoxia. They can be exceedingly difficult to oxygenate in spite of high oxygen levels in their breathing mix and ventilatory support. The use of extracorporeal membrane oxygenation (ECMO) has not offered a noticeable advantage in this group of severely affected patients. Anecdotally, hyperbaric oxygen has been very successful in delivering adequate oxygen to COVID patients in the chamber. Many of these patients show persistent improvement after a hyperbaric treatment when returned to their ICU room.

Much of the pathophysiology of COVID-19 relates to an excessive immune response by those infected. This immune response generates significant inflammatory and proinflammatory reactions, causing damage not only to the lung, but to the kidney, gastrointestinal tract, and other organ systems, although those who die typically do so because of respiratory failure. These inflammatory and proinflammatory effects are mediated by the production and release of excessive cytokines and chemokines, including IL-1 α , IL-1 β , IL-10, TNF- α and, prominently, IL-6. This produces what has been termed a “cytokine storm.” Usually seen several days after hospital admission, this massive release of cytokines has been noted in some patients who commonly progress to ventilator dependence, and of these, many die. Those who become ventilator-dependent have been reported to succumb to their disease in various series at rates of 50-80%. In certain other disease entities hyperbaric oxygen has been shown to return elevated cytokines to normal ranges. The work by Bosco and colleagues examining the inflammatory nature of femoral head avascular necrosis showed that HBO₂ reduced TNF- α and IL-6 [32]. In a model of traumatic brain injury, Qian and co-investigators demonstrated a reduction of IL-1 β and NLRP-3 after HBO₂ therapy [28]. HBO₂ has also been useful in other situations with high levels of inflammation such as pancreatitis, sepsis, and ulcerative colitis [37-41] and may be useful in COVID-19.

An additional major cause of morbidity and mortality is hypercoagulability contributing to the lung and other organ damage (including ARDS) and leading to myocardial and brain infarctions as well as pulmonary emboli in some patients. Anticoagulation is essential for those who develop hypercoagulability. The outcomes section of this report recommends serial assays of D-dimer to assess the severity and response to treatment of the COVID-induced hypercoagulation. In Thibodeaux’s publication, one patient receiving HBO₂ therapy had significant reductions in D-dimer with treatment, although other investigators have not reported this decrease. In a recent webinar sponsored by the

UHMS on June 20, 2020, Dr. Thibodeaux reported a consistent drop in D-dimer in his group, which now numbers 12 patients treated with hyperbaric oxygen.

Patients experiencing days of inadequate oxygenation may incur an oxygen debt. This is an additional insult related to but not identical to acute hypoxia. It has been observed in severe chronic anemia, CO poisoning, and even in sepsis. Van Meter has explained this phenomenon and reviewed the favorable effects of HBO₂ in paying the oxygen debt. Untreated, oxygen debt is a major cause of multiorgan failure [40]. With the improvement in oxygenation that occurs, HBO₂ therapy may pay the oxygen debt incurred during the patient's severely hypoxic interval.

The putative benefits of HBO₂ for COVID-19 patients, therefore, include relief of hypoxia that persists after leaving the chamber, possible repayment of any accrued oxygen debt, reduced inflammation, and a possible improvement in hypercoagulation.

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UHMS PROPOSED RESEARCH TEMPLATE CONSENT TO BE PART OF A RESEARCH STUDY

1. KEY INFORMATION ABOUT THE RESEARCHERS AND THIS STUDY

Study title: **Hyperbaric oxygen therapy in COVID-19**

Principal Investigator: [Name, credentials, institutional affiliation]*

Co-Investigator(s): [Name, credentials, institutional affiliation]

Delete if this does not apply.

Study Sponsor: [Name]

Dr. [INSERT NAME HERE] is asking you or your legally authorized representative (in which case the word “you” will refer to the person you are representing) to take part in a clinical research study with an investigational treatment for COVID-19 called hyperbaric oxygen therapy. You are being asked to participate because you have a serious condition with a newly identified coronavirus called SARS-CoV-2 infection, and there are no currently approved treatments. SARS-CoV-2 infection may result in a serious infection. SARS-CoV-2-infected patients are currently managed with general supportive care and oxygen.

This Participant Information and Informed Consent Form explains the experimental treatment to you. Your doctor or nurse will go over this form with you. Your doctor or nurse will answer all questions you have about the information in this form.

If you agree to take part, you or your legally authorized representative will be asked to sign and date this form. You will be given a signed and dated copy to keep. If neither you nor your legally authorized representative can give consent, your doctor may also decide the treatment is necessary to be given to you in an emergency situation. If this happens you will be informed that you have been enrolled in the study as soon as possible, and you will be given the chance to decide if you want to continue in the study. No one can force you to take part in or stay in this study.

This form contains information that will help you decide whether to join the study.

1.1 KEY INFORMATION

Things you should know:

- The purpose of the study is to study the effects of hyperbaric oxygen therapy on the known hypoxia (low tissue oxygen levels) and inflammatory response that is characteristic of serious COVID-19 pneumonia. Hyperbaric oxygen is FDA-approved for other conditions that have hypoxia and inflammation as part of their pathophysiology. The use of hyperbaric oxygen in the treatment of COVID-19 is experimental and considered research.
- If you choose to participate you will be asked to undergo hyperbaric oxygen treatments once or twice a day until the protocol is completed. Each treatment usually lasts about two hours.

