NHS England

Evidence review: Recompression with or without Hyperbaric Oxygen Therapy for Decompression Illness/ Gas Embolism

Draft for consultation

NHS England

Evidence review: Recompression with or without Hyperbaric Oxygen Therapy for Decompression Illness/ Gas Embolism

First published:	July 2017
Updated:	Not applicable
Prepared by:	Solutions for Public Health (SPH) on behalf of NHS England Specialised Commissioning

Draft for consultation

Contents

1 Introduction 4

2 Summary of results 5

3 Methodology 6

4 Results 7

5 Discussion 9

6 Conclusion 10

7 Evidence Summary Table 12

8 Grade of evidence table 20

9 Literature Search Terms 27

10 Search Strategy 30

11 Evidence Selection 30

12 References 31

Draft for consultation

1 Introduction

- Spending time at raised environmental pressure (e.g. SCUBA diving, compressed air work such as tunnelling) causes additional inert gas from air or other breathing mixtures to dissolve in the tissues. A return to a lower pressure is known as decompression. If decompression is sufficiently controlled, the excess gases can be excreted safely in exhaled breath by the lungs.
- If decompression occurs too quickly to allow excretion by the lungs, these gases can form bubbles (gas emboli) within the tissues, most often in venous blood. Decompression to sub-atmospheric pressures, such as during altitude training for aircrew, can also generate or exacerbate gas emboli. Disease caused by evolved gas in this manner is known as decompression sickness.
- If lung tissue is ruptured by expansion of gas during decompression, gas can escape into the systemic arterial circulation via the pulmonary veins and the left heart. This escaped gas is termed arterial gas embolism.
- The term decompression illness encompasses decompression sickness and gas embolism arising from decompression. In a diver, it is often not possible to determine whether a patient has evolved gas disease, escaped gas disease or both. Decompression sickness (DCS) has also been subdivided into Type I (DCS-I), which includes joint pain, symptoms involving the skin or swelling and pain in lymph nodes, and Type II (DCS-II), which includes symptoms in three categories: neurological (e.g. paraesthesiae, numbness, muscle weakness, and mental state changes), inner ear (e.g. tinnitus, hearing loss, vertigo and nausea) and cardiopulmonary (e.g. chest pain, increased breathing rate) (US Navy Department, 2008). Gas emboli can also enter the circulation during medical procedures such as renal dialysis, mechanical ventilation (life support machines) or certain types of surgery. This is termed iatrogenic gas embolism.
- Regardless of the mechanism, gas emboli can cause clinical manifestations ranging from lethargy and pain to severe neurological impairment, multi-organ failure and death. Bubble formation within the circulation and tissues causes harm by mechanical distortion of tissues, the obstruction of arteries or veins and the initiation of immune mechanisms that can lead to oedema (tissue swelling), and hypoxia (lack of oxygen availability).
- The application of high environmental pressure (recompression) forces gas emboli to dissolve once more and discourages formation of new emboli. Slow, controlled decompression then allows the gas to be excreted safely through the lungs.
- Administration of oxygen at a partial pressure significantly higher than 100 kiloPascals is known as hyperbaric oxygen therapy (HBOT). It takes place in a chamber. It was first introduced over 50 years ago for the treatment of decompression illness along with recompression as described, for example, by Goodman et al (1965).
- However, it is recognised that the evidence base supporting the use of HBOT in the treatment of decompression illness and gas embolus is not well developed and the rationale for treatment has been based on knowledge of the gas laws of physics, observational symptom resolution and the absence of a credible alternative. There is no relevant NICE guidance.
- Retreatment with HBOT is also proposed in a number of circumstances, for example when patients have a relapse or persistent symptoms after initial treatment (thought to be due to the reappearance of circulating bubbles), or for the treatment of bubble-related damage after the bubbles themselves have been eliminated.
- Exact figures for the numbers of those affected by decompression illness are uncertain because not all those with minor symptoms will present to or be referred on to hyperbaric facilities. In FYs 2011/12 to 2013/14, an average of 293 divers and two cases of gas embolism were treated with hyperbaric oxygen annually in HBOT providers in the UK (NHS England, 2017).

