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A systematic review of the literature reporting the application of hyperbaric oxygen prevention and treatment of delayed radiation injuries: An evidence based approach

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Feldmeier JJ, Hampson, NB. A systematic review of the literature reporting the application of hyperbaric oxygen prevention and treatment of delayed radiation injuries: An evidence based approach. Undersea Hyper Med 2002, 29(1):4-30. The treatment of delayed radiation injuries (soft tissue and bony radiation necrosis) is one of thirteen conditions approved by the Hyperbaric Oxygen Therapy Committee of the Undersea and Hyperbaric Medical Society as appropriate indications for hyperbaric oxygen (HBO_2). This paper provides a systematic review of the literature reporting the results of HBO_2 therapy in the treatment and/or prophylaxis of delayed radiation injury. Since the introduction of the concept of evidence based medicine, the medical community in general has set out to apply more critical and stringent standards in evaluating published support for therapeutic interventions. Evidence based medicine is designed to discover the best evidence available and apply it in daily practice for treatment of the individual patient. The preferred level of evidence is the randomized controlled trial, however, other evidence has merit as well. In this review, seventy-four publications are represented reporting results of applying HBO_2 in the treatment or prevention of radiation injuries. These are appraised in an evidence-based fashion by applying three established systems of evaluation. All but seven of these publications report a positive result when HBO_2 is delivered as treatment for or prevention of delayed radiation injury. These results are particularly impressive in the context of alternative interventions. Without HBO_2, treatment often requires radical surgical intervention, which is likely to result in complications. Other alternatives including drug therapies are rarely reported, and for the most part have not been the subject of randomized controlled trials. Based on this review, HBO_2 is recommended for delayed radiation injuries for soft tissue and bony injuries of most sites. Of note, an increasing body of evidence supports HBO_2 for radiation-induced necrosis of the brain. For other radiation-induced neurological injuries, additional study is required before recommendations for routine hyperbaric therapy can be made.
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hyperbaric oxygen, radiation injury, complications of cancer treatment, systematic review

Introduction:

Approximately 1.2 million new cases of invasive cancer will be diagnosed this year in the United States and approximately one half of these patients will receive radiation therapy as part of the management of their malignancy.[1] About one half of patients treated for cancer become long term survivors. Serious radiation complications are rare but occur in up to 5% of those patients receiving therapeutic radiation.[2]These complications characteristically occur after a latent period that varies from several months to several years. The etiology of delayed radiation injury is not fully understood though most would agree that endarteritis, tissue hypoxia and fibrosis are consistent findings and are certainly major contributors to pathogenesis.[2] Historically, conservative management of delayed radiation injuries including frank radionecrosis has been unsatisfactory. Radiation injuries may be life

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threatening and may significantly reduce quality of life under certain circumstances. Definitive treatment may require surgical resection or bypass of the affected part. In a patient who has in many cases already survived aggressive therapy including chemotherapy and surgery in addition to radiation, the prospect of further radical treatment possibly including a major surgical intervention is most unwelcome. Additionally surgical intervention in a heavily radiated field may result in delayed wound healing, dehiscience or infection. These post-operative complications may be life threatening in severity.

Mandibular radiation necrosis has been treated with hyperbaric oxygen for some time with consistently positive results. Hyperbaric oxygen therapy is applied now with increasing frequency to radiation injuries and necrosis of other tissues and at other anatomic sites. It is felt to be effective by enhancing angiogenesis and in so doing, providing oxygen to meet the metabolic demands of radiation impaired tissues.

This paper reviews and critically assesses the literature in radiation injury as one of 13 indications approved as appropriate for therapeutic intervention with hyperbaric oxygen by the Undersea and Hyperbaric Medical Society.[3] It summarizes the published literature reporting use of hyperbaric oxygen (HBO_2) in the comprehensive treatment, or prophylaxis of delayed radiation injury. A major limitation in this effort is the paucity of randomized controlled clinical trials available to support or refute this intervention. Although randomized controlled trials are indeed the gold standard for establishing the efficacy of a therapeutic intervention, other evidence including pre-clinical studies and retrospective case series have merit.[4] The literature presented herein is evaluated using three previously published review schemes designed to critically assess the strength of literature in support of employing a therapeutic intervention. The first of these has been developed by the American Heart Association.[4,5] The second is the system developed and utilized by the National Cancer Institute's PDQ Editorial Board in their presentation of ongoing reviews of cancer treatment information.[6] The third is an adaptation of the approach developed by the BMJ Publishing Group and used in the publication, Clinical Evidence.[7]

Three Models for Literature Assessment:

In 1995, the American Heart Association (AHA) published a scheme to evaluate and subsequently to recommend to the Federal Drug Administration (FDA) and to the Health Care Finance Administration or HCFA (now CMS) the value of therapeutic interventions.[4] In 1998, the AHA updated and further defined and clarified this system.[5]. Table 1 specifies levels of evidence as defined and applied by this system to interventions. Randomized controlled trials are given the most weight and historical acceptance given the lowest weight. Human case series and animal studies are given intermediate weighting.

Table 1.

AHA Emergency Cardiovascular Care Levels of Evidence

Level 1: Statistically significant randomized controlled trials (RCT's).

1A: Meta-analysis of multiple positive RCT's.

1B: One or more positive RCT's with statistically positive results

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1C: Meta-analysis with inconsistent but significant results

Level 2: Statistically insignificant RCT's

2A: Meta-analysis of positive RCT's but not statistically significant

2B: One or more positive RCT's; not statistically significant

2C: Meta-analysis of inconsistent RCT's; not statistically significant

Level 3: Prospective, controlled, but not randomized cohort studies

Level 4: Historic, non-randomized cohort or case-control studies

Level 5: Human case series

Level 6: Animal or mechanical model studies

Level 7: Reasonable extrapolations from existing data; quasi-experimental designs

Level 8: Rational conjecture (common sense); historical acceptance as standard practice

Table 2 demonstrates the principles of the AHA system as applied to specific therapeutic interventions and as related to assessing the evidentiary support for such interventions.

Table 2.

The American Heart Association System

Class I: Definitely Recommended. Excellent evidence provides support.

Class II: Acceptable and Useful.

IIa: Very good evidence provides support.

IIb: Fair-to-good evidence provides support.

Class III: Not Acceptable, Not Useful, May be Harmful.

Indeterminate: A Continuing Area of Research; no recommendation until further research is available.

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After a review of the published evidence for a particular therapy, the AHA system assigns interventions into categories according to the strength of the evidence supporting their use. Interventions designated as Category I, IIa or IIb are recommended for application to clinical practice while category III interventions are not supported. Therapeutic interventions assigned to the "Indeterminate Category" are judged to require additional investigation prior to recommendation for or against their application.