* **NOTE:** *The text highlighted in gray indicates that the sponsoring institution must supply this information.*

- Risks or discomforts from this research include:
 - trouble clearing your ears and sinuses, which can cause pain (also called barotrauma)
 - possible, but rare, injury to your lungs both from pressure and high concentrations of oxygen
 - oxygen toxicity seizures
 - hypoglycemia/low blood sugar levels
 - changes to vision
 - risk of fire
 - chance of complication while being transported to the hyperbaric chamber room
- All of these risks are low and would be the same for each treatment in a series; the combined risk is about 1 in 10,000.
- The direct benefits of your participation are an increase in oxygenation of your tissues and a reduction in inflammation, which may decrease the severity of the disease.

Taking part in this research project is voluntary. You do not have to participate, and you can stop at any time. Please take time to read this entire form and ask questions before deciding whether to take part in this research project.

2. PURPOSE OF THIS STUDY

Hyperbaric oxygen is near 100% oxygen that is delivered at pressures greater than sea level, the equivalent of going greater than 20 feet underwater. **(Note: This can be adapted to the pressure used at your center for treatment.)** By increasing the amount of oxygen that can be carried in the blood, the tissues of the body can be oxygenated. Additionally, at high levels oxygen has a drug-like effect in reducing inflammation, particularly cytokines (inflammatory molecules). The pneumonia associated with serious COVID-19 symptoms causes a reduction in the amount of oxygen that is absorbed by the blood in the lungs, leading to hypoxia. This hypoxia is thought to trigger an inflammatory response in the lungs known as the cytokine storm. Hyperbaric oxygen is known to have a positive impact on both of these clinical manifestations in other medical conditions; this study is designed to see if hyperbaric oxygen will have the same impact on COVID-19.

3. WHO CAN PARTICIPATE IN THE STUDY

3.1 Who can take part in this study?

Eligibility criteria:

Age: 18 years or older

Sexes: All

Accepting healthy volunteers: No

Inclusion criteria:

In order to be eligible for this study an individual must meet all of the following criteria:

1. be a male or female patient older than 18 years
2. be an inpatient
3. have a positive COVID-19 test

4. experience respiratory compromise defined by oxygen saturations (SpO₂) lower than 90% on room air. (**Note: the individual institution can set its own determinant for serious compromise in oxygen status.**)
5. Ability to sign the consent form or availability and willingness of designated responsible party to sign.

Exclusion criteria:

1. pregnancy
2. have an untreated pneumothorax
3. unstable blood pressure or irregular heartbeats
4. mechanical ventilation, invasive or non-invasive
5. local guidelines for exclusion for hyperbaric oxygen therapy

3.2 How many people are expected to take part in this study?

Note: See Appendix 1 of the 'Study design' section for a calculator that may be used to determine the sample size.

4. INFORMATION ABOUT STUDY PARTICIPATION

4.1 What will happen to me in this study?

The procedures or document completion listed in the following table will be accomplished for you at the specified time intervals:

(See the chart on the following page)

PROCEDURE (what will happen)	Baseline (to see if you qualify)	Days 1, 2, 3, 4, 5 (up to 10)	Day X* follow up	Day Y* follow up	Z* month follow up
Informed consent	X				
Review of your health history	X				X
Review of any changes in your health since last visit, including any side effects you get		X	X	X	X
Review of medications you are taking	X	X	X	X	X
Physical examination	X	X	X	X	X
Measure of your vital signs: (blood pressure, heart rate, breathing rate, temperature, incentive spirometry)	X	X	X	X	X
Take blood samples for routine/ordered tests (chemistry, hematology, liver function tests, kidney function tests, blood gases, TCOM)	X	X	X	X	X
Review your X rays or CT, if available	X	X	X	X	X
Get study treatment		X			
Wong-Baker FACES (for respiratory effort) or NEWS-2 (National Early Warning Score)		X	X	X	X

* Indicates suggested time intervals for follow-up to be determined locally:

Suggested Intervals: X = Day 3 • Y = Day 7 • Z = 3 to 6 months

Note: The local investigator may choose different time intervals.

Follow-up visits	Description
Day X and Day Y follow-up visits	If you are still in the hospital on Day X and Day Y all the procedures described in the procedures table will be performed. If you have been discharged from the hospital you will have a phone call on Day X and Day Y; the study doctor or study staff will only review any health changes since your last visit, including any side effects you experience, and review medications you are taking. NOTE: Some centers may opt for in clinic follow-up visits.

Suggested Intervals: X = Day 3 • Y = Day 7 • Z = 3 to 6 months

NOTE FOR INVESTIGATORS: Long-term follow-up is highly recommended at three to six months, then annually for five years. All health events to include but not limited to brain, heart, lung, renal and thrombotic events (pulmonary embolus, thrombotic MI, digit or extremity thrombosis, cerebral or mesenteric thrombosis) should be recorded.

Additional information that should be provided in your personalized consent form should include:

- The location where research activities/procedures will take place
- Description of all research interactions/experimental activities or interventions
 - hyperbaric oxygen treatment
 - transcutaneous monitoring (non-invasive)
 - daily blood draws for standard/required testing
 - pulse oximetry
 - all hospitalist-ordered interventions
- Data collection procedures
 - FACES for respiratory effort
 - NEWS-2 evaluation
 - quality of life surveys (as determined by researchers)
 - AV recording as determined to be necessary
 - observation of patient while under treatment

NOTE FOR INVESTIGATORS: A visual analogue scale employing facial expressions to pictorially describe severity of dyspnea similar to a scale commonly used for pain level is available and referenced in the 'Outcome Section.'

- Experimental intervention
- Standard interventions
 - All hospitalist/ICU physician-ordered therapy/interventions
- Use of medical records
- Linking of data collected or created as part of the research to other information, such as protected health information, administrative data such as from the U.S. Census or state agencies, or publicly available information

4.2 How long will this experimental treatment last?

The experimental treatment will be given for 5 to 10 hyperbaric treatments depending upon the response and follow-up as defined in Section 4.1.