Draft for consultation

2 Summary of results

- This rapid evidence review identified one randomised controlled trial (RCT) (in Bennett et al 2012) and five retrospective studies (Hadanny et al 2015, Lee et al 2015, Xu et al 2012, Sayer et al 2009, Koch et al 2008) of recompression with or without HBOT in patients with decompression illness (DCI) or decompression sickness (DCS), and one prospective study of HBOT in patients with iatrogenic gas embolus (IGE) (Bessereau et al 2010).
- Most studies presented findings in broad categories such as complete recovery, partial recovery or no improvement, with varying or no definitions of these categories, assessed at time points ranging from immediately after treatment to one year after discharge from hospital.
- The most commonly used recompression schedule was US Navy Table 6 (USN T6) or Royal Navy Table 62 (RN T62), but most studies included patients in whom a number of other schedules were also used and three studies used different schedules specified in other countries.
- The rate of complete recovery immediately after one session of HBOT (USN Table 5 or T6) in 195 patients with Type I DCS was reported to be 33%, with 92% of patients reporting complete recovery without further treatment on telephone follow-up one month later (Lee et al 2015).
- Recovery at discharge from hospital was reported in several studies. In one, complete recovery after treatment (the majority with USN T6) for DCI was reported in 67% of 168 patients at discharge, and 82% of 164 patients at 4-6 week follow-up (Bennett et al 2012). An overall 'good' outcome at discharge was reported in 96% of more than 650 patients treated for DCI with four main schedules, most commonly RN T62 (Sayer et al 2009). Complete recovery at discharge was found in 89.8% of more than 5000 patients with DCI treated with one of four recompression schedules, but it was not clear whether all of these included HBOT (Xu et al 2012).
- In patients with IGE who had a single session of HBOT, crude mortality at discharge from an intensive care unit (ICU) was 12%, at hospital discharge 16%, at six months 17.6% and at one year 21% (Bessereau 2010).
- There was no evidence comparing the effects of recompression without or without HBOT in different groups of patients. The only patient factor found to be related to outcomes of DCI or DCS was severity of initial symptoms, but the studies did not provide evidence on whether patients with more or less severe symptoms had a greater or lesser benefit from HBOT. Koch et al (2008) reported significantly worse mean outcome scores in 42 patients with more severe DCS-II, than in 225 patients with less severe DCS-II ($p<0.001$), all of whom received hyperbaric treatments according to German Navy guidelines. Xu et al (2012) found a significant relationship between whether patients had mild (n=3831), moderate (n=1124) or severe (n=314) DCI and rate of complete recovery both after initial recompression therapy ($p<0.001$) and at hospital discharge ($p<0.001$). However it was not clear to what extent this analysis had adjusted for confounders.
- In 125 patients with IGE, neurological sequelae at one year were found to be associated with the patient having a Babinski sign ($p=0.0007$) or focal motor deficit ($p<0.0001$) at presentation, and mortality at one year with the patient having a Babinski sign ($p=0.04$) or acute renal failure ($p=0.03$). However the relevance of these signs in planning treatment for such patients is not clear (Bessereau et al 2010).
- There was no evidence demonstrating that any particular treatment schedule was more or less beneficial than any other.

Draft for consultation

- The evidence on whether outcomes varied with delay in receiving treatment was mixed. The odds ratio (OR) for residual symptoms immediately after treatment was significantly higher (OR 3.31, 95% CI 1.08-10.13) in patients who had treatment for Type I DCS more than 96 hours after the appearance of symptoms compared with those who had treatment within 24 hours (Lee et al 2015). However the longer term clinical significance of this outcome was unclear. Complete recovery 10 to 14 days after treatment with various recompression schedules (most commonly USN T6) was reported to be 78% in 128 divers with DCS who had recompression within 48 hours, and 76% in 76 divers who had recompression more than 48 hours after surfacing (p=0.955, no significant difference between early and delayed recompression) (Hadanny et al 2015). In contrast, Xu et al (2012) found a significant relationship (p<0.0001) between complete recovery and the number of hours' delay between symptom onset and recompression treatment in over 5000 Chinese divers, but it was not clear whether this analysis adjusted for confounders.
- Overall the majority of patients with DCI or DCS in all studies were deemed to have a good outcome. However, it is not possible to define in what way and to what extent the outcomes were influenced by recompression treatment with or without HBOT as all the patients in these studies received some form of recompression with or without HBOT and there were no comparisons with patients who did not receive these treatments. In the study of patients with IGE, mortality and morbidity rates were reported to be high but the contribution of HBOT to outcomes was not clear.
- Three studies reported data on safety or adverse effects. In Bennett et al (2012), during initial recompression three out of 179 patients experienced aural barotrauma, two had premonitory signs of cerebral oxygen toxicity and one had persistent nausea. Xu et al (2012) reported symptoms of oxygen toxicity during initial recompression in nine (0.17%) of 5269 divers with DCI. Out of 125 patients with IGE, one experienced seizures during HBO, which resolved on shifting the patient from pure oxygen to air (Bessereau et al 2010).
- No studies were identified which considered cost-effectiveness.
- The studies were generally of poor to moderate quality, and none were designed to answer questions about the effect of adding recompression with or without HBOT to supportive treatment.
- The evidence is insufficient to draw any conclusion about the impact of HBOT in DCI, DCS or IGE.