The National Cancer Institute (NCI) provides Physicians' Data Query (PDQ) as an Internet-accessible summary of current treatment and diagnostic standards for the diagnosis and therapeutic management of common childhood and adult malignancies. Through the NCI, summaries are available to the clinician, and separate summaries are available to the layperson written in appropriate language and level for comprehension by an inquiring patient or family member. Recently, the PDQ Editorial Board has begun to include assessments of the level of supporting evidence for a particular intervention utilizing their own quantitative system (summarized in Table 3).

Table 3.

National Cancer Institute: Physicians Data Query (PDQ)
Level of Evidence

1. Evidence Supported by Randomized Controlled Trials (RCT)
   1i is a Double Blinded RCT
   1ii is an RCT that is not blinded
2. Evidence Supported by Controlled but Non-Randomized Trials
   (e.g. allocation to a given group is determined by birth date or day of week enrolled)
3. Evidence is Supported by Case Studies
   3i is a case series that is population based and consecutive
   3ii is a case series which is consecutive but not population based
   3iii is a case series which is neither population based nor consecutive

This system is a two-tiered system. The first or numeric portion is assigned in the following fashion:

Level 1 represents evidence supported by a randomized controlled trial(s) (RCT). This numeric grade is further modified so that 1i represents a double-blinded study and 1ii represents an RCT that is not blinded. Meta-analyses of RCT's are given level 1 status with the suffix modifier applied in the same fashion in regard to blinding as a single RCT.

Level 2 represents non-randomized but controlled clinical trials. This group would include trials in which the allocation of a patient to the treatment or control group is set by birth date, day of clinic appointment, bed availability or any other determinant, which would make allocation known to the investigator prior to obtaining informed consent.

Level 3 are case series. Category 3i is a series, which is consecutive and population based. Category 3ii is a case series reporting consecutive but not population based cases. Category 3iii reports cases which are neither consecutive nor population based.

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The PDQ grading system includes a secondary component based on the "strength of the end points." For Category A, the end point is total mortality. For Category B, the end point is disease specific mortality. Category C represents quality of life outcome measures and Category D reports other surrogate measures of outcome such as disease-free survival and tumor response rate. This second set of categorizations of PDQ evidence is more or less specific to cancer treatment and will not be applied strictly in reviewing the evidence available for hyperbaric oxygen for radiation injuries. However, it is noted that unresolved serious delayed radiation injuries cause death under certain circumstances and certainly decrease quality of life in most circumstances.

The PDQ system evaluates individual papers in regard to the strength of evidence but does not numerically sum the evidence in a formal fashion to assign an overall assessment of the strength of the evidence for any particular therapeutic modality in a given circumstance.

In Clinical Evidence, the editors seek to provide the practicing clinician with a handy reference providing evidence-based reviews of interventions for common conditions seen in primary care and hospital practice. This publication, which is updated every six months, begins each section by asking a question about available therapies for a particular clinical problem. For example, in the section on metastatic breast cancer, a question asked is "what are the effects of treatment for bone metastases". Then, individual therapies are discussed in terms of "Benefits", "Harms" and "Comments."

The "Benefits" sections first presents published evidence from systematic reviews and randomized controlled trials. These are the preferred levels of evidence. If randomized controlled trials are not available for a given question, other published evidence supporting a therapeutic strategy is presented and discussed to develop arguments supporting that intervention. A discussion of potential complications and side effects follows and is included in "Harms" so that the adverse effects can be compared to the evidence in favor of therapy, and decision making based on risk to benefit considerations can be made by the clinician.

"Comments" present additional considerations, amplifying or modifying information to clarify further the application of a particular therapy in relevant circumstances.

As we apply the "Clinical Evidence" approach to hyperbaric oxygen for radiation injuries, the recent reports of Plafki et al[8] and Sheffield and Desautels[9] are considered in regard to "Harms". Both of these publications demonstrate the hyperbaric oxygen therapy is a very safe modality and unlikely to be accompanied by significant morbidity if delivered appropriately. For this particular application, concern has been voiced that hyperbaric oxygen may increase the likelihood of recurrent cancer. A review by Feldmeier et al[10] in 1994 failed to uncover evidence of increased risk of cancer recurrence or progression for patients treated for radiation injuries. In applying the "Clinical Evidence" approach to review each of the individual anatomic sites or tissues involved by injury, we are asking the question, "Is hyperbaric oxygen effective in resolving or palliating this disorder?"

The BMJ scheme assigns a verbal description of the strength of support for a particular modality in a given circumstance based on a compilation of all evidence available in that particular circumstance. To illustrate these principles in Tables 4 through 11, we have modified the system slightly to assign a verbal description of the strength of the evidence for each paper. We then combine these to give an overall strength for a particular indication within the discussion portion for each indication.

Application of the Three Models to Hyperbaric Oxygen Intervention for Radiation Injury: Site Specific Summaries: To discuss the application of evidence-based models to radiation injury, we will follow the discussion site by site in the same order as used in Tables 4 through 12. For ease in reading the Table, negative studies are entered in bold italics and the author's name underlined. Single

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case reports are considered a case series of "one" for classification and entry into Tables 4 through 12. Papers discussing the application of hyperbaric oxygen to the treatment or prevention of the various radiation injuries were sought by searching several Internet accessible databases including "Pubmed" and "Cancerlit". Once a paper was found, its references were manually reviewed to search out additional appropriate references. Previous proceedings of the annual meeting of the Undersea and Hyperbaric Medical Society and meetings of the International Congress of Hyperbaric Medicine were searched manually.

I. Prophylaxis of Mandibular Osteoradionecrosis

Table 4 summarizes literature in which hyperbaric oxygen has been applied to the prevention of mandibular osteoradionecrosis (ORN). Robert E. Marx, D.D.S. has published a randomized controlled trial reporting the successful use of hyperbaric oxygen in preventing mandibular radiation necrosis by giving hyperbaric oxygen before and after dental extractions. This report provides us with AHA and NCI level 1 evidence.[11] Two additional clinical series present their results in the prophylactic treatment of 53 additional patients (AHA level 4 or 5 and NCI level 3ii evidence). If we combine the patients from all three reports, we find an incidence of osteoradionecrosis (ORN) in 4.5% (4 of 90) in the HBO_2 prophylaxis group (2 of 37 Marx; 1 of 29 Vudiniabola[12]; and 1 of 24 David[13]). In Marx's control group, the incidence of osteoradionecrosis was 29.9% (11 of 37).

The AHA therapeutic intervention classification for ORN prophylaxis merits a designation as a "Class Ia" indication for HBO_2.

The BMJ Clinical Evidence review of this indication would be "Beneficial" based on the randomized controlled trial and the low incidence of "Harms".

Table 4.