4.2.1 When will my participation in the study be over?

Your participation will end when the last interview takes place X-Y months after your discharge from the hospital.

4.3 If I decide not to take part in this study, what other options do I have?

There may be other ways of treating your condition if you do not want to be in this research study. Check with your health care provider to discuss other options.

5. INFORMATION ABOUT STUDY RISKS AND BENEFITS

5.1 What risks will I face by taking part in the study? What will the researchers do to protect me against these risks?

The researchers will try to minimize these risks by instruction as to how to clear your ears, careful monitoring of blood sugar levels if necessary, and by careful chamberside monitoring by staff.

As of 2020, over 1 million people have been treated with hyperbaric oxygen therapy. Patients who received hyperbaric oxygen shows no significant long-term complications. As of June 1, 2020, more than 100 people have been treated with hyperbaric oxygen therapy for COVID-19. Published trials have shown very few, if any, complications. None of these trials had a placebo (like a sugar pill) arm since oxygen is necessary for the treatment of COVID-19 viral pneumonia. In these published trials no one experienced significant side effects from the hyperbaric oxygen therapy. Some patients still went onto intubation because of disease progression.

For informational risks state: Because this study collects information about you, a risk of this research is a loss of confidentiality. See Section 8 of this document for more information on how the study team will protect your confidentiality and privacy.

5.1.1 What happens if I get hurt, become sick or have other problems because of this research?

If you become sick or injured as a direct result of taking the experimental treatment and/or following the procedures, the site/treating doctor will provide you with medical treatment. You should immediately contact your doctor at the contact information shown on the first page of this form in the event you experience any experimental treatment-related illness or injury.

You do not give up any legal rights by signing this form. You are not prevented from seeking to collect compensation for injury related to malpractice, fault or blame on the part of those involved in the experimental treatment.

A new public health declaration called the *Public Readiness and Emergency Preparedness Declaration* (PREP) was issued by the Department of Health and Human Services on March 10, 2020.

“This declaration may limit the legal rights of a subject participating in a COVID-19 clinical study that uses a drug, device or vaccine designed to treat, diagnose, cure or prevent COVID-19.”

5.2 How could I benefit if I take part in this study? How could others benefit?

You may not receive any personal benefits from being in this study. However, you might benefit from being in the study by reducing your risk of worsening lung function. This includes the potential need to place a breathing tube in your lungs and attach you to a ventilator. It may also reduce your length of stay in the hospital. Additionally, others may benefit from the knowledge gained from this study.

5.3 Will the researchers tell me if they learn of new information that could change my willingness to stay in this study?

Yes, the researchers will tell you if they learn of important new information that may change your willingness to stay in this study.

6. ENDING THE STUDY

6.1 If I want to stop participating in the study, what should I do?

You are free to leave the study at any time. If you leave the study before it is finished there will be no penalty to you. If you decide to leave the study before it is finished, please tell one of the persons listed in Section 9 under "Contact Information." If you choose to tell the researchers why you are leaving the study your reasons may be kept as part of the study record. The researchers will keep the information collected about you for the research unless you ask us to delete it from our records. If the researchers have already used your information in a research analysis it will not be possible to remove your information. In any case, you will never be identified.

7. FINANCIAL INFORMATION

7.1 Will I be paid or given anything for taking part in this study?

The experimental protocol, hyperbaric oxygen treatment used in this treatment, will be given to you at no charge.

You may be responsible for fees for lab tests and procedures.

You or your usual health care payer will be responsible for any other health care costs.

7.2 Who could profit or financially benefit from the study results?

Note: This section pertains to the financial circumstances applicable to the center treating patients.

This information as identified by gray shading must be supplied by the local center.

The subheadings under this question relate to potential conflict of interest scenarios. Delete this section 7.2 if none of these scenarios apply to this study. If a person or organization involved in the conduct of this study has or may have a conflict of interest, address any of the following issues that may apply:

- How is the research supported or financed?
- Where and by whom was the study designed (i.e., industry-sponsored versus investigator-initiated)?
- Do individuals or the institution receive any compensation that is affected by the study outcome?
- Do individuals or the institution
 - (1) have any proprietary interests in the product (including patents and licensing agreements)?
 - (2) have an equity interest in the sponsor?
 - (3) receive significant payments of other sorts (e.g., grants or consultant retainers); and/or
 - (4) receive payment per participant or incentive payments?

The company whose product is being studied:

Disclose under this subheading if a company or other organization has an ownership or other financial interest in the product or technology under study, and might profit or otherwise benefit from the outcome of the study, particularly if the company/organization is also the sponsor of the study or has a financial relationship with the investigators (as described under the next sub-heading). Delete this subheading if it does not apply.

The researchers conducting the study:***Information regarding suggested language for this section:***

If any of the investigators on the study have an ownership, consulting, or similar financial relationship with the sponsor, they should disclose it here. If your plan is reviewed and approved by the Institutional Conflict of Interest Committee (ICOC), your plan may include suggested/required language. Please review your plan accordingly. Delete this sub-heading if it does not apply.

Suggested language if there is stock ownership:

[STATE CONFLICTED INDIVIDUAL'S NAME HERE] owns stock or stock options in [COMPANY NAME] who is the [SPONSOR/MANUFACTURER] of the [PRODUCT] being studied. Delete this subheading if it does not apply.

Suggested language if there are other financial interests (paid):

[STATE CONFLICTED INDIVIDUAL'S NAME] serves as a paid [STATE POSITION] for [COMPANY NAME] on topics [RELATED/UNRELATED] to this study. [COMPANY NAME] is the [SPONSOR/MANUFACTURER] of the [PRODUCT] being studied. Delete this subheading if it does not apply.

