UHMS Position Statement: Hyperbaric Oxygen (HBO_2) for COVID-19 Patients

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As the worldwide crisis of COVID-19 increased and without any substantial therapeutic or preventative breakthroughs, increased consideration was given to the utilization of hyperbaric oxygen (HBO_2) therapy to overcome COVID-19 hypoxemia. This application has its origins in the demonstrated success in treatment of severe anemia and carbon monoxide poisoning, both conditions where hypoxemia is treated by hyperbaric oxygen. In response to requests for guidance the UHMS published the original position statement on April 8, 2020; this position statement was also jointly approved by the American College of Hyperbaric Medicine (ACHM).

This position statement supported IRB (Institutional Review Board) approved clinical trials but did not advocate treatment off-protocol. In the interim, as knowledge about the SARS-Cov-2 and its mechanisms of injury has evolved, there still have been no major successes in developing definitive pharmacologic interventions. Studies have reported some advantage for patients treated with convalescent plasma, remdesivir and steroids, although none of these provide outright cures and at best mitigate severity and modestly impact length of hospital stays or survival. The initial fervor for hydroxychloroquine with or without azithromycin has mostly faded. Prone patient positioning has empirically been shown to improve patient oxygenation. Some have employed ECMO (extracorporeal membrane oxygenation) as a last-ditch intervention to provide patients with adequate oxygen to support minimum metabolic requirements and sustain life. Significant and rapid progress has been reported in the development of vaccines, and our hopes are that a safe and effective vaccine will be available no later than early next year (2021). Until that time the need for more effective therapies persists.

It is in this light that we present a brief discussion of the role for hyperbaric oxygen in COVID-19 and state the updated position of the Undersea and Hyperbaric Medical Society, also approved by the ACHM (American College of Hyperbaric Medicine) in its appropriate application. The United States now leads all nations of the world in both incidence and fatalities due to COVID. In response, therapeutic approaches have included new pharmacologic agents as well as novel applications of existing therapies [1]. Hyperbaric oxygen intervention in COVID-19 has been reported in the original case series out of China [2] and centers within the U.S. to include a case series out of Louisiana [3] and most recently a small case-control trial from NYU [4].

A consistent finding from these publications is that HBO_2 has been safe despite concerns that this group of patients, who are maintained continuously on high FiO_2s (fractions of inspired oxygen), would be especially sensitive to pulmonary oxygen toxicity when a course of HBO_2 was

added to their oxygen load. Additionally, investigators report an almost instantaneous relief in fatigued patients laboring to breathe when placed in the hyperbaric chamber under pressure. They are observed to relax and even achieve some much-needed sleep due to the success of HBO_2 in delivering adequate oxygenation [3,5].

"Rationale, study design considerations, and protocol recommendations for treating COVID-19 patients with hyperbaric oxygen" posted on the UHMS website is a report to the UHMS membership from the UHMS Research Committee which presents a strong physiologic and biologic basic science case to support the use of hyperbaric oxygen [6]. In addition to effectively delivering oxygen to patients who may suffer from bilateral pneumonias and exhibit a ventilation perfusion mismatch due to emboli and microemboli preventing perfusion of functional bronchoalveolar units, hyperbaric oxygen has been shown to mitigate inflammatory reactions. Much of the pathogenesis of COVID-19 is due to an overly active immune response generating inflammation that becomes a major etiology of subsequent consequences of the infection [7]. Hyperbaric oxygen has been shown to offer potent anti-inflammatory stimuli. It also has been reported to "pay back" the oxygen debt incurred in these patients with ongoing undersupply of oxygen to vital organs [8]. In at least one clinical series hyperbaric oxygen has been demonstrated to significantly reduce D-dimers which are a marker for coagulation [9]. If indeed the reduction of coagulation is a consistent effect, pulmonary function and subsequent oxygen delivery to the entire body will be improved.

A much more extensive discussion of mechanisms whereby hyperbaric oxygen is likely to favorably impact the pathologic features of COVID-19 is available in the Research Committee Report posted on the UHMS website [6]. Based on a broad and well-studied and documented description of likely physiologic effects of hyperbaric oxygen and based on the published reports demonstrating consistently positive responses in the trials cited above, the UHMS has updated its position statement jointly approved by the ACHM to the following:

1. The UHMS continues to advocate strongly for well-designed IRB-approved clinical trials of hyperbaric oxygen for COVID-19. Well-designed trials are necessary to establish a proper mechanistic and clinical foundation for COVID-19 treatment and increase our understanding of this disease and the potential role of hyperbaric oxygen as part of a multidisciplinary approach.

2. The UHMS recognizes the special value of Phase III randomized controlled trials in providing Level I evidence and strongly supports funding and conduct of these definitive studies.

3. The UHMS now recognizes that hyperbaric oxygen treatment on an off-protocol basis for COVID-19 at the physician's discretion may be appropriate in some cases and recognizes that community centers and free-standing facilities may have limited access to IRBs (Institutional Review Boards). The UHMS strongly encourages well-documented scientific observations of the impact, patient selection criteria, and treatment methodology for those utilizing HBO_2 to treat COVID-19 patients off-protocol.

4. The UHMS strongly encourages well-documented scientific observations of the impact, patient selection criteria, and treatment methodology for those utilizing HBO_2 to treat COVID-19 patients. The UHMS Research Committee has published key outcome determinants and therapeutic guidance. The formalized structure provides a sound basis for the 'off-protocol'

application of HBO_2 irrespective of whether such treatments are provided with or without IRB approval and oversight. A listing of recommended diagnostic studies is provided in the Research Committee Report previously cited. This document also provides guidelines for patient selection and eligibility for treatment as well as a discussion of treatment specifics, including total number of treatments, frequency, total length of each treatment as well as treatment pressure. Valuable additional information is available at this site that we believe will aid those who take on the difficult task of treating these seriously ill patients.

5. The UHMS recognizes that the final determination of all aspects of patient care should be made at the local level, but because of the novelty of this application, the UHMS provides this guidance as a model for individualized care that reflects the clinical experience of intellectual and clinical leaders in the field to avoid the need to "reinvent the wheel" when considering the use of hyperbaric oxygen in the treatment of these critically ill patients. The Research Committee has also recommended some standardization of patient selection and specific elements of the treatment protocol to allow for a valid evaluation and analysis of the combined number of patients treated.

*Off-protocol treatment is a term that has its origins in the medical oncology literature. It describes the delivery of a promising investigational treatment which is undergoing study in clinical trials. It is often employed in a situation where established treatments are unlikely to be effective and where the absence of effective treatment is likely to result in the patient's disease progression and death. Selection of this treatment is made by the physician based on his or her clinical judgment that the treatment in question offers promising results. The use of this off-protocol treatment may be precipitated by the patient's request. If Phase III studies are locally available, the patient may refuse to enter the trial and face the usual 50% chance of not receiving the treatment under study after randomization. It typically applies to a drug or therapy that has been approved by the FDA for other diseases. A valuable review of this practice was authored by Peppercorn et al. in 2008 [10]. It reports that 81% of medical oncologists have provided off-protocol treatments. The reader's review of this article is recommended.

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