3 Methodology

- The methodology to undertake this review is specified by NHS England in their 'Guidance on conducting evidence reviews for Specialised Commissioning Products' (2016).
- A description of the relevant Population, Intervention, Comparison and Outcomes (PICO) to be included in this review was prepared by NHS England's Policy Working Group (PWG) for the topic (see section 9 for PICO).
- The PICO was used to search for relevant publications in the following sources: PubMed, Embase, Cochrane, TRIP and NHS Evidence (see section 10 for search strategy).
- The searches were conducted on 2nd May 2017 and included publications since 1st January 2007.
- The titles and abstracts of the results from the literature searches were assessed using the criteria from the PICO. Full text versions of papers which appeared potentially useful were obtained and reviewed to determine whether they were appropriate for inclusion. Papers which matched the PICO were selected for inclusion in this review.

Draft for consultation

- It was agreed with the PWG to exclude a number of smaller retrospective cohort studies all of which had less than 70 subjects because they were significantly smaller than the seven included studies and did not add any information which would contribute to answering the research questions for this review.
- Evidence from all papers included was extracted and recorded in evidence summary tables, critically appraised and their quality assessed using National Service Framework for Long term Conditions (NSF-LTC) evidence assessment framework (see section 7).
- The body of evidence for individual outcomes identified in the papers was graded and recorded in grade of evidence tables (see section 8).

4 Results

A total of seven papers matching the PICO were identified, which reported the use of various recompression/ HBOT schedules in patients with decompression illness (DCI), decompression sickness (DCS) or iatrogenic gas embolus (IGE). The only systematic review identified (Bennett et al 2012) included one relevant randomised controlled trial (RCT). Although published in 2003, this RCT was included because it was the only RCT identified, it was well-conducted and randomised 196 subjects with DCI. In addition there were five retrospective cohort studies including patients with various presentations of DCI or DCS (Hadanny et al 2015, Lee et al 2015, Xu et al 2012, Sayer et al 2009, Koch et al 2008), ranging from 195 to more than 5000 subjects. There was also one prospective cohort study of 125 patients with IGE (Bessereau et al 2010).

Clinical effectiveness

1. In the patient populations of interest, what is the effect of adding recompression with or without HBOT in addition to supportive treatment on the specified outcomes?

No studies were identified which could contribute to answering this question as none included a comparator group of patients receiving supportive treatment alone and none compared the effects of recompression with or without HBOT. It is therefore not possible to determine from this evidence the effect of adding recompression with or without HBOT to supportive treatment.

All the included studies considered outcomes in patients with various presentations of DCI, DCS or IGE who received various recompression treatments with or without HBOT. In the absence of evidence to answer the research question these findings will be summarised here. The descriptions of DCI, DCS, and types of DCS used here are as presented in the original studies.

The treatment schedules referred to here are also as presented in the original studies; the ones most commonly used were US Navy Table 6 (USN T6), US Navy Table 5 (USN T5), Royal Navy Table 62 (RN T62), Royal Navy Table 61 (RN T61), 2 to 2.8 Atmospheres Absolute (ATA), and Comex-30 (CX30).

Most studies presented findings in broad categories such as complete recovery, partial recovery or no improvement, but these categories were not always clearly defined. Outcomes were presented at various time points ranging from immediately after treatment to one year after discharge.