Suggested language if there is other non-financial interests (unpaid):

[STATE CONFLICTED INDIVIDUAL'S NAME] serves as an unpaid [STATE POSITION] for [COMPANY NAME] on topics [RELATED/UNRELATED] to this study. [COMPANY NAME] is the [SPONSOR/MANUFACTURER] of the [PRODUCT] being studied. Delete this sub-heading if it does not apply.

Suggested language if there is a relative/family-related conflict of interest:

[STATE CONFLICTED INDIVIDUAL'S NAME, STATE RELATIONSHIP TO YOU.] Delete this sub-heading if it does not apply.

8. PROTECTING AND SHARING RESEARCH INFORMATION**8.1 How will the researchers protect my information?**

Describe procedures that will be followed to keep participant information secure and confidential.

Note: any research data that will be linked to individual identifiers is considered identifiable.

8.2 Who will have access to my research records?

There are reasons why information about you may be used or seen by the researchers or others during or after this study. Examples include: Study sponsors or funders, auditors and/or the Institutional Review Board (IRB) may need the information to make sure that the study is done in a safe and proper manner.

8.3 What will happen to the information collected in this study?

NOTE: *Gray shaded areas here are also unique to the investigational site and information must be supplied by the local center.*

We will keep the information we collect about you during the research to report our results and make future recommendations about the use of hyperbaric oxygen in the treatment of patients[for future research projects/for study recordkeeping or other purposes (describe)]. Your name and other information that can directly identify you will be stored securely and separately from the research information we collected from you. Note: any research data that will be linked to individual identifiers is considered identifiable. Linking of data to individual identifiers, length of time data will be linked to identifiers, and whether destruction of identifiers will occur should be described here.

For longitudinal research: The researchers [plan to/may] contact you again as part of this project.

Or: We will not keep your name or other information that can identify you directly.

The results of this study could be published in an article or presentation but will not include any information that would let others know who you are.

If the investigator wishes to identify a participant in a presentation or article, state: The results of this study could be published in an article or presentation but would not include any information that would let others know who you are without your permission.

8.4 Will my information be used for future research or shared with others?

The Common Rule requires that investigators tell participants whether their data will be stored and shared for future research, even if de-identified.

We may use or share your research information for future research studies. If we share your information with other researchers it will be de-identified, which means that it will not contain your name or other information that can directly identify you. This research may be similar to this study or completely different. We will not ask for your additional informed consent for these studies.

If you plan to retain and share identifiable information for unspecified future research, state: We would like to share your identifiable information with other researchers for future research. We will ask for your consent to do so at the end of this form. You can be a part of this current research project without agreeing to this future use of your identifiable information.

Or: We will not store your research information or share it with other researchers. The IRB does not recommend the use of this statement, as it will preclude the secondary use of these data in the future.

8.4.1 Special Requirements

Gray shaded areas must be supplied by the local center.

If you will register your project on *clinicaltrials.gov* voluntarily or in order to meet journal or other requirements, include the following: This trial will be registered and may report results on *www.clinicaltrials.gov*. This site will not include information that can identify you. At most, the website will include a summary of the results. You can search this website at any time.

For projects that will contribute research data to a repository, use the following language: We will put the information we collect from you into a repository. The repository contains information about many people. Your information will be [de-identified – or: labeled with a code, instead of your name or other information that could be used to directly identify you.] Add additional information regarding data protections provided by the repository.

9. CONTACT INFORMATION

Gray shaded areas must be supplied by the local center.

Who can I contact about this study?

Please contact the researchers listed below to:

- Obtain more information about the study
- Ask a question about the study procedures
- Report an illness, injury, or other problem (you may also need to tell your regular doctors)
- Leave the study before it is finished
- Express a concern about the study

Principal investigator:

Email:

Phone:

Study coordinator (if applicable; delete if does not apply):

Email:

Phone:

If you have questions about your rights as a research participant, or if you wish to obtain information, ask questions or discuss any concerns about this study with someone other than the researcher(s), please contact the following: (The local investigator should give the contact information for another official at his or her institution including the hospital CEO, chief of staff or chairperson of the ethics committee or IRB.)

10. YOUR CONSENT

Gray shaded areas must be accomplished by the local center.

Consent/Assent to participate in the research study

By signing this document, you are agreeing to be in this study. Make sure you understand what the study is about before you sign. I/We will give you a copy of this document for your records and I/we will keep a copy with the study records. If you have any questions about the study after you sign this document, you can contact the study team using the information in Section 9 provided above.

I understand what the study is about, and my questions so far have been answered. I agree to take part in this study.

Print Legal Name: _____

Signature: _____

Date of Signature (mm/dd/yy): _____

Investigators are reminded that they should give a copy to the participant and retain a full copy of the consent including a copy of the signature page as part of your research records. Participants must complete all of the required information (printed name, signature and date).

Parent or legally authorized representative permission (*delete this section if it does not apply*)

By signing this document, you are agreeing to [your child's] **or** [the person's named below] participation in this study. Make sure you understand what the study is about before you sign. I/We will give you a copy of this document for your records. I/We will keep a copy with the study records. If you have any questions about the study after you sign this document, you can contact the study team using the information provided above.

I understand what the study is about, and my questions so far have been answered. I agree for [my child] **or** [the person named below] to take part in this study.

Print Participant Name

Print Parent/Legally Authorized Representative Name

Relationship to participant: Parent Spouse Child Sibling Legal guardian Other

Signature

Date

Printed Parent/Legally Authorized Representative Name (when two parent signatures are required)

Two signatures are required for more than minimal risk research with no direct benefit to the child.