Published Reports of Hyperbaric Oxygen for Prevention of Mandibular Necrosis

Author	Type of Report	AHA Grade	NCI Grade	Clinical Evidence	Comments
Marx (1985)[11]	RCT-74 patients	1B	1ii	Beneficial	5.4% ORN in HBO Group 29.9% in non-HBO Group
Vudiniabola (1999)[12]	Case Series-37 patients	4	3ii	Likely to be Beneficial	1 of 29 HBO and 7 of 8 non-HBO developed ORN
David (2001)[13]	Case Series-24 patients	5	3ii	Likely to be Beneficial	1 of 24 developed ORN

II. Treatment of Existing Osteoradionecrosis of the Mandible:

The literature for existing mandibular osteoradionecrosis (ORN) is summarized in Table 5. [13–26] A total of 14 publications are reviewed.

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Table 5.

Published Reports of Hyperbaric Oxygen as Treatment for Mandibular Necrosis

Author	Type of Report	AHA Grade	NCI Grade	Clinical Evidence	Comments
Mainous (1975)[14]	Case Series-14 patients	5	3ii	Likely to beBeneficial	Relief of pain and resolution of sinus tracts in all patients
Hart (1976)[15]	Case Series-46 patients	5	3ii	Likely to be Beneficial	37 of 46 Resolved
Farmer (1978)[16]	Case Series-13 patients	5	3ii	Likely to be Beneficial	Radiographic Improvement in 10 of 13 patients
Tobey (1979)[17]	RCT-12 patients 100% O2 at 1.2 vs 2.0 ATA	1B	1ii	Beneficial	Significant improvement in those at 2.0 vs 1.2 ATA
Davis (1979)[18]	Case Series-23 patients	5	3ii	Likely to be Beneficial	20 of 23 resolved
Marx (1983)[19]	Case Series-58 patients	5	3ii	Likely to be Beneficial	100% resolution with HBO and aggressive surgery
Marx (1984)[20]	Case Series-70 patients		3ii	Likely to be Beneficial	100% resolution with HBO and aggressive surgery
Mounsey (1993)[21]	Case Series-41 patients	5	3ii	Likely to be Beneficial	34 of 41 had significant improvement
McKenzie (1993)[22]	Case Series-26 patients	5	3ii	Likely to be Beneficial	18 of 26 pertsistent mucosal and epithelial healing
van Merkestey n (1995)[23]	Case Series-29 patients	5	3ii	Likely to be Beneficial	20 of 29 patients resolved
Epstein[24]	Case Series-20 patients with long	5	3ii	Likely to be Beneficial	12 of 20 resolved with

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	term follow up				long term followup
Maier (2000)[25]	***Case Series-41 patients***	*3*	*2*	***Not** Beneficial*	*A negative trial of hyperbaric compared to historic controls; 13 of 20 HBO resolved*
Curi (2000)[26]	Case Series-18 patients	5	3ii	Likely to be Beneficial	14 of 18 resolved
David (2001)[13]	Case Series-51 patients	5	3ii	Likely to be Beneficial	48 of 51 showed improvement

One very small randomized controlled trial of 12 patients by Tobey et al[17] is positive. These patients were randomized to 100% oxygen at 1.2 vs 2.0 ATA. The authors state that those patients treated at 2.0 ATA "experienced significant improvement" compared to the group receiving oxygen at 1.2 ATA. No details are given regarding randomization or outcome determination. In fact we cannot tell how many patients were assigned to each group. The study is randomized and doubly blinded in that neither the patient nor the clinician assessing the patient knew which therapy the patient was receiving. Even though it is a small study, it does present level 1 evidence. This study is therefore assessed an AHA 1B and a NCI 1ii level of evidence classification.

In addition to Tobey's trial, thirteen additional reports are listed in Table 5. All of these trials present AHA Level 5 evidence and NCI Level 3ii evidence. Twelve of the 13 trials are positive. Only the report by Maier et al fails to show an advantage for hyperbaric oxygen in the treatment of existing ORN. In this paper, hyperbaric oxygen is given only after an attempt is made at surgical correction. No hyperbaric oxygen was given prior to surgery. Marx has previously established the important principle of pre-operative HBO prior to surgical wounding in irradiated tissues, which has been widely accepted for applying HBO_2 to the treatment of ORN.

Combining all of the reported cases in Table 5 (excluding those of Tobey and noting that Marx's second report includes the 58 patients reported earlier) provides a total of 371 cases of mandibular ORN. Improvement is reported in 310 cases or 83.6%. Although resolution would be a better endpoint, hyperbaric oxygen was not combined with aggressive extirpation of necrotic bone or with surgical reconstruction of bony discontinuity, especially in the earlier reports. Marx[21] has reported the best results of any author and identified and emphasized the need for optimizing surgery and HBO_2 by the pre-surgical application of HBO_2. Marx reports 100% success, but this includes mandibulectomy and reconstruction in 73% of his patients. Dr. Marx also sets high standards for successful intervention in those patients requiring mandibulectomy and reconstruction by requiring not only successful re-establishment of bony continuity but also functional success in supporting dentures for cosmesis and mastication.

Based on one small single RCT and consistent experience reported in case series, HBO_2 as treatment for ORN is probably an AHA class IIa indication (Acceptable and Useful Based on Very

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Good Evidence). Applying the BMJ standards, the treatment of ORN by HBO_2 is "Likely to be Beneficial" once again recognizing the low likelihood of "Harms" and consistent reports of success.

III. Treatment of Soft Tissue Radiation Necrosis of the Head and Neck Including Laryngeal Necrosis:

Table 6 includes 7 published reports of HBO_2 applied to soft tissue injuries of the head and neck.[18, 27-32]

Table 6.

Hyperbaric Oxygen as Treatment for Soft Tissue Radiation Injury of the Head and Neck

Author	Type of Report	AHA Grade	NCI Grade	Clinical Evidence	Comments
Davis (1979)[19]	Case Series-16 patients	5	3ii	Likely to be Beneficial	15 of 16 resolved
Ferguson (1987)[27]	Case Series-8 patients with laryngeal necrosis	5	3ii	Likely to be Beneficial	Dramatic improvement in 7 of 8
Feldmeier (1993)[28]	Case Series-9 patients with laryngeal necrosis	5	3ii	Likely to be Beneficial	Resolution in all 9 patients
Neovius (1997)[29]	Case series of 15 patients compared to historical control group	4	3ii	Likely to be Beneficial	Healing in 12 of 15 patients; 2 improved; 1 non-healing; compared to 7 of 15 healed in the control group with 1 fatal bleed
Marx (1999)[30]	Prospective controlled but not randomized study of 160 patients	3	2	Likely to be Beneficial	Statistically significant reduction in wound infection, dehiscience and delayed healing in HBO group
Filintisis (2000)[31]	Case Series-18 patients with laryngeal necrosis	5	3ii	Likely to be Beneficial	13 of 18 had major improvement

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Narozny (2001)[33]	Case Series-2 patients soft tissue necrosis including larynx and pharynx	5	3ii	Likely to be Beneficial	Resolution in both patients