Draft for consultation

Complete recovery immediately after one session of HBOT (USN T5 or T6) in 195 patients with Type I DCS was reported to be 33% (Lee et al 2015), with 67% having residual symptoms. On telephone follow-up one month later, 92% of patients were reported to have completely recovered without further treatment. However, the relevance of residual symptoms immediately after treatment as a predictor of longer term outcomes and the contribution of the HBOT treatment to the outcomes were unclear.

Complete recovery at discharge from hospital was reported to be 67% after treatment of DCI (the majority with one or more sessions of USN T6) in 168 patients enrolled in a RCT (Bennett 2012). At 4-6-week follow-up 82% of 164 patients were reported to have completely recovered. There was no significant benefit of adding treatment with Tenoxicam (a non-steroidal anti-inflammatory drug (NSAID)) to hyperbaric treatment.

An overall 'good' outcome (no symptoms or minor pain or sensory symptoms only) at discharge from hospital was reported in 96% of more than 650 patients treated for DCI with four main schedules, most commonly RN T62 (Sayer et al 2009). Complete recovery at discharge was found in 89.8% of more than 5000 patients with DCI treated with one of four recompression schedules (not all of which may have included HBOT) at hyperbaric facilities in China (Xu et al 2012). Both these studies were based on retrospective review of patient records.

Mortality was reported in a prospective study of 125 patients with IGE who had a single session of HBOT. Crude mortality at intensive care unit (ICU) discharge was 12%, at hospital discharge 16%, at six months 17.6% and at one year 21% (Bessereau et al 2010).

Three studies reported data on safety or adverse effects. In Bennett et al (2012), during initial recompression three out of 179 patients experienced aural barotrauma, two had premonitory signs of cerebral oxygen toxicity and one had persistent nausea. There was no information about whether these adverse effects of treatment had any longer-term impact on these patients. Xu et al (2012) reported symptoms of oxygen toxicity during initial recompression in nine (0.17%) of 5269 divers with DCI. Oxygen breathing was suspended for 30-60 minutes then resumed, after which none of the patients had any recurrence of symptoms. Out of 125 patients with IGE, one experienced seizures during HBO, which resolved on shifting the patient from pure oxygen to air (Bessereau et al 2010).

2. Is there is evidence that some patients benefit more than others from HBOT as a treatment for decompression illness/gas embolism and what are the patient characteristics of this group?

There were no studies which considered the relative benefit of HBOT in different groups of patients. Three studies attempted to identify patient characteristics which were associated with better or worse outcomes, but they did not provide evidence on whether this represented a greater or lesser benefit from HBOT. The relationship between severity of initial symptoms and outcomes of DCI or DCS was explored in two retrospective studies. In one study hyperbaric treatments were provided according to German Navy guidelines (no details were available) for patients with DCS Type 2 (assumed to be the same as Type II DCS), split into more severe (n=42) and less severe (n=225) groups. Mean outcome scores were significantly worse for the more severe group ($p<0.001$), but the clinical significance of the outcome scores and the contribution of HBOT to the outcomes were not clear (Koch et al 2008). A second study found a significant association between patients with mild (n=3831), moderate (n=1124) or severe (n=314) symptoms of DCI and the rate of complete recovery both immediately after recompression treatment ($p<0.001$) and at discharge from hospital ($p<0.001$) (Xu et al 2012). However it was not

Draft for consultation

clear to what extent adjustment had been made for confounders, or whether all the patients had received hyperbaric oxygen.

In 125 patients with IGE more neurological sequelae at one year were found to be associated with the patient having a Babinski sign (p=0.0007) or focal motor deficit (p<0.0001) at presentation, and crude mortality at one year with the patient having a Babinski sign (p=0.04) or acute renal failure (p=0.03) (Bessereau et al 2010). However the relevance of these signs in planning treatment for such patients is not clear.

3. Which treatment schedules were the most effective in achieving best outcomes?

There was no evidence directly comparing different treatment schedules. Two studies attempted to compare outcomes retrospectively for patients who received different treatment schedules. One compared outcomes between divers with DCS who received recompression more than 48 hours after surfacing with either USN T6 (n=46) or 2ATA (n=27), and found no difference between the two groups (Hadanny et al 2015). The second concluded that response to initial treatment for patients with DCI treated with 'shorter shallower tables' such as RN T61 were worse, but there were no measures of the significance of differences between treatment groups, and the extent to which this analysis controlled for confounders was not clear. In addition the authors reported that response to initial treatment did not necessarily relate to the outcome at discharge (Sayer et al 2009).