Relationship to participant: Parent Sibling Legal guardian Other

Signature

Date

Reason second parent permission was not collected:

- Parent is unknown
- Parent is deceased
- Parent is incompetent
- Only one parent has legal responsibility for care and custody
- Parent is not reasonably available*; explain:

* Note: "Not reasonably available" means the other parent cannot to be contacted by phone, mail, email, or fax, or his or her whereabouts are unknown. It does not mean that the other parent is at work or home, or that he or she lives in another city, state or country.

11. OPTIONAL CONSENT

Gray shaded areas must be accomplished by the local center.

Separate signatures should be obtained for specific activities when those activities are optional. Whether an activity is required or optional must be clearly described in the main body of the consent document. Some common optional research activities are included below. Delete this section or any of the following consent statements that do not apply to your research. Participants must complete all of the required information (printed name, signature and date) if an optional consent section is offered.

**Consent to use [video recordings/audio recordings/photography] for purposes of this research.
(Use this ONLY if recording is not required to participate in the research.)**

This study involves [video recordings/audio recordings/photography]. If you do not agree to be [video recorded/audio recorded/photographed], you can still take part in the study.

- _____ Yes, I agree to be [video recorded/audio recorded/photographed].
- _____ No, I do not agree to be [video recorded/audio recorded/photographed].

Print Legal Name: _____

Signature: _____

Date of Signature (mm/dd/yy): _____

Consent to use of video recordings, audio recordings or photographs for publications, presentations or for educational purposes.

I give permission for audio recordings/video recordings/photographs made of me as part the research to be used in publications, presentations or for educational purposes.

- _____ Yes
- _____ No

Print Legal Name: _____

Signature: _____

Date of Signature (mm/dd/yy): _____

Consent to use and/or share your identifiable information for future research

The researchers would like to use your identifiable information for future research that may be similar to or completely different from this research project. Identifiable means that the data will contain information that can be used to directly identify you. The study team will not contact you for additional consent to this future research. We may also share your identifiable information with other researchers. You can contact us at any time to ask us to stop using your information. However, we will not be able to take back your information from research projects that have already used it.

Note: This separate consent is not necessary if you will only store and share de-identified data or biospecimens.

_____ Yes, I agree to let the researcher(s) use or share my personally identifiable information for future research.

_____ No, I do not agree to let the researcher(s) use or share my personally identifiable information for future research.

Print Legal Name: _____

Signature: _____

Date of Signature (mm/dd/yy): _____

Include this HIPAA Authorization form if your research project requires access to or disclosure of identifiable Protected Health Information from a HIPAA-covered entity as part of the research

HIPAA authorization

Authorization to Use or Disclose (Release) Health Information that Identifies You for a Research Study

If you sign this document you give permission to [name or other identification of specific health care provider(s) or description of classes of persons, e.g., all doctors, all health care providers] at [name of covered entity or entities] to use or disclose (release) your health information that identifies you for this research study.

The health information to be used for this research includes: [Provide a description of information to be used or disclosed for the research project. This may include, for example, all information in a medical record, results of physical examinations, medical history, lab tests, or certain health information indicating or relating to a particular condition.]

The health information listed above may be used by and/or disclosed (released) to: [Name or class of persons involved in the research; i.e., researchers and their staff]

[Name of covered entity] is required by law to protect your health information. By signing this document, you authorize [name of covered entity] to use and/or disclose (release) your health information for this research. Those persons who receive your health information may not be required by Federal privacy laws (such as the Privacy Rule) to protect it and may share your information with others without your permission, if permitted by laws governing them.

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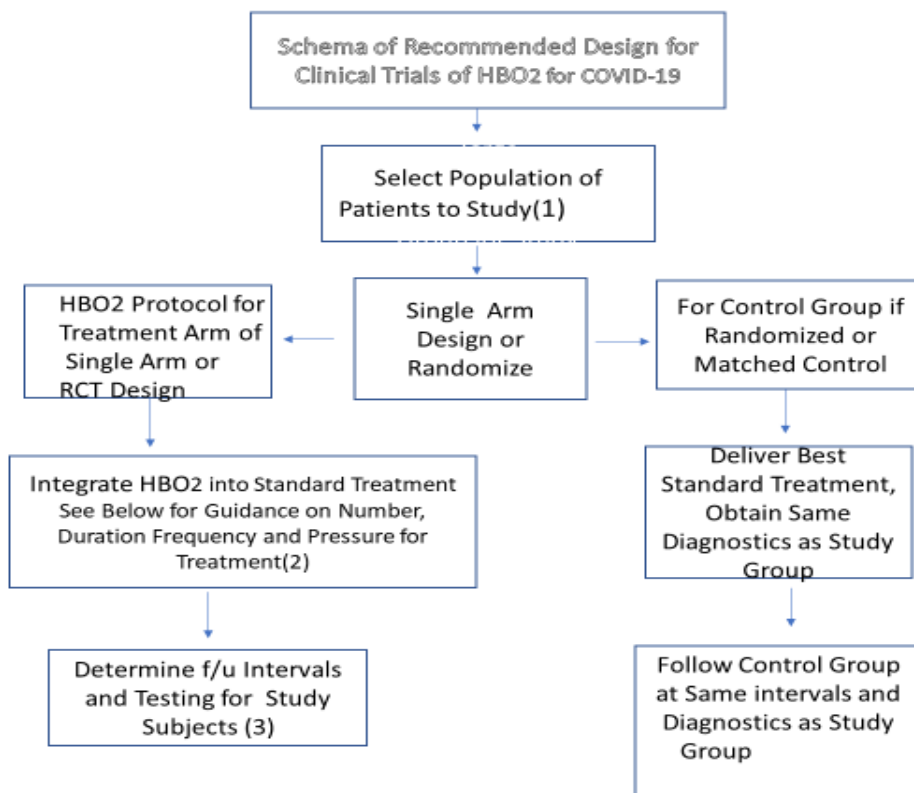
Signature of participant or participant's personal representative

