Appendix A. Indications for HBOT

Food and Drug Administration		Undersea and Hyperbaric Medical Society	Centers for Medicare and Medicaid Services
1.	Air or gas embolism	Air or gas embolism	Gas embolism, (ICD-9-CM diagnosis 958.0, 999.1).
2.	Carbon monoxide poisoning and smoke inhalation	Carbon monoxide poisoning	Acute carbon monoxide intoxication, (ICD-9-CM diagnosis 986) .
3.	Carbon monoxide poisoning complicated by cyanide poisoning	Carbon monoxide poisoning complicated by cyanide poisoning	Cyanide poisoning (ICD-9-CM diagnosis 987.7, 989.0).
4.	Clostridial myonecrosis	Gas gangrene	Gas gangrene, (ICD-9-CM diagnosis 0400).
5.	Crush injury	Crush injury	Crush injuries and suturing of severed limbs. (ICD-9-CM diagnosis 927.00-927.03, 927.09-927.11, 927.20-927.21, 927.8-927.9, 928.00- 928.01, 928.10-928.11, 928.20-928.21, 928.3, 928.8-928.9, 929.0, 929.9, 996.90-996.99.)
6.	Compartment syndrome, acute traumatic ischemias	Compartment syndrome and other acute traumatic ischemias	Acute traumatic peripheral ischemia. (ICD-9-CM diagnosis 902.53, 903.1, 903.01 904.0, 904.41.)
7.			Acute peripheral arterial insufficiency, (ICD-9-CM diagnosis 444.21, 444.22, 444.81).
8.	Decompression sickness	Decompression sickness	Decompression illness, (ICD-9-CM diagnosis 993.2, 993.3).
9.	Enhancement of healing in selected problem wounds	Enhancement of healing in selected problem wounds	
10.	Exceptional blood loss	Exceptional blood loss (anemia)	
11.	Necrotizing soft tissue infections	Necrotizing soft tissue infections	Progressive necrotizing infections (necrotizing fasciitis), (ICD-9-CM diagnosis 7278.86).
12.	Osteomyelitis (refractory)	Refractory osteomyelitis	Chronic refractory osteomyelitis (ICD-9-CM diagnosis 730.10-730.19).
13.	Radiation tissue damage	Delayed radiation injury (soft tissue and bony necrosis)	Osteoradionecrosis (ICD-9-CM diagnosis 526.89).

	Food and Drug Administration	Undersea and Hyperbaric Medical Society	Centers for Medicare and Medicaid Services
14.			Soft tissue radionecrosis (ICD-9-CM diagnosis 990).
15.	Skin grafts & flaps (compromised)	Skin grafts & flaps (compromised)	Treatment of compromised skin grafts, (ICD-9-CM diagnosis 996.52; excludes artificial skin).
16.	Thermal burns	Thermal burns	
17.	Adjunctive hyperbaric oxygen in intracranial abscess	Intracranial abscess	
18.		Actinomycosis	Actinomycosis(ICD-9-CM diagnosis 039.0-039.4, 039.8, 039.9).

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Appendix C. Literature Search Strategies

Summary of Online Searching

Stroke or Brain Injury Search Terms

MeSH Terms
Explode brain diseases
Explode confusion
Explode meningitis
Explode coma
Explode craniocerebral trauma

Textwords
Stroke
TIA
Transient ischemi$
Transient ischaemi$
Brain
Cerebro$
Cerebral$
Intracranial$
Concussion$
Confusion$
Coma$
Stupor$
Encephalopath$
Meningitis
Encephalitis
Dementia
Leukoencephalopath$
Leukodystroph$
Cortical dysplas$
Craniocerebral$

Hyperbaric Oxygen Therapy Search Terms

MeSH Terms
Hyperbaric oxygenation

Textwords
Hyperbaric oxygen$
Hyperbaric therap$

Search Strategy

[sh] = subject heading, [ti] = title word, [ab] = word in abstract

1 exp Brain Diseases/ [sh]
2 exp CONFUSION/ [sh]
3 exp MENINGITIS/ [sh]
4 exp COMA/ [sh]
5 exp Craniocerebral Trauma/ [sh] or exp Head Injury/ [sh]
6 (stroke or tia or brain or cerebro$ or cerebral$) [ti,ab,sh]
7 (transient ischemi$ or transient ischaemi$) [ti,ab,sh]
8 (intracranial$ or concussion$ or confusion$ or coma$) [ti,ab,sh]
9 (stupor$ or encephalopath$ or meningitis) [ti,ab,sh]
10 (encephalitis or dementia or leukoencephalopath$) [ti,ab,sh]
11 (leukodystroph$ or craniocerebral$) [ti,ab,sh]
12 cortical dysplas$ [ti,ab,sh]
13 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12
14 Hyperbaric Oxygenation/ [sh]
15 hyperbaric oxygen$ [ti,ab,sh]
16 hyperbaric therap$ [ti,ab,sh]
17 14 or 15 or 16
18 13 and 17
19 limit 18 to (human and english language)