Three studies considered the impact of delay in receiving treatment. One found that the odds ratio for residual symptoms immediately after treatment was significantly higher (OR 3.31, 95% CI 1.08-10.13) in patients who had treatment for Type I DCS more than 96 hours after the appearance of symptoms compared with those who had treatment within 24 hours (Lee et al 2015). However the longer term clinical significance of this outcome was unclear. One study found no difference in outcomes following one or more sessions of hyperbaric treatment in patients with DCS who received treatment (the majority with USN T6) either less than 48 hours or more than 48 hours after surfacing (Hadanny et al 2015). Complete recovery 10 to 14 days after treatment was reported to be 78% in 128 divers who had recompression within 48 hours, and 76% in 76 divers who had recompression more than 48 hours after surfacing (p=0.955, no significant difference between early and delayed recompression). The third study found a significant association (p<0.0001) between delay from symptom onset to recompression treatment, and complete or incomplete recovery at discharge (Xu et al 2012). However it was not clear whether this analysis adjusted for confounders, or whether all the patients had received hyperbaric oxygen..

Cost effectiveness

4. What is the cost effectiveness of the use of HBOT in the treatment of decompression illness and of iatrogenic gas embolism?

No published evidence was identified on the cost effectiveness of HBOT in DCI, DCS or gas embolism.

5 Discussion

The studies identified in this rapid evidence review were generally of poor to moderate quality. Six studies included patients with various presentations of DCI or DCS, including one RCT which was reasonably well-conducted. However the comparator in this RCT (the addition of treatment with a NSAID to hyperbaric treatment for DCI) was not of direct relevance to this review, so the findings

Draft for consultation

for all patients have been included here. Five studies involved retrospective analysis of patient datasets (ranging in size from 195 to more than 5000 subjects), with associated methodological problems including post-hoc allocation of patients to various groups. One study collected data prospectively on patients with IGE.

In most of the studies there were limited details about patient characteristics and outcomes. The treatments given were incompletely described in several of the studies, so that it was difficult to determine how many patients had how many sessions of recompression with or without HBOT, and how this related to the outcomes.

Most studies provided limited descriptions of the approach to analysis and limited or unclear controlling for confounders where comparative analyses were undertaken. Several had limited or no definitions of the outcomes used and little information about their clinical significance, for example the longer term significance of short-term outcomes where these were reported. The longest follow-up reported in any of the studies of patients with DCS or DCI was six weeks; the study of patients with IGE reported outcomes at one year. Results were often incompletely presented or not clearly tabulated and in some studies described in the text only.

None of the studies was designed to answer questions about the effect of adding recompression with or without HBOT to supportive treatment, and none included patients receiving supportive treatment only. All the patients included in these studies received some form of recompression with or without HBOT. Overall the majority of patients with DCI or DCS in all studies were deemed to have a good outcome, but it is not possible to define how the outcomes were influenced by recompression treatment with or without HBOT. In the study of patients with IGE, mortality and morbidity rates were reported to be high but the contribution of HBOT to outcomes was not clear.

None of the studies provided reliable evidence of the superiority of any particular treatment schedule, and none demonstrated that any patients were more likely to benefit than others. Three studies reported data on safety or adverse effects. One found adverse effects of initial recompression in six out of 179 patients with DCI; in a second study symptoms of oxygen toxicity during initial recompression were reported in nine (0.17%) of 5269 divers with DCI, and in the third study one patient out of 125 with IGE experienced seizures during HBO. No studies were identified which considered cost-effectiveness.

The evidence is insufficient to draw any conclusion about the impact of recompression with or without HBOT in DCI, DCS or IGE.

Further research would need to be designed to specifically address the questions of interest, with prospective collection of data and planning of analyses, controlling for confounding factors, and clear and complete presentation of results. Regarding the original research questions, it appears unlikely that controlled studies exploring the addition of recompression to supportive treatment would be deemed ethical, given that recompression has been an established treatment in these indications for many years. However, given the lack of evidence identified here for a benefit of the addition of HBOT to recompression in DCI, DCS or IGE, comparative studies of HBOT may be considered feasible in selected patients.