Date

Printed name of participant or participant's personal representative

If applicable, a description of the personal representative's authority to sign for the participant

Clinical Trial Design Recommendations



1. We recommend initially that studies target the moderately severely affected (see text)
2. We favor a standard profile to expedite multi-center analysis (2.0 ATA, 90 minutes, without air breaks 5-10 treatments) (see text)
3. We offer recommendations for diagnostics and time and interval to be obtained. Some are felt to be essential. Others obtain if possible (See text)

Research protocol recommendations for COVID-19 studies

This guidance is designed to encourage researchers to conduct clinical trials investigating the role of hyperbaric oxygen (HBO₂) treatment in COVID-19 care. These recommendations are designed to fit local, national, and international regulations for research subject protection [1] (refer also to online resources at *clinicaltrials.gov* [2]) and may evolve as experience with the virus grows.

Rationale

- Initial experience from sites using HBO₂ to treat COVID-19 patients indicates that patients receive definitive relief from hypoxia and slow their respiratory rates. This may provide them with a needed break from otherwise unremitting hypoxia.
- Experience to date has not shown evidence of immediate adverse effects of HBO₂ (e.g. worsening respiratory status during or immediately after treatments). Data on longer-term effects are needed.
- Because HBO₂ virtually always requires patient transport from the hospital bed to the hyperbaric unit, safety during this vulnerable time is an important issue.

Primary recommended targets for study:

For many centers Phase I/II trials may be most practicable [2]. Oxygen is already established as a mainstay of therapy in COVID-19 treatment. Studies that establish the additional benefits or potential harms from HBO₂ are needed. These studies should focus on safety, dosing, and response to treatment. Results should establish unique benefits from HBO₂ (e.g., definitive hypoxia relief for a period of time) versus adverse effects.

The Committee encourages well-designed randomized controlled trials as the gold standard for the highest level of evidence.

Patient selection presents a challenge. The patients most in need of better options for oxygenation are those in the severe category (those with progressive hypoxemia requiring high flow oxygen, NRB, BIPAP or who are within 24-48 hours of intubation). These patients also are at higher risk for decompensation during transport to and from the hyperbaric chamber and when leaving the hyperbaric chamber transitioning back to normobaric oxygen. Facilities proceeding with clinical trials must be prepared to provide adequate respiratory support for this vulnerable patient subset at all points in their care.

Those caring for these patients must be able to provide intubation, mechanical ventilation, and resuscitation in the hyperbaric facility if needed. Staff versed in critical care skills and ACLS™ [3] need to be readily available or include direct supervision by a BC/BE intensivist assisting those providing HBO₂ care [4,5]. In-chamber EKG monitoring should be used. Continuous pulse oximetry monitoring during transport is essential. Emergency protocols must be rehearsed prior to initiating treatments.

- Safety concerns and protection must be extended to include staff and those unintentionally exposed during patient transport and within the hyperbaric facility. Adequate disinfection of the chamber after a COVID-19 patient treatment is essential [6]. If treating non-COVID patients on the same day as COVID-19 patients, follow all CDC and hospital recommendations necessary to prevent cross-contamination.

- Recommendations for selection criteria:
 - Patients judged stable for treatment according to the facility capabilities.
 - Non-intubated patients or those requiring mechanical ventilation.
 - Those with recalcitrant hypoxia despite ongoing oxygen supplementation with the following results:
 - Increased oxygen debt noted by progressive increases in oxygen supplementation.
 - Impending progression to endotracheal intubation.
 - Persistent tachypnea with respiratory rate > 24.
 - Persistent progressive desaturation <90% despite oxygen supplementation.
 - Patients with cognitive ability to consent for their own treatment [7].
 - Able to comply with instructions . . .
 - With no overriding contraindications for HBO₂ [8] and,
 - Able to tolerate at least an initial recommended treatment target protocol of 2.0 ATA for 90 minutes without planned air breaks once a day.
 - Utilization review mechanism required after 10 treatments within any two- to 10-day period
 - Post-treatment follow-up at three, six and 12 months, then annually for up to five years.
- Study sites may elect to study lower pressures (<2.0 ATA) or higher pressures (>2.0 ATA) with longer or shorter treatment times and air breaks; however, we highly recommend adhering to standardized protocols to allow greater consistency for possible future combined analysis of trials from multiple sites.
 - Preliminary clinical experience shows evidence of patient deterioration even in chamber during air breaks. We therefore advise against providing air breaks. Restricting treatment protocol to no greater than 2.0 ATA eliminates the need for air breaks.
- We encourage all study sites to stage patients according to severity scoring schemata, recommended in the outcomes section, along with collection of clinical and laboratory data to promote consistency in methods and outcomes for comparative analysis.
- We recommend studies that will incorporate matched control groups into the study design:
 - As possible all study designs should eventually transition to a randomized controlled trial.
 - We encourage investigators to collect data on other COVID-19 positive patients or persons under investigation for COVID-19 with similar risk profiles and progression of serious respiratory and critical illness who are not offered HBO₂ treatment, for comparative analysis.

Secondary outcome measures

- Investigators must collect data with application to the overall treatment of COVID-19. Patients presenting in earlier stages may contribute to better understanding of the severity of illness scoring, providing improved prognostic power for more accurate predictions for resource utilization, isolation, intubation and other surrogate, short term outcomes with or without HBO treatment.
- Investigators should keep a focus on eventually expanding research beyond Phase I/II trials. If adequate evidence supports initiation of a large multi-institutional RCT, apply for grant support from government and independent foundations. Such studies should incorporate HBO₂ into other evolving treatment paradigms. For sample size calculation to achieve adequate study power, see Appendix 1.