In Hyperbaric Medicine Practice[30], Marx reports his experience in a prospective controlled but not randomized study. Those patients who refused HBO_2 or for whom treatment was not practical due to distance from a chamber or other financial reasons were assigned to the control group. These cohorts of patients were treated concurrently and all other aspects of their treatment were identical. This study is therefore considered AHA level 3 and NCI level 2 evidence. In his report of 160 patients receiving hyperbaric oxygen in support of surgical resection or flap reconstruction in heavily irradiated patients comparing wound infection, wound dehiscence and delayed wound healing, Marx reports the incidence of complications in the HBO_2 group versus the control group in the following fashion: 1. Wound infection: 6% versus 24%; 2. Wound dehiscence: 11% versus 48%; and 3. Delayed wound healing: 11% versus 55%. Applying the Chi square test to these results we obtain P values of 0.004, less than 0.0001 and less than 0.0001 respectively. These patients received 20 pre-operative HBO treatments followed by 10 post-operative treatments at 2.4 ATA.

In addition to the large controlled trial reported by Marx, six additional publications reporting case series are listed in Table 6. These consistently report a positive outcome in patients treated with HBO for soft tissue radionecrosis of the head and neck. A case series by Davis et al reports success in 15 of 16 patients treated for soft tissue radionecrosis of the head and neck. Many of these patients had large chronic soft tissue wounds as a result of their radiation injury. In 1997 Neovius[29] and colleagues reported 15 patients treated with HBO_2 for wound complications within irradiated tissues. They compared this group to a historical control group from the same institution. Twelve of the 15 patients in the HBO_2 group healed completely with improvement in 2 and no benefit in 1. In the control group only 7 of 15 patients healed. Two patients in the control group developed life-threatening hemorrhage and 1 of them ex-sanguinated.

The effects of HBO on chondroradiation necrosis of the larynx are reported by 3 authors from 3 different institutions.[27,28,31] The majority of these patients had severe (Chandler's Grade III or IV necrosis). Most patients with severe laryngeal chondroradionecrosis will require laryngectomy.[33-36] If the results from these 3 trials are combined, only 6 of 35 patients underwent laryngectomy The rest maintained their larynx and most had good voice quality after HBO.

Based on the Marx controlled trial and the consistent outcome in the reported case series, soft tissue radiation injury of the head and neck can be considered an AHA category IIb (acceptable and useful based on fair to good evidence). Applying the BMJ system, the application of hyperbaric oxygen to soft tissue radiation injuries of the head and neck would be rated "likely to be beneficial" based again on the consistently positive outcome and low likelihood of substantial side effects or "harms".

IV. Treatment of Radiation Cystitis

Table 7 lists 17 published reports detailing results of HBO_2 interventions in the treatment hemorrhagic radiation induced cystitis.[37-53] These publications are all case series. The report by

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Bevers[46], which includes the largest number of patients, was a prospective but not a controlled trial. In the final report by Weiss et al[48], the earlier patients reported by the same author were included. The second paper by Lee[43] reporting 25 patients includes the 20 patients previously reported by the same author. If the patients in these 17 publications are combined, a total of 190 patients were treated with HBO_2 with 145 patients or 76.3% resolving with HBO_2 treatment.

Table 7.

Hyperbaric Oxygen as Treatment for Radiation Cystitis

Author	Type of Report	AHA Grade	NCI Grade	Clinical Evidence	Comments
Weiss (1985)[37]	Case Series-3 patients	5	3ii	Likely to be Beneficial	3 of 3 resolved
Schoenrock (1986)[38]	Single Case Report	5	3ii	Unknown Benefit	1 of 1 resolved
Weiss (1989)[39]	Case Series-8 patients	5	3ii	Single positive case Likely to be Beneficial	7 of 8 resolved
Rijkmans (1989)[40]	Case Series-10 patients	5	3ii	Likely to be Beneficial	6 of 10 resolved
Norkool (1993)[41]	Case Series-14 patients	5	3ii	Likely to be Beneficial	8 of 14 resolved
Lee (1994)[42]	Case Series-20 patients	5	3ii	Likely to be Beneficial	16 of 20 resolved
Lee(1994)[43]	Updated Case Series 25 patients	5	3ii	Likely to be Beneficial	21 of 25 resolved
Akiyama (1994)[44]	Case Series-2 patients	5	3ii	Likely to be Beneficial	2 of 2 resolved
Weiss (1994)[45]	Case Series-13 patients	5	3ii	Likely to be Beneficial	12 of 13 resolved
Bevers(1995)[46]	Prospective non-randomized trial of 40 patients	5	3ii	Likely to be Beneficial	37 of 40 resolved
Del Pizzo (1998)[47]	*Case-Series-11 patients*	*5*	*3ii*	*Not likely to be Beneficial*	*3 of 11 resolved*
Weiss (1998)[48]	Case Series-29 patients	5	3ii	Likely to be Beneficial	26 of 29 resolved; average f/u 18.5 mos
Miyazato (1998)[49]	Case Series-10 patients	5	3ii	Likely to be Beneficial	7 of 10 resolved
Suzuki	Case Series-3 patients	5	3ii	Likely to be Beneficial	3 of 3 resolved

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(1998)[50]					
Mathews (1999)[51]	Case Series-17 patients	5	3ii	Likely to be Beneficial	11 of 17 resolved
Mayer (2001)[52]	Case Series-8 patients	5	3ii	Likely to be Beneficial	6 of 8 resolved
Hendicks (2000)[53]	Case Series-20 patients	5	3ii	Likely to be Beneficial	14 of 20 resolved

Many patients reported in the HBO_2 experience had already failed conservative management including irrigation and instillation of alum or formalin. Severe hemorragic radiation cystitis is unquestionably a life threatening and quality of life limiting disorder. Cheng and Foo[54] have reported their experience in managing 9 serious refractory cases of hemorrhagic radiation cystitis without HBO_2. Six patients were treated with bilateral percutaneous nephrostomies. Three patients required ileal loop diversions of their urinary stream. Four of nine (44%) patients ultimately died in spite of these aggressive treatments. Similarly, Sun and Chao[55] reported 3.7% mortality due to bladder injury in their review of 378 patients treated with radiation for cervical cancer.

A success rate of 76.3% with HBO_2 is impressive when results with other more aggressive interventions are considered. It is also noteworthy that 16 of 17 publications listed in Table 3 are positive reports. Patients listed in Table 3 represent patients treated in several different countries on 3 different continents with consistent benefit seen in a large majority of patients in each study except that of Del Pizzo.[46]

Although there are no randomized controlled trials supporting this indication for HBO_2, the results of the case series reviewed are so consistent that a Class IIa AHA designation (Acceptable and Useful) and a BMJ designation of "Likely to be Beneficial" for radiation cystitis appears to be reasonable.