6 Conclusion

The included evidence on recompression treatment with or without HBOT in DCI, DCS or IGE consists of one RCT, five retrospective studies and one prospective study, which were generally of poor to moderate quality. In the six studies which included patients with DCI or DCS, the majority were considered to have a 'good' outcome or 'complete' recovery, but it is not possible to

Draft for consultation

say from any of these studies what the contribution of recompression with or without HBOT was to the patient outcomes. In the study of patients with IGE who received HBOT there was significant mortality and morbidity at one year, but it was not possible to determine the specific contribution of HBOT to the outcomes.

Recompression has been an established treatment in these indications for many years and studies comparing supportive treatment with or without recompression are likely to be deemed unethical. However, the evidence identified here demonstrates uncertainty around the contribution of HBOT in these conditions, and there appears to be insufficient evidence on which to base clear recommendations for commissioning. Further research may be considered justifiable, provided it is well-designed and conducted to answer the questions of interest.

Draft for consultation

7 Evidence Summary Table[1]

Recompression with HBOT alone vs recompression with HBOT plus a non-steroidal anti-inflammatory drug (NSAID) for treatment of DCI									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
Bennett 2012 (systematic review reporting Bennett 2003) (Drewry 1994 was also included in Bennett 2012 but only interim results reported in an abstract with no more recent update, so is not included here)	P1-Randomised control trial (data taken from systematic review)	n=196 randomised 16 (8.9%) lost to follow-up Results reported on n=180 Patients presenting for management of DCI defined as any symptom and/or sign arising after compressed gas breathing and assessed as likely to represent bubble injury. Patients with clinical diagnosis of AGE excluded	Patients randomised to either routine recompression therapy + Tenoxicam (a NSAID) or routine recompression therapy + placebo. Recompression schedule prescribed at the discretion of the treating physician, with repeat recompressions as necessary: 88% had USN T6. Intervention group: Tenoxicam 20mg administered at first air break in recompression and daily for 7 days Control group:	Primary Clinical efficacy	Proportion of patients completely recovered at discharge	Tenoxicam 53/84 (63%) Placebo 59/84 (70%) RR 0.85 (0.64 to 1.18) Total 112/168 (67%)	5	Direct	Randomisation by computer-generated numbers Subjects and medical officers blinded to treatment allocation All outcomes reported Intention to treat analysis Authors' conclusion: The addition of a NSAID may reduce the number of recompressions required, but does not improve the odds of recovery. The modest number of patients studied demands a cautious interpretation. The RCT appears to have been of reasonably high quality. The conclusion that adjunctive treatment with Tenoxicam provides no clinical benefit either at discharge or at 6 weeks' follow up appears reasonable based on their findings. Overall 67% of 168 patients had completely recovered at discharge and 82% of 164 at 6 weeks' follow up. The contribution of recompression therapy (including HBOT) to recovery is unclear from this study. Adverse events during initial recompression were reported in 6/179 patients (3.4%). There was no information on whether these adverse effects had any longer-term impact or on the longer-term outcomes of patients who experienced adverse effects.
				Primary Clinical efficacy	Proportion of patients completely recovered at 6 weeks' follow up (not stated whether this was 6 weeks after treatment completion or after discharge)	Tenoxicam 70/84 (83%) Placebo 64/80 (80%) RR 1.12 (0.78 to 1.77) Total 134/164 (82%)			
				Secondary	Adverse events	During initial recompression (n=179): Aural barotrauma (n=3) Premonitory signs of cerebral oxygen toxicity (n=2) Nausea (n=1)			
				Safety					

Draft for consultation

[1] See list at the end of section 8 for definitions of abbreviations used in these tables