Databases & Results

Database	Date of search	Time period covered	Search interface	Citations	Comments
MEDLINE & PreMEDLINE	3/23/01	1966-	OVID	400	
HealthStar	3/23/01	1975-2000	OVID	2	Excluding MEDLINE citations
CINAHL	3/23/01	1982-	OVID	17	
Cochrane Database of Systematic Reviews	3/23/01	Issue 1 2001	Update Software CD	2	
Cochrane Controlled Trials Register	3/23/01	Issue 1 2001	Update Software CD	16	Excluding MEDLINE citations
DARE	3/23/01	Issue 1 2001	Update Software CD	1	
AltHealthWatch	3/23/01	1990-	EBSCOhost	4	
MANTIS	3/23/01	1880-	OVID	1	
EMBASE	3/27/01	1980-	OVID	269	Much overlap with MEDLINE

Update Searches and Results

Database	Date of search	Time period covered	Search interface	New Citations	Comments
MEDLINE & PreMEDLINE	1/30/02	April 2001 -	OVID	46	
	7/31/03	February 2002 -	OVID	10	
HealthStar					Defunct database
CINAHL	1/30/02	April 2001 -	OVID	2	
	7/31/03	February 2002 -	OVID	0	
Cochrane Database of Systematic Reviews	2/6/02	Issue 1 2002	OVID	5	
Cochrane Controlled Trials Register	2/6/02	Issue 1 202	OVID	29	Excluding MEDLINE citations
DARE	2/6/02	Issue 1 2002	OVID	1	
AltHealthWatch	2/12/02	April 2001 -	EBSCOhost	3	
MANTIS	2/12/02	April 2001 -	OVID	2	
EMBASE	2/11/02	April 2001 -	OVID	34	Much overlap with MEDLINE
	7/31/03	February 2002 -	OVID	6	Overlap with MEDLINE
Health Technology Assessment (HTA)	2/12/02		University of York website	6	
Undersea & Hyperbaric Medical Society Database	2/26/02		UHMS proprietary system	416	Much overlap with MEDLINE

A small amount of overlap between the databases, including overlap with the previous search, was apparent in the Cochrane Controlled Trials Register, EMBASE, and the Undersea & Hyperbaric Medical Society Database. After eliminating these duplicate citations and conducting dual abstract assessment, 110 full papers were ordered. Eighty-seven of these were

from the Undersea & Hyperbaric Medical Society Database, which did not provide abstracts for titles and included a large number of meeting abstracts. In addition to these, one member of the Technical Expert Advisory Group provided articles and meeting abstracts from his personal library (Dr. Paul Harch).

Appendix D. Quality Assessment Criteria

US Preventive Services Task Force Criteria for Grading the Internal Validity of Individual Studies

(Harris RP, Helfand M, Woolf SH, et al. Current methods of the third U.S. Preventive Services Task Force. Am J Prev Med. 2001;20(3S):21-35.)

Randomized Controlled Trials and Cohort Studies

Seven categories of criteria apply to RCTs and cohort studies. They include:

1. Initial assembly of comparable groups.
   a. For RCTs: adequate randomization, including first concealment and whether potential confounders were distributed equally among groups.
   b. For cohort studies: consideration of potential confounders with either restriction or measurement for adjustment in the analysis; consideration of inception cohorts.
2. Maintenance of comparable groups (includes attrition, cross-overs, adherence, contamination).
3. Levels of follow-up: differential loss between groups; overall loss to follow-up.
4. Measurements: equal, reliable, and valid, and including masking of outcome assessment.
5. Clear definition of interventions.
6. All important outcomes considered.
7. Analysis:
   a. For RCTs: intention-to-treat analysis.
   b. For cohort studies: adjustment for potential confounders.

The definitions of the three rating categories for these types of studies are as follows:

Good: Comparable groups assembled initially and maintained throughout the study; follow-up at least 80 percent; reliable and valid measurement instruments applied equally to the groups; outcome assessment masked; interventions defined clearly; all important outcomes considered; appropriate attention to confounders in analysis; for RCTs, intention-to-treat analysis.