- Collection of data is recommended in the outcome section for ongoing biorepository and data registry storage for future analysis as the science develops.
- We encourage all investigators to publish all individual study results, conclusions and meta-analyses in high impact journals, both within and outside of the hyperbaric community for greatest distribution and effect.

Appendix 1

An online calculator for determining the sample size needed for an adequately powered clinical trial

The online calculator whose address is given below provides guidance for determining the sample size needed to generate results with adequate power to show the desired change:

<https://clincalc.com/stats/samplesize.aspx>

The following example illustrates a calculation using the following assumptions:

1. Absolute survival is the primary outcome.
2. Survival for patients with moderately severe disease is estimated to be 60%. When hyperbaric oxygen is added to the management, the investigators want to show an improvement to 85%. (Note these numbers are given only for illustration and should not be used unless confirmed by the local investigator.)
3. After entering these assumptions, the calculator indicates that 49 subjects each in the study group and control group would be required to detect this change with only a 5% chance of a false positive result and only a 20% chance of a false negative result. Medical literature typically allows for this level of uncertainty for the so-called Type I and Type II errors.

This is an example only. The individual investigator will have to decide on anticipated level of improvement for the outcome determinants they want to detect. These calculations are important since they may show that it is impractical for a single center to enroll all the patients needed (98 in this case). If a multicenter approach is needed, the consistent HBO₂ protocol offered here provides advantages because results from several centers can be combined to achieve results that are scientifically and statistically significant.

For those who want to do a more involved power calculation, the program G*Power at the link below is one option.

<https://www.psychologie.hhu.de/arbeitsgruppen/allgemeine-psychologie-und-arbeitspsychologie/gpower.html>

Outcome determinants for COVID-19 studies

Gather all measures in this section in the same manner from both matched or randomized control and treatment arms.

Primary outcome measures (*Collect this data on all patients for any HBO₂/COVID-19 trial*):

- Primary outcome is a 28-day all-cause mortality from study enrollment following final HBO₂ treatment
 - Long-term follow-up is highly recommended at three and six months, then annually for five years – all health events to include but not limited to brain, heart, lung, renal and thrombotic events (pulmonary embolus, thrombotic MI, digit or extremity thrombosis, cerebral or mesenteric thrombosis).
- Duration for return to full activities of daily living (ADLS) or Modified Rankin scale for persistent disability.
- Clinical response criteria is the second most important outcome:
 - Highly recommended is use of clinical improvement based on the World Health Organization (WHO) Ordinal Scale (Tables 1 and 2).
 - At a minimum the following parameters must be recorded: respiratory rate, vitals, pulse oximetry, O₂ requirements and delivery route (including CPAP/BiPAP/etc.), serial blood gases—per local protocol.
- Incidence of intubation (within 24 hours of initiating HBO₂ and for duration of hospitalization) and disposition to home, rehab or skilled nursing facility.
- Total number of days on supplemental oxygen both before and after HBO₂ with type of oxygen therapy delivery method specified to include: low flow oxygen by nasal cannula, high-flow nasal cannula (HFNC), non-invasive positive pressure ventilation (NIPPV – includes BiPAP, CPAP), and invasive mechanical ventilation (intubation)).
- Duration of intubation or NIPPV.
- Length of hospital stay (LOS).
- Use and duration of ECMO (if treated).

Table 1. WHO Ordinal Scale

1. Ambulatory, no limitation of activities
2. Ambulatory, limitation of activities
3. Hospitalized, no oxygen therapy
4. Hospitalized, oxygen by mask or nasal prongs
5. Hospitalized, non-invasive ventilation or high flow oxygen
6. Hospitalized, intubation and mechanical ventilation
7. Hospitalized, ventilation + additional organ support (pressers, RRT, ECMO)
8. Death

Table 2. Proposed Modified WHO Ordinal Scale

1. Ambulatory, no limitation of activities
2. Ambulatory, limitation of activities
3. Hospitalized, no oxygen therapy
4. Hospitalized, ≤4 liters per minute (lpm) oxygen by nasal cannula
5. Hospitalized, > 4 liters per minute (lpm) oxygen by nasal cannula or face mask (no high flow oxygen)
6. Hospitalized, oxygen by CPAP, BIPAP, high-flow mask, or high-flow nasal cannula
7. Hospitalized, intubation and mechanical ventilation
8. Hospitalized, ventilation + additional organ support (pressers, RRT)
9. Hospitalized, ECMO
10. Death

NOTE: A visual analogue scale employing facial expressions to pictorially describe severity of dyspnea similar to the scale commonly used for pain level is available and referenced below.

Secondary outcome measures

- Incidence of renal injury
- Change from pre-treatment to post treatment values for liver function tests (LFT's), LDH, CRP, ESR, procalcitonin, ferritin, D-dimer and fibrinogen. If available IL-1-a/b, IL-6, TNF- α .
- Time to defervescence (temperature lower than 100°F/37.8°C sustained for more than 24 hours)
- Additional association with comorbidities specified below
- Change in pre-treatment to post-treatment respiratory status determined by pulmonary function tests (if pre-treatment PFTs are available) and CXR/CT improvement
- Collect sera, plasma and DNA for later use or analysis – see frozen serum recommendations below

Demographic and other data collected for each patient:

- Age, sex, ethnicity
- Social history: tobacco use, alcohol use, illicit drug use/abuse
- Comorbidities: obesity, diabetes, PAD/CVD, immunologic or neurologic disease, malignancy, autoimmune diseases, sickle cell, etc.
- List of pre-hospital medications