V. Treatment of Radiation Induced Chest Wall and Breast Injury

Four reports of HBO_2 treatment of chest wall and breast radiation injury are listed in Table 8[16, 56-58] These are considered AHA level 5 or NCI level 3ii evidence with the exception of the publication of Carl[54] which has a concurrent non-randomized control group and would therefore be considered an AHA level 4 study.

Table 8.

Hyperbaric Oxygen as Treatment for Radiation Injury of the Chest Wall and Breast

Author	Type of Report	AHA Grade	NCI Grade	Clinical Evidence	Comments
Hart (1976)[15]	Case Series-6 patients	5	3ii	Likely to be Beneficial	HBO2 as adjunct to skin graft into irradiated bed all 6 grafts successful
Feldmeier (1995)[56]	Case Series-23 patients-8 soft	5	3ii	Likely to be Beneficial	6 of 8 soft tissue resolved

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	tissue-15 bone+ soft tissue necrosis of chest wall				8 of 15 soft tissue+bone resolved
Carl (1998)[57]	Case Report Single positive case	5	3ii	No category for single case report	Resolution of breast edema and pain
Carl (2001)[58]	Case Series-44 patients 32 received HBO;12 control	4	2	Likely to be Beneficial	Statistically significant improvement in pain, erythema and edema of breast in HBO group compared to control

In the first series, Hart[16] reports the use of HBO_2 as an adjunct to skin grafting with all patients experiencing graft take. In the second, Feldmeier[52] reports 23 cases: eight with soft tissue only necrosis and 15 with a combination of bone and soft tissue necrosis. Resolution of soft tissue involvement only was 75%, while resolution in those with a component of bone necrosis was 53% and all required resection of necrotic bone.

In a case report Carl and Hartmann[53] in 1998 published their results in treating a patient with long standing symptomatic breast edema following lumpectomy and irradiation. The patient received 15, 90 minute HBO_2 treatments at 2.4 ATA. The patient had complete resolution of pain and edema.

Carl and his associates[54] in 2001 reported outcome in 44 patients who suffered complications after lumpectomy and irradiation for early breast cancers. These patients were found to have pain, edema, fibrosis and telengectasias. Each patient experienced these complications in various combinations. The severity of symptoms was assessed a score for each patient based on a modified LENT-SOMA score. Only patients with at least grade 3 pain (persistent and intense) or a summed LENT-SOMA score of 8 were studied. Each patient was assessed a score from 1 to 4 in the severity of symptoms in the categories of pain, edema, fibrosis/ fat necrosis and telangectasia/erythema. Thirty-two patients agreed to undergo HBO_2 treatment while 12 women refused HBO_2 and constituted the control group. Women who received HBO_2 had a statistically significant reduction in post treatment SOMA-LENT scores compared to those who did not. Fibrosis and telangectasia were not reduced. Women in the control group continued to demonstrate symptoms at the completion of the trial with no improvement in pain or edema. Seven women in the HBO_2 group had complete resolution of their symptoms.

Based on the information above and delineated in Table 3, hyperbaric oxygen for radiation induced chest wall or breast injury would qualify as an AHA level IIB (Acceptable and Useful based on Fair to Good Evidence) indication. In the BMJ scheme it would be considered "Likely to be Beneficial."

VI. Treatment of Radiation Proctitis and Enteritis

Table 9 lists 14 publications reporting experience in applying hyperbaric oxygen as treatment for radiation enteritis and proctitis.[59-71] The first paper is a case report detailing the successful treatment of a single patient with hemorrhagic proctitis.

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Table 9.

Author	Type of Report	AHA Grade	NCI Grade	Clinical Evidence	Comments
Bouachour (1990)[59]	Case Series-8 patients	5	3ii	Likely to be Beneficial	6 of 8 patients with hemorrhagic proctitis resolved
Charneau (1991)[60]	Single Case Report	5	3ii	Positive Case	Single patient with successful treatment of hemorrhagic proctitis
Nakada (1993)[61]	Single Case Report	5	3ii	Unknown Effectiveness Single Positive Case	Single patient with successful treatment of hemorrhagic proctitis
Feldmeier (1995)[62]	Animal Study	6	Not Clinical	Not Clinical but Positive Study	Reduced Fibrosis and reduced gross appearance of enteritis in murine ileum
Feldmeier (1996)[63]	Case Series-8 patients: 7 proctitis/colitis; 1 enteritis	5	3ii	Likely to be Beneficial	4 of 7 proctitis/colitis resolved; 1 enteritis did not resolve
Woo (1997)[64]	Case Series-18 patients	5	3ii	Likely to be Beneficial	2 patients had complete resolution; 8 partial and no change in 8
Warren (1997)[65]	Case Series-14 patients	5	3ii	Likely to be Beneficial	7 patients complete resolution; 2 improved 5 patients non-responders
Bredfelt (1998)[66]	Case Series-19 patients	5	3ii	Likely to be Beneficial	Complete resolution in 47%; 37% improved 16% non-responders

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Feldmeier (1998)[67]	Animal Study	6	Not Clinical	Not Clinical but Positive Study	Quantitative morphometry showed decreased Collagen in Bowel Wall
Carl (1998)[68]	Case Series-2 patients	5	3ii	Likely to be Beneficial	One patient completely resolved;the other stopped at 38 treatments without improvement
Gouello (1999)[69]	Case Series-36 patients	5	3ii	Likely to be Beneficial	2/3's of patients followed long term were improved or cured; 1/3 failed to improve
Bem (2000)[70]	Case Series-2 patients	5	3ii	Likely to be Beneficial	Both patients with anorectal ulcers resolved
Mayer (2001)[52]	Case Series-10 patients	5	3ii	Likely to be Beneficial	5 of 5 with rectal bleeding resolved; Statistically significant decrease in late morbidity score
Boyle (2002)[71]	Case Series-19 patients	5	3ii	Likely to be Beneficial	13 of 19 patients had major resolution of symptoms at completion of hyperbarics

An additional 8 case series reports are detailed in Table 3. Of the 114 cases reported in these 9 publications, 41 (36%) resolved and 68 (60%) improved after HBO_2 treatment.

The animal studies of Feldmeier[57,62] demonstrate a decrease in fibrosis and an improvement in compliance in the small bowel of animals receiving HBO_2 before frank necrosis was evident. In these studies enough time was allowed to elapse for the vascular changes and fibrosis of late radiation injury to be established prior to autopsy. Characteristically, a latent period of several months to years is observed to occur between the completion of radiation and clinical expression of radiation damage.[58]

These case reports represent AHA level 5 evidence and the 2 controlled animal studies present AHA level 6 evidence. In the NCI models, the case reports are level 3ii evidence and the animal studies are not given a categorization.

Based on the consistency of the findings, an AHA IIb indication category is assigned (Fair to good evidence provides support). Applying the BMJ scheme hyperbaric oxygen would be deemed to "Likely to be Beneficial" for this indication.