Fair: Generally comparable groups assembled initially but some question remains whether some (although not major) differences occurred with follow-up; measurement instruments acceptable (although not the best) and generally applied equally; outcome assessment masked; some, but not all important, outcomes considered; appropriate attention to some, but not all, potential confounders; for RCTs, intention-to-treat analysis.

Poor: Groups assembled initially not close to being comparable or not maintained throughout the study; measurement instruments unreliable or invalid or not applied at all equally among groups; outcome assessment not masked; key confounders given little or no attention; for RCTs, no intention-to-treat analysis.

Criteria for Grading the Overall Evidence

Aggregate Internal Validity

This category refers to the overall extent to which data are valid for conditions addressed within studies. It would be rated according to quality grading information about individual studies.

Aggregate External Validity

This category concerns the generalizability of evidence to questions addressed by the linkage. This would include the concordance between populations, interventions, and outcomes in the studies reviewed (on the one hand) and those to which the linkage pertains (on the other). In short, this category reflects the applicability of the evidence to real-world conditions.

The Methods Work Group expects that differences between conditions examined in studies and those addressed by the linkages should be considered if they could potentially influence outcomes. These might include (but not necessarily be limited to): (a) biologic or pathologic characteristics; (b) incidence and prevalence of clinical conditions; (c) distribution of comorbid conditions that might affect outcomes; and (d) likelihood of acceptability and adherence on the part of patients or providers (or both).

Consistency

This category relates to the overall "coherence" of the body of evidence relating to the linkage. Specifically, it includes the number of studies, the homogeneity of those studies (in terms of clinical conditions, populations, settings, and the like), the level of precision of findings in the studies, and the direction of results. In addition, it can include dose-response relationships.

NHS Centre for Reviews and Dissemination, based at University of York

(Available at http://www.york.ac.uk/inst/crd/crd4_ph5.pdf)

Experimental Studies

1. Was the assignment to the treatment groups really random?
   Adequate approaches to sequence generation
   - Computer-generated random numbers
   - Random numbers tables

   Inadequate approaches to sequence generation
   - Use of alternation, case record numbers, birth dates or week days
2. Was the treatment allocation concealed?
   Adequate approaches to concealment of randomization
   - Centralized or pharmacy-controlled randomization

    - Serially-numbered identical containers
    - On-site computer based system with a randomization sequence that is not readable until allocation
    - Other approaches with robust methods to prevent foreknowledge of the allocation sequence to clinicians and patients

  Inadequate approaches to concealment of randomization
    - Use of alternation, case record numbers, birth dates, or week days
    - Open random numbers lists
    - Serially numbered envelopes (even sealed opaque envelopes can be subject to manipulation)
3. Were the groups similar at baseline in terms of prognostic factors?
4. Were the eligibility criteria specified?
5. Were the outcome assessors blinded to the treatment allocation?
6. Was the care provider blinded?
7. Was the patient blinded?
8. Were the point estimates and measure of variability presented for the primary outcome measure?
9. Did the analyses include and intention-to-treat analysis?

Observational Studies

Cohort studies:

- Is there sufficient description of the groups and the distribution of prognostic factors?
- Are the groups assembled at a similar point in their disease progression?
- Is the intervention/treatment reliably ascertained?
- Were the groups comparable on all important confounding factors?
- Was there adequate adjustment for the effects of these confounding variables?
- Was a dose-response relationship between intervention and outcome demonstrated?
- Was outcome assessment blind to exposure status?
- Was followup long enough for the outcomes to occur?
- What proportion of the cohort was followed up?
- Were dropout rates and the reasons for dropout similar across intervention and unexposed groups?

Case series:

- Is the study based on a representative sample selected from a relevant population?
- Are the criteria for inclusion explicit?
- Did all individuals enter the survey at a similar point in their disease progression?
- Was followup long enough for important events to occur?
- Were outcomes assessed using objective criteria or was blinding used?
- If comparisons of sub series are being made, was there sufficient description of the series and the distribution of prognostic factors?

