RESPONSE FROM DR. SADLER

Regarding the letter to UHM Editor about 24/7 chamber access in Hawaii, I spoke earlier today on the phone with Jim Chimiak and Dan Nord at DAN about this matter since DAN was consulted regarding hyperbaric chamber contacts and transport.

From the letter to the editor we all agreed that UH is taking aim at the 'lack of 24/7 access in Hawaii' statements made in several spots throughout the text.

While it is accurate that the UH chamber closed for three months – 10/19/17 to 1/14/18 – as stated in the letter from Dr. Steinemann (and verified by DAN records), the chamber had made a 'soft' reopening in January of 2018.

Rather than lack of chamber access, Dr. Steinemann notes that it was the severity of the case that prompted the personnel in Hawaii to opt to fly the injured diver to UCSD. She wrote in her letter:

'The hyperbaric physician that fielded the call for this patient made the (I think correct) decision to have her flown to the mainland, rather than to Oahu, based upon her multiple organ failure, the time lapse (>1 day) before hyperbaric treatment was considered appropriate, and the fact that she was a visitor from the mainland.'

The permanent closure of hyperbaric facilities is becoming more of an issue for timely treatment, as everyone involved in this discussion can agree. What we can emphasize here is that everyone made the best decision possible in a difficult case. Additionally, Dr. Chimiak and Dan Nord both emphasized the clear thinking on the part of the UH personnel in sending this injured diver to the facility that could provide the best care at the time: UCSD.

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HBO_2 FOR RADIATION CYSTITIS

To the Editor:

Efficacy studies are those designed to determine maximum achievable treatment response in a tightly controlled research environment, and the capacity for any demonstrated effect in everyday practice. Clinical decision-making places increasing emphasis on such high-level evidence, as do those who purchase health care. Efficacy data supporting hyperbaric medicine have long been in short supply. Practice decisions frequently rest on a mix of laboratory findings, the 'matching' of disease pathophysiology to a therapeutic mechanism, retrospective reports and uncontrolled prospective case series, alone or in any combination. When hyperbaric efficacy research does become available, then, it is deserving of particular attention, analysis and dissemination.

Oscarsson, et al. have generated one such example that serves to elevate efficacy evidence for hyperbaric oxygen (HBO_2) treatment of less severe yet common forms of radiation cystitis [1]. The term *radiation cystitis* refers to a collection of signs and symptoms (see Table). It is only the second randomized controlled trial to investigate hyperbaric oxygen HBO_2 therapy for this condition [2] and the first to demonstrate a statistically significant healing advantage over standard care. Importantly, the trial was registered with International Committee of Medical Journal Editors approved trial registries. A clinical trial (defined as prospective assignment of participants to one or more health-related interventions to evaluate outcomes) registration is essential if results are to be considered for publication in ICMJE participating journals.

Of 223 patients assessed, 87 met inclusion criteria and were subsequently enrolled. This 39% conversion ratio suggests that their reported improved outcomes are largely generalizable. Although not reported, the 'Number Needed to Treat' (NNT, an epidemiological measure used to communicate effectiveness of an intervention, and representing the average number of patients needed to be treated in order to produce one favorable outcome) was computed as an encouraging [3]. This value was the same for the subjective Expanded Prostate Index Composite (EPIC) and objective Late Radiation Morbidity Grading Scheme (LRMGS) scores, rounded up by convention from 2.56 and 2.17, respectively. An identical NNT was reported in the HBO_2 radiation proctitis randomized controlled trial [3]. One would hope that the authors' decision to exclude from 'Intention to Treat'

analysis those patients who withdrew consent immediately upon learning of their randomization would not be judged too harshly by evidence 'purists'. Shorter intervals between diagnosis and initiation of HBO_2 therapy were associated with improved responses, as were reduced radiation therapy to HBO_2 periods. This interval-related response has been reported elsewhere [4] and further supports HBO_2's earlier application. Patients suffering concurrent radiation proctitis also experienced improvement in this condition, suggesting a unique benefit of systemically delivered HBO_2 in the setting of multi-organ involvement. One would not expect a favorable response of more localized standard care to extend to other radiation-damaged organs and structures. Improved bladder findings per LRMGS scores add to the contention that HBO_2 therapy is uniquely disease-modifying [3,5,6]. This effect serves to limit the frequency of, and in many cases eliminate altogether, the remitting-relapsing consequences of more common elements of standard management directed principally at relief of symptoms such as arrest of bleeding while not overcoming its cause.