VII. Miscellaneous Abdominal Wall and Pelvic Injuries

Farmer and his colleagues[16] in 1978 as part of a report, which included radiation injuries to many sites, reported a single case of vaginal necrosis that resolved with HBO_2. Williams and associates[66] reported their results in treating 14 patients with vaginal radiation necrosis in 1992. Thirteen of 14 patients had resolution of their necrosis with hyperbaric treatment. One patient required 2 courses of HBO_2. In 1996 Feldmeier and colleagues[57] reported a series of 44 patients treated with various abdominal and pelvic injuries. The results in treating small and large bowel injuries have already been discussed above. Twenty-six of 31 patients who experienced injuries to the abdominal wall, groin, perineum, vagina or pelvic bones and who received at least 20 hyperbaric treatments had complete

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resolution with treatment. This group included 6 patients with vaginal necrosis, all of who experienced complete resolution with treatment. The combined results reported in these 3 papers show complete resolution in 40 of 46 patients (87%). All but one of the 21 patients reported in these three papers with soft tissue vaginal necrosis were treated successfully. See Table 10.

Table 10.

Hyperbaric Oxygen as Treatment for Delayed Miscellaneous Radiation Injuries of the Abdomen and Pelvis

Author	Type of Report	AHA Grade	NCI Grade	Clinical Evidence	Comments
Farmer (1978)[16]	Single Case Report	5	3ii	Unknown Effectiveness	Single case of vaginal necrosis resolved
Williams (1992)[72]	Case Series-15 patients	5	3ii	Likely to be Beneficial	13/14 patients with vaginal necrosis resolved
Feldmeier (1996)[63]	Case Series-37 patients	5	3ii	Likely to be Beneficial	26/31 who received at least 20 HBO sessions resolved including 1of 2 with pelvic osteoradionecrosis

All three publications in this section are AHA category 5 and NCI category 3ii. Based on the consistent positive outcome in treating pelvic injuries, an AHA category IIb is assessed to this indication. In the BMJ system, HBO_2 is "Likely to be Beneficial" for miscellaneous pelvic and abdominal injuries. Additional support for treating these injuries is found in the response of pathologically similar injuries at other anatomical sites including bowel, bladder and soft tissue injuries of the head and neck.

VIII. Neurologic Injuries

Table 11 lists 14 publications wherein HBO_2 has been applied to radiation-induced neurologic injuries. [15, 73-85] These injuries include radiation myelitis of the spinal cord, radiation necrosis of the brain, optic nerve injury and brachial plexopathy.

Table 11.

Hyperbaric Oxygen as Treatment for Radiation Injuries of the Nervous System

Author	Type of Report	AHA Grade	NCI Grade	Clinical Evidence	Comments
Hart (1976)[15]	Case Series-5 myelitis patients and 1 with brain necrosis	5	3ii	Unknown Effectiveness (mixed result)	Sensory but no motor improvement for myelitis patients; brain patient

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					improved
Glassburn (1977)[73]	Case Series-9 patients with Myelitis	5	3ii	Likely to be Beneficial	6 of 9 improved
Guy (1986)[74]	Case Series-4 patients optic nerve	5	3ii	Likely to be Beneficial (if initiated within 72 hrs)	2 of 2 improved if started within 72 hrs; if beyond 72 hrs, neither responded
Roden (1990)[75]	Case Series-13 patients optic nerve injury	5	3ii	Not likely to be Beneficial	No patient had improvement in vision
Fontanesi (1991)[76]	Single Case Report optic nerve	5	3ii	Unknown Effectiveness Single Positive Case	Visual acuity significantly improved in spite of persistent tumor
Feldmeier (1993)[77]	Animal Study of Myelitis	6	Not Clinical	Not Clinical but Positive Study	Onset of myelitis delayed for 9 weeks in a statistically significant fashion for animals treated prophylactically
Borruat (1993)[78]	Single Case Report	5	3ii	Unknown Effectiveness	Single patient with bilateral optic neuritis; resolution in more recently affected eye; slight improvement in earlier affected eye
Chuba (1997)[79]	Case Series-10 patients brain necrosis	5	3ii	Likely to be Beneficial	All ten initially improved; 4 died from tumor; 5 of remaining 6 still improved
Leber (1998)[80]	Case Series-2 patients brain necrosis	5	3ii	Likely to be Beneficial	One lesion disappeared; the other was reduced in size
Calabro (2000)[81]	Single Case report of radiation myelitis	5	3ii	Unknown Effectiveness Single Positive Case	Progressive improvement following HBO
Cirafisi (2000)[82]	Single Case Report of rhombencephalopathy	5	3ii	Unknown Effectiveness Single Negative Case	No improvement with HBO, steroids or anticoagulants
Pritchard (2001)[83]	RCT: Brachial Plexopathy	1B	1ii	A Negative Study: No Benefit	No improvement in brachial plexopathy

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					6 patients with lymphedema had significant reduction
Gesell (2002)[84]	Case Series 29 Patients with Brain Necrosis	5	3ii	Likely to be Beneficial	Neurologic exam improved in 58%; steroid requirements decreased in 69%
Dear (2002)[85]	Case Series 20 Patients with Brain Necrosis	5	3ii	Unknown Effectiveness (Mixed Study)	Only 1 of 11 patients with Glioblastoma Multiforme improved; with other tumors 8/9 subjectively better and 3 of 5 tested objectively improved

Hart and Mainous[15] in 1976 reported 5 cases of myelitis treated with HBO_2 without significant improvement. Glassburn and Brady[75] have reported 9 cases of myelitis in which patients received hyperbaric oxygen. Six of these 9 patients improved, including improvement in motor function. In 2000 Calabro and Jinkins[81] reported a single case of myelitis in which the patient demonstrated progressive improvement including imaging documentation by MRI after treatment with HBO_2. Feldmeier and colleagues[77] reported a statistically significant delay in the onset of transverse myelitis in mice receiving HBO_2 in a prophylactic fashion. The clinical papers present AHA category 5 and NCI category 3ii evidence. The animal study provides AHA category 6 evidence.

There are no other known successful treatments for radiation-induced transverse myelitis and the consequences of myelitis are permanent paralysis and loss of sensation below the level of involvement. The experience reviewed above shows improvement in 7 of 15 patients. Based on the evidence available this indication would be considered "Indeterminate" by the AHA scheme and of "Unknown Effectiveness" in the BMJ model. In this desperate circumstance with a low likelihood of harms and no other effective treatment, HBO_2 based on humanitarian considerations appears justifiable if initiated promptly.