Other considerations for cohort comparison in both arms:

- Exposure history: including occupation, adherence to social distancing, sick contacts
- Source of infection: community-acquired vs. hospital/health worker-acquired
- Duration of symptoms (time from symptoms to presentation in ED)
- Prevalence of COVID-19 in area or region
- CT/CXR evidence of interstitial opacity (severity/evidence of consolidation)
- O₂ saturation and respiratory rate averaged over 2-4 hours prior to HBO₂ treatment and 2-4 hours post treatment, with indication of respiratory rate counted or mechanically documented.
- Local assessment of severity of disease, consider using the Brescia-COVID respiratory severity scale (BCRSS) schema [9].
- Prevalence of other patients evaluated at the hospital for other infections, pneumonias or desaturation episodes as well as persons of interest for COVID-19 who did not receive HBO₂
- Other signs: stridor, apprehension, level of consciousness, ability to speak in full sentences while at rest without respiratory difficulty
- Consider using the asthma visual analog scale (VAS) [10-12] or incentive spirometry as other measures of respiratory effort
- Documented increase in FiO₂ whether by nasal cannula, mask or NIPPV over preceding 12 hours
- Evidence of hypercoagulable disorders – thromboembolic events and multi system inflammatory syndrome in children (MIS-C) including cutaneous manifestations such COVID toes.
- Other treatments used in the patient's course of care prior to HBO₂ treatment including:
 - proning
 - convalescent plasma
 - remdesivir
 - hydroxychloroquine
 - azithromycin
 - BiPap/CPAP
 - aerosolized treatments
 - anticoagulant therapy
 - acetaminophen/NSAID or steroids
 - drugs that work on the CRS factors such as IL-a/b antagonists, tocilizumab (IL-6 antagonist/antibody), JAK inhibitors, TNF antagonists are especially important to document
 - interferon
 - any other new treatments as they develop

Consider use of the following algorithms:

BCRSS – outcome per algorithm (wheezing, unable to speak in full sentences while at rest or minimal effort, RR>22, PaO₂<65mmHg or SVO₂< 90%, repeat CXR significantly worsening).

- This system has not been externally validated outside of Italy.
- A Yes answer to one of the 4 questions puts the patient at a Level 1, with recommendations for treatment to include supplemental oxygen and monitoring oximetry, plus addition of antivirals and/or CQ/HCQ.
- A Yes answer to any 2 puts the patient at a Level 2 for treatment recommendations to include increased monitoring with frequent clinical evaluation and consider adding dexamethasone to Level 1 recommendations.
- A Yes answer to 3 or 4 puts the patient at a Level 3 for treatment recommendations includes addition of CXR every 2 days, ABGs BID and NIPPV or high flow oxygen
- For worsening beyond a Level 3 treatment regimen intubation is recommended

Table 1: Brescia-COVID Respiratory Severity Scale (BCRSS)/Algorithm

[Patient has COVID-19 pneumonia or COVID-19 symptoms for ≥7 days] AND [Patient is PCR+ OR high suspicion for COVID-19/PCR pending]	
Patient wheezing OR unable to speak in full sentences while at rest/with minimal effort	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes
Respiratory rate >22	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes
PaO ₂ <65 mmHg or SpO ₂ <90%	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes
Repeat CXR is significantly worsening	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes

National Early Warning System (NEWS): Determines the degree of illness of a patient and prompts critical care intervention [13].

- The NEWS was retrospectively validated against other early warning systems and found to be more sensitive, but this validation has not yet been published.
 - It has been endorsed by the UK National Health System
- NEWS should not be used in patients under 16 years of age or pregnant women.
- NEWS should be administered and rechecked frequently for patients at risk with confirmed or suspected COVID-19 infection
- Increase in score from baseline needs clinical evaluation but a set numeric score has not been validated to determine when intubation is necessary

Chart 1: The NEWS scoring system

Physiological parameter	Score						
	3	2	1	0	1	2	3
Respiration rate (per minute)	≤8		9–11	12–20		21–24	≥25
SpO ₂ Scale 1 (%)	≤91	92–93	94–95	≥96			
SpO ₂ Scale 2 (%)	≤83	84–85	86–87	88–92 ≥93 on air	93–94 on oxygen	95–96 on oxygen	≥97 on oxygen
Air or oxygen?		Oxygen		Air			
Systolic blood pressure (mmHg)	≤90	91–100	101–110	111–219			≥220
Pulse (per minute)	≤40		41–50	51–90	91–110	111–130	≥131
Consciousness				Alert			CVPU
Temperature (°C)	≤35.0		35.1–36.0	36.1–38.0	38.1–39.0	≥39.1	

Laboratory data to collect (depending on availability):

- D-dimer*
- fibrinogen
- CRP* and or any other inflammatory markers – specific or non-specific, daily
- LDH daily*
- lactic acid
- blood gases* (venous or arterial)
- ferritin*
- procalcitonin
- CBC-with differential*
- CMP (LFTs)*
- additional inflammatory markers including IL-1, IL-6, IL-10, TNF-α
- CXR/ CT*
- Frozen sera for biorepository use is highly recommended.
 - Hospital or facility protocols for obtaining and storing frozen serum should apply.
- If hospital policy is unavailable consider attached suggested instructions from the Buckey Research Lab for blood processing for the isolation and cryopreservation of plasma from whole blood as an example.
- If protocols are not available consider drawing three red-top tubes, one blue-top, one green-top (for plasma), and two purple-top tubes (for DNA).
- Biorepository collection should be mandatory for any RCT considered.

**Essential minimum laboratory data to collect at onset of HBO₂ treatment and within 24 hours after completing final treatment.*

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