The absence of a sham component was unfortunate. Human behavior is influenced by what we know or believe, so blinding of patients to the treatment they will receive in a controlled trial is particularly important when response criteria are subjective [7], which was the case with this study. Adoption of sham controls and blinding would have further elevated this work within the evidence-based medicine hierarchy. This decision eliminated the ability to blind patients, as it did LRMGS assessors. The authors' arguments against sham were unconvincing, and neither example provided to suggest a study had been negatively impacted by inclusion of sham was correct. Sham control and double-blinding trial design was successfully incorporated into the study of HBO_2 for treatment of radiation proctitis [3]. Blinded sham controls may have also served to minimize the 16% drop-out rate post randomization in patients allocated to the control group, thereby permitting these patients to becoming eligible to receive HBO_2 therapy 'off protocol'. Attempts to evaluate de facto indications for HBO_2 at higher levels of scientific scrutiny are challenging. Providers may be ethically reluctant to commit patients to a sham exposure when clinical experience is associated with generally favorable responses. There is also the specter of medical-legal recourse. For example, a patient randomized to sham may suffer disease advancement during their study inclusion period, perhaps resulting in a fistula or bladder rupture, thereby necessitating a surgical procedure that arguably would not have been required if HBO_2 had been delivered as 'standard care'. These concerns can be lessened somewhat when treating chronic conditions by inclusion of a crossover arm. The benefit of crossover is that it assesses response in previously untreated control patients. A statistically significant improvement observed in crossover patients represents powerful confirmation of therapeutic effect. Its principal criticism is that it eliminates the potential to analyze an intervention's enduring effect. When both groups have received active treatment, long-term comparisons are no longer possible. One might argue that for treatment of late radiation tissue injury, however, any lessening or elimination of aforementioned remitting-relapsing characteristics represents an enduring effect surrogate. It is encouraging to note that eventual reporting of histologic data will have involved blinded assessors.

The full extent of radiation-induced bladder injuries was not included. The authors believed that withholding HBO_2 therapy for more advanced cases would have been unethical. This position is somewhat difficult to reconcile, as the authors note elsewhere that evidence supportive of HBO_2 as treatment for radiation cystitis 'is weak.'

References were well chosen, peer-reviewed and reflective of the current era. This is refreshing for a hyperbaric publication, where inclusion of publications that are more dated, textbook chapters and meeting abstracts is common. The former rather than the latter principally influence referring physicians and those who undertake literature reviews in order to generate clinical practice recommendations and guide reimbursement policy.

The hyperbaric dosing protocol was appropriate for this condition and slight inter-institutional variances of no consequence. Reported harms were those commonly anticipated in routine clinical practice. Each was minor in degree, largely self-limiting and supportive of the position that hyperbaric medicine is a well-tolerated, relatively safe and mastered medical technology.

Leading U.S. commercial insurers and U.S. Medicare approve the use HBO_2 therapy for radiation cystitis and reimburse accordingly. The basis for these policy decisions is the sum of modest yet consistent effectiveness data in the absence of prospective randomized efficacy studies. This new publication will certainly augment these positions. One also

hopes that reimbursement policy will evolve to recognize HBO_2 therapy as essential standard care. A recent scoping report and meta-analysis, predating the Oscarsson, et al. publication, concludes that 'using hyperbaric oxygen therapy early in the development of radiation cystitis may be associated with greater success' [8]. At present, health insurers commonly approve the use of HBO_2 therapy only after 'standard care' has proven unsuccessful. Of interest, none of the intravesical and other systemic agents used to treat radiation cystitis have been studied and proven efficacious to the level HBO_2 now enjoys.

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TABLE: RADIATION CYSTITIS MANIFESTATIONS

Dysuria
Incontinence
Frequency, urgency, decreased stream
Pain
Inflammation
Vascular telangiectasia, marked hyper-vascularity
Bullous erythema
Microscopic hemorrhage
Macroscopic hemorrhage
Clot retention, obstruction
Reduced bladder capacity
Hemorrhagic ulceration
Loss of mucosal integrity
Urethral stricture +/- fibrosis
Bladder neck contracture
Tissue necrosis
Vesicovaginal fistula; colovesical fistula
Ulceration, rupture
Death

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