Table 11 lists 6 publications in which HBO_2 has been applied to the treatment of brain necrosis. In the publication by Hart and Mainous[15], a single case of brain necrosis is presented and this patient had improvement after treatment. In the paper by Chuba and associates[79], HBO_2 treatment led to temporary improvement initially in all 10 pediatric patients treated. Ultimately, four patients died as a result of their malignancy. At the time of their publication, five of the surviving 6 patients had maintained their improvement. Leber and colleagues[80] reported the results in delivering HBO_2 to 2 patients suffering from radiation necrosis as a result of radiosurgery for arteriovenous malformations. Both patients had shrinkage of their lesions by imaging studies and one had complete resolution. In the paper of Cirafisi and Verderamae[82] a single patient is presented who failed to respond to HBO_2. The patient also failed to respond to steroids and anti-coagulants. Gesell and colleagues[84] have reported the largest experience to date in applying hyperbaric oxygen to the treatment of radiation-induced brain necrosis at the 2002 Annual Meeting of the Undersea and Hyperbaric Medical Society. After hyperbaric oxygen treatment 17 of 29 patients had improved neurological examinations and in 20 of 29 patients, it was possible to decrease steroid requirements. At the same meeting Dear and

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associates[85] presented their experience in treating 20 patients with radiation-induced brain necrosis. In 11 patients with Glioblastoma Multiforme, only one patient showed objective improvement. However, 7 of 11 patients were dead of tumor within a short time following HBO_2 and obviously had active tumor at the time of treatment. It is very likely that the presence of tumor contributed to the neurologic deficits manifested by the patients. We have observed for some time that soft tissue necrosis lesions will not heal with HBO_2 therapy if tumor is present. In the other 9 patients with other tumors reported by Dear, eight were improved subjectively and 3 had objective improvement. All 6 of these publications represent AHA level 5 and NCI level 3ii evidence. If we combine the results from these 6 publications, we find that 29 of 63 (46%) patients reported had some improvement after HBO_2. No other treatments short of surgical resection of the necrotic focus have been effective. Based on the evidence available, this indication would be considered Category IIb (Acceptable and Useful based on fair to good evidence) by the AHA scheme and of "Likely to be Effective" in the BMJ model.

Table 11 also includes four references reporting the results of HBO_2 in treatment of radiation induced optic neuritis. Again all four of these publications are case series including the single case report by Fontanesi.[76] Only four of the 19 patients reported in these publications had visual improvement. Guy and Schatz[74] report in their series that HBO_2 must be initiated promptly. In their series, two patients had complete restoration of their sight when they began HBO_2 treatment within 72 hours of loss of their sight. The other two patients who began HBO_2 at 2 weeks and 6 weeks after loss of vision had no improvement. In the paper by Borruat et al[78], a single patient with bilateral radiation-induced optic neuritis had complete resolution in the more recently affected eye and improvement in the eye first affected. These results also suggest the importance of early intervention in order to obtain a positive outcome.

Based on these 4 publications, HBO_2 would be considered "Indeterminate" in the AHA scheme and "Unknown Effectiveness" in the BMJ scheme. No other effective therapy exists for radiation-induced optic neuritis. In this desperate circumstance where permanent blindness is likely to occur, a trial of HBO_2 would appear to be justified based on humanitarian considerations. This therapy must be promptly initiated.

Finally, in regard to peripheral nerve injury treated by hyperbaric oxygen, Table 11 includes a randomized controlled trial conducted by Pritchard and colleagues[76]. This study was designed to investigate the effect of HBO_2 in treatment of radiation-induced brachial plexopathy. This trial is negative and fails to demonstrate a therapeutic advantage for HBO_2. The median time from onset of symptoms until enrollment into the trial was 11 years. As noted above in many neurological disorders, an effect of HBO_2 occurs only after prompt intervention. Importantly and interestingly, patients in the HBO_2 arm demonstrated statistically less post study deterioration in neurological function compared to the control group. Six patients in the HBO_2 arm also experienced a reduction in symptomatic lymphedema of the affected arm. Based on the presently available evidence, we would consider this indication for hyperbaric oxygen to be "Not Acceptable" in the AHA scheme and "Unlikely to be Beneficial" in the BMJ scheme.

IX. Radiation Necrosis of the Extremities

HBO_2 has also been reported as a useful therapy in radiation necrosis of the extremities. Table 12 lists two studies that discuss HBO_2 results in treating radiation injuries of the extremities.

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Table 12.

Hyperbaric Oxygen as Treatment for Radiation Injuries of the Extremities

Author	Type of Report	AHA Grade	NCI Grade	Clinical Evidence	Comments
Farmer (1978)[17]	Single Case Report	5	3ii	Unknown Effectiveness Single Negative Case	1 of 1 failed to respond
Feldmeier (2000)[86]	Case Series-17 patients	5	3ii	Likely to be Beneficial	11 of 17 resolved; 11 of 13 if those lost to followup or with active cancer are excluded

In the report previously discussed by Farmer and his colleagues[16] a single case of foot injury did not respond to HBO_2 (AHA level 5 evidence and NCI level 3ii evidence). In a series reported by Feldmeier and associates[86], 17 patients with necrosis of the extremities treated with HBO_2 were reported (AHA level 5 and NCI level 3ii evidence). Sixteen of 17 patients had only soft tissue necrosis. Eleven of 17 had resolution with HBO_2. If analysis is restricted to those patients in whom follow-up was available and in whom there was no evidence of recurrent cancer, eleven of 13 (85%) had resolution.

Although based on a small number of patients, this indication can be considered AHA level IIb and by the BMJ system "Likely to be Beneficial". This determination is made in part based on successful intervention in soft tissue and bony radiation necrosis at other sites as reported above.

X. Hyperbaric Oxygen for Radiation Damage in Children

Published experience in applying HBO_2 to radiation-induced injury in children is very limited. The report of Chuba and colleagues[79] of improvement in 10 pediatric patients with radiation-induced brain necrosis has already been discussed in the section on neurological injuries. Ashamalla and colleagues[87] reported their experience at the University of Pennsylvania in delivering HBO_2 to 10 children either as a prophylaxis against radiation injury or for treatment of established radiation necrosis. Six patients had pre-operative HBO_2 prior to dental extractions, root canals or coronoidectomies for mandibular ankylosis. All had successful outcomes without subsequent necrosis or surgical complications. Four other patients were treated for manifest radiation injury. One patient was treated for a 7th cranial nerve neuropathy. Three others were treated for osteoradionecrosis (ORN) of various sites (mastoid bone, temporal bone and sacrum). Hyperbaric oxygen was given in conjunction with sequestromy for the ORN patients. The patients with ORN had complete resolution while the patient with the 7th nerve injury did not have sustained improvement.

There are no compelling biochemical or physiologic reasons to think that the response of radiation injuries to HBO_2 in children is likely to be different to response in adults. Certainly children present special problems in conjunction with therapeutic radiation including complications not seen in adults such as growth retardation and decreased intellectual development as evidenced by a decrement

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in intelligence testing. No targeted research has been done in these special complications experienced in children; however, this would appear to be a fruitful area for future research.