Appendix E. Excluded Studies

1. Brain Injury Improves with Hyperbaric Oxygen. Life Extension. 1999;5(7), 71.

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Appendix H. Outcome measures used in HBOT studies[1;2]

Test Name	Description	Strength of Test	Weakness of Test
2-Point Discrimination Test	With eyes closed, pt asked whether he feels 1 or 2 pins touching tip of finger	Part of Neurological exam; a test of parietal lobe function (sensory part of the brain)	Not very sensitive and not very specific
Ashworth Scale (Spasticity)	Amount of resistance that examiner feels when passively moving a joint	Inexpensive; no equipment needed; a test of muscle tone	Unreliably unless examiner very well trained; inter-rater reliability is generally poor; not specific for spasticity
Bender-Gestalt Test	Pt asked to reproduce figures; a written test	Inexpensive; can be given in 10 minutes; a test of visual-perception	Assumes that pt had normal visual-perception prior to the injury
CT Scan White Matter Low Attenuation Volume	Area of decreased blood flow in the Scan in the white matter part of the brain	High correlation with poor blood flow in the brain	Requires availability of equipment; about $500 per test
Digit Span	Part of the WAIS-R; ask pt to repeat digits as presented by examiner; a test of attention	Reliable; validated and easily administered	Not sensitive
Disability Rating Scale	Sum of ratings over different scales of disability and impairment	Validated, excellent reliability and administered in 5 minutes	Not helpful for mild to moderate TBI
Double Simultaneous Stimulation Test	Same as 2-point discrimination		
Electroencephalogram (EEG)	Recording the electrical activity of the brain	Easily performed; excellent reliability	Not specific for a disability
Functional Independent Measure (FIM)	Measures the degree of assistance a pt requires following recovery from a TBI	30 minute or less to administer; reliable	Cognitive, and behavioral aspects of test not adequate to evaluate TBI pts
Glasgow Coma Scale (GCS)	A scale that semi-objectifies the level of coma (3-15)	Administered at the bed-side; used for assessment of a pt in coma	Must use with other evaluations before offering a prognosis of recovery from the TBI
Glasgow Outcome scale (GOS)	Ordinal rating of Global Outcome (1-5)	Good reliability; administrated at bedside; correlates with GCS	Not very sensitive
Gross Motor Function Measure (GMFM)	Developed to measure changes in motor function in children with CP	Validated, reliable and sensitive	Limited to Children less than age 7 years
Mental Status Examination	Part of Routine Neurological Examination; a screening test for memory, general knowledge, attention, etc.	Easily administered; reliable and valid	A Screening test; not sensitive and not specific.

Outcome measures used in HBOT studies (continued)

Test Name	Description	Strength of Test	Weakness of Test
Motor power of hand by dynamometer	Hand held gauge to determine strength of hand grasp	Reliable and easily administered	Very specific for strength; not correlated with function
Multiple Modality Evoked responses	Tests of pathway for vision, hearing and sensation	Easily administered, reliable	Non-specific
Repetitive Thumb/finger Movements	Ask pt to rapidly oppose finger and thumb; standardized part of the neurologic exam; test of coordination of fine motor movements	Easily administered	Non-specific; very subjective
SPECT (Single Photon Emission Computed Tomography)	Single proton emission computed tomography (SPECT) measures the uptake and distribution of a radioactive nucleotide within the brain and is believed to be proportional to cerebral blood flow (CBF). The CBF demonstrated by SPECT correlates with the metabolic activity that is shown by proton emission tomography (PET).	Less expensive form of functional imaging than the PET scan. This procedure can detect generalized hypo metabolism secondary to anoxia for example. In severe head trauma there is a strong association between axonal injury and decreased metabolism within the brain	Limited prognostic value for recovery for stroke; clinical significance of abnormal SPECT in TBI unknown. To date, there are no studies correlating a change in CBF asdemonstrated by SPECT and a functional change in the patient.
Token Test-test for receptive aphasia	Tokens presented to patient of increasing length and complexity	Educational level does not contaminate the test	
Volume of hypodensity on CT Scan	A finding on CT scan that is consistent with an infarction	Well standardized	Not specific; a finding caused by change in blood flow to the brain
WAIS-R (Wechsler Adult Intelligence Scale –Revised)	A validated and reliable test of Intelligence	Good predictor of academic intelligence, especially when recovering form a TBI	May be preserved after TBI despite debilitating problems with executive functions or memory
Wechsler Memory Scale	Well standardized test of immediate recall and long-term memory		Insensitive for pts with profound memory deficits

The following tests were utilized in one or more of the studies cited; references for these tests could not be found.

Guild Memory test
Hunt-Minnesota Test
Jebsen's test (Fine Motor Function)
Memory Drum test
Neurologic Disability Evaluation
Neurology Recovery Score
Orgogozo Scale
Rankin Disability Scale
Reaction Time (visual and auditory)
Rheology studies
Stockton Geriatric Scale
Tien's Organic integrity Test
Trouilla Scale
Wechsler Mental status

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