Discussion:

Few randomized controlled trials have been published to support efficacy of HBO_2 in treating delayed radiation injuries, yet the literature consistently provides lower levels of evidence supporting its application for this indication. Positive reports have been generated in multiple anatomic sites and in multiple tissue/organ types and from multiple investigators from a number of different countries and continents. A characteristic of valid scientific methodology is consistency of reproducibility of outcome by other investigators in other venues. Tables 4 through 12 list 74 studies (some are included in more than 1 section). Of these 74 publications, all but 7 give positive indications of success with HBO_2 therapy. Four of the 7 negative reports are related to intervention with HBO_2 in neurological injuries where the pathophysiology is unique and where the promptness of intervention may be critical.

Experts are not in complete agreement as to the exact pathophysiology of delayed radiation injuries, but there is general agreement that endarteritis and resultant tissue hypoxia are consistent findings and contribute substantially to its etiology.[88-9 3] Hyperbaric oxygen has been shown to enhance neovascularization at the microscopic level and to improve tissue oxygenation. Mechanisms by which HBO_2 offers therapeutic effect have been revealed by animal studies of Marx and associates and by Feldmeier and collaborators. Marx et al[92] have shown a dose dependent increase in vascular density in irradiated rabbits treated with HBO_2. Feldmeier and co-workers[62,67] have shown evidence of decreased fibrosis in the pelvic and abdominal organs of mice receiving whole abdominal irradiation and then receiving post-irradiation HBO_2 compared to those receiving the same of radiation course without HBO_2. Quantitative morphometry identifying and contrasting the relative percentages of collagenous vs non-collagenous components in small and large bowel and kidney in these animals confirm the reduction of tissue fibrosis in animals receiving HBO_2 seven weeks after radiation exposure.[67,94,95]

For this review, published materials were classified by anatomy or organ system. Perhaps from a pathological perspective, it would be more appropriate to divide tissues broadly into soft tissue and bony injuries. The response to and mechanisms of response to HBO_2 in soft tissue wounds resulting from radiation necrosis from the head and neck to the abdominal wall to the groin to the perineum to the extremities is likely to be similar analogous to the response to antibiotics in cellulitis affecting soft tissues at many anatomic sites. Of course, the therapeutic agent must be deliverable in adequate dose to the site of pathology. Similarly, the response to HBO_2 in bone necrosis of the mandible is unlikely to be different from radiation necrosis of rib, pelvic bone or long bone of the extremities as long as an appropriate arterial supply is available to allow oxygen transport to the site of radiation injury.

Damage to the nervous system, especially the central nervous system, certainly presents a special case and mechanisms whereby HBO_2 might be effective in the treatment of CNS injuries are not likely to be as simple as enhancing neovacularization. Though some have recently challenged the concept that ischemic injury of the CNS is irreparable, no one would deny that the repair of central nervous system tissues as the result of ischemia is very limited and that only very innovative research, e.g. stem cell transplantation, is likely to yield a substantial increment resolution of ischemic injury of the CNS.

The systematic literature review contained herein would certainly have benefited from a larger number of prospective randomized clinical trials and formal meta-analyses to substantiate

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conclusions. In the preparing this review, the authors did not uncover large randomized controlled trials supporting other interventions for radiation injuries. A recent meeting convened at the National Cancer Institute designed to examine strategies for reducing radiation injuries presented the results of several pre-clinical studies but only identified a very few ongoing clinical trials. One clinical trial is ongoing which employs FGF7 (a fibroblast growth factor).[96] One avenue of research, which appears promising based on pre-clinical study, is designed to block the renin-angiotensin system, but no clinical trials are yet underway. A number of trials are now published in the medical literature reporting some success in preventing radiation damage with Amifostine given during therapy as a radioprotector.[97-101] Two papers have presented very early information from a pilot study and a small retrospective review suggesting that pentoxifylline may have efficacy in the treatment of some delayed radiation injuries.[102,103]

The Baromedical Research Foundation is currently sponsoring the HORTIS trials, a series of eight randomized blinded placebo-controlled trials investigating the effects of HBO_2 on a variety of delayed radiation injuries.[104] Seven of the eight trials are designed to investigate the effects of HBO_2 on existing injuries in a variety of tissues. The final trial is designed to investigate the efficacy of HBO_2 as a prophylaxis against radiation injuries in a group of patients at high risk. When these studies are completed and analyzed, we should have type 1evidence elucidating the effects of HBO_2 for a broad range of radiation injuries. The HORTIS trial design makes use of the SOMA/LENT system.[105,106] This system for quantifying the severity of radiation injuries was the result of a cooperative project jointly developed by the RTOG, an NCI sponsored, cooperative research group, and the EORTC, the corresponding multi-national European radiation research cooperative group. These criteria for reporting the severity of radiation injuries should be applied to future reports of radiation toxicity or treatment of toxicity. In the SOMA/LENT system, for each organ the severity of injury is assigned a numerical grade. If a therapeutic modality is applied, its effects can be quantified by comparing pre-treatment and post-treatment scores. Until the results of these ongoing randomized trials are available, we must make do with limited evidence.

Other specialists dealing with other disease states also face the dilemma of producing evidence-based reviews in the absence of randomized prospective controlled trials. For instance, a recent publication by Bennett et al[107] in the dermatology literature presents an evidence-based evaluation recommending the use of oral steroids in the treatment of infantile cutaneous hemangiomas based entirely on 10 case series and positive experience in a total of 184 patients.

In the BMJ publication, Clinical Evidence[7], therapies are reviewed even when no randomized controlled trials are available. For example in the review of treatment of cerebral metastases from metastatic breast cancer, the editors state, "We found no systematic review and no RCT's comparing one form of treatment with another...Non-randomized evidence suggests that symptoms from cerebral metastases can be successfully controlled with radiotherapy." The editors deem radiotherapy "Likely to be Beneficial" for breast cancer metastatic to the brain. This is standard treatment virtually anywhere in the world in spite of the absence of type 1 evidence.

Sackett and associates[108] define evidence-based medicine as the use of the best current evidence in making decisions about the care of individual patients. The best current evidence for HBO_2 in the treatment of radiation injury is presented in this paper in a systematic fashion. This evidence includes two randomized controlled trials, two prospective cohort controlled trials, numerous case series and several animal studies. The great majority of these papers are positive in their support of HBO_2 for delayed radiation injury. The associated harms are few and generally of minor consequence. The NCI model judges the strength of evidence with an eye to the severity of the problem and the consequences of effective treatment, especially when the treatment is life saving or enhances quality of life in a

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highly significant fashion.[6] It therefore seems appropriate to judge the success of HBO_2 for delayed radiation injury as rather notable when the alternatives are death, radical surgery in already compromised patients or severe limitations in quality of life without successful treatment.

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