Draft for consultation

			placebo						

Recompression with or without HBOT for treatment of DCS, DCI or IGE. No comparator.									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
Hadanny 2015	S2 Retrospective cohort study Divers divided into early recompression (<48 hrs from surfacing, mean/SD 19+/-11 hrs) (n=128) and delayed recompression (>48hrs from surfacing, mean/SD 93+/-90 hrs) (n=76). Delayed group divided into time lag from	n=204 Divers suffering from DCS treated at one centre in Israel 2000-2014 DCS classified as Type 1 or Type 2 (not defined) according to clinical symptoms, signs and diving history. Also into mild, moderate and severe defined by type and severity of symptoms. Patients with AGE excluded.	Recompression table decided by physician. Recompression table used: Early group: USN T6 84%, USN T5 3%, CX30 11%, 2ATA 2%. Delayed group: USN T6 60%, USN T5 3%, CX30 1%, 2ATA 35% Significant difference between groups (p<0.0001) Additional HBOT sessions given in cases of partial recovery until patient fully recovered or no further improvement	Primary Clinical efficacy	No improvement, partial recovery, complete recovery (not defined) 10-14 days post treatment in early vs delayed recompression	All patients: Delayed recompression: 6.6%, 17.1%, 76% Early recompression: 6.2%, 15.6%, 78% (p=0.955) 'Neurological DCS subset' (n not stated) Delayed recompression: 4.3%, 17%, 78.7% Early recompression: 8%, 19.5%, 72.4% (p=0.765)	4	Direct	Early recompression group had significantly shorter time to symptom onset (4+/-6 hrs) than delayed recompression group (8.7+/-11hrs) (p=0.001) No significant difference between groups in DCS Type and severity No significant difference found in clinical outcome with early/ delayed recompression for all patients and for 'neurological subset' (not defined, n not stated) Concluded that delayed recompression has value and should be used No significant difference in clinical outcome in delayed recompression with USN T6 or 2ATA Significant association reported between use of USN T6 and better clinical outcome, but no details shown Retrospective analysis of patient dataset Retrospective classifications used to define post-hoc subgroups, so should be treated with caution; completeness and consistency of data on which these were based was unclear. Resulted in small (some undefined) subgroups. Clinical outcome groups not defined Incomplete presentation of results; details of some results commented on in the text were not shown, and some results shown in tables or figures were too incomplete to use. The impact and significance of additional HBOT sessions was unclear. The study did not demonstrate a benefit with any particular recompression schedule or of early
				Primary Clinical efficacy	No improvement/ partial recovery/ complete recovery (not defined) 10-14 days post treatment with USN T6 vs 2ATA in delayed recompression group	USN T6 (n=46) 3%, 13%, 84% 2ATA (n=27) 14.8%, 18.5%, 66.7% (p=0.07)			
				Primary Clinical	Multivariate analysis of clinical outcome 10-14	USN T6 had more favourable outcomes			

Draft for consultation

	surfacing to symptom onset <12hrs (n=53) or >12 hrs (n=23)		observed. No significant difference between groups in % of patients who received adjunctive HBOT (45% early and 54% delayed)	efficacy	days post treatment vs patient /treatment variables (details not provided)	(p=0.009) No other statistically significant associations			compared with delayed recompression. However the considerable problems with methodology and reporting mean findings should be treated with caution. Around three-quarters of all patients were reported to have 'complete recovery' but the contribution of recompression therapy (including HBOT) to this is unclear.
Lee 2015	S2 Retrospective cohort study (using HBOT registry data) Patients divided into 2 groups: residual symptoms or complete resolution after a single HBOT session	n=195 Patients with Type I DCS who underwent HBOT at one centre in Republic of Korea between 2004-2013 Type I DCS defined as patients with symptoms limited to muscles, joints, skin and lymphatic system Type II DCS and AGE excluded	USN T5 for patients who arrive at 60 feet and symptoms are eliminated within 10 mins USN T6 for patients who have residual symptoms after 10 mins	Primary Clinical efficacy	Clinical outcome after a single HBOT session	32.8% (n=64) complete recovery 67.2% (n=131) residual symptoms	4	Direct	Investigated rapid therapeutic response because 94.9% had complete resolution at 1 month, therefore number of treatment failures (5.1%, n=10) deemed too small to investigate Patients retrospectively divided into 2 post-hoc groups; potential bias due to unknown accuracy and completeness of recording Follow-up data was from subjective patient report on telephone interview; no objective assessment Outcome measures not defined. Residual symptoms were reported 'according to the patient's statement'; there were no further details on how these were assessed. Outcome (early response) is of limited clinical significance; the relationship to long-term outcomes is unclear Overall 33% of patients were reported to be completely recovered from Type I DCS immediately after treatment, and 92% at one month. The contribution of recompression therapy (including HBOT) to this is unclear.
				Primary Clinical efficacy	Outcome on telephone follow-up at 1 month of those with residual symptoms (n=131)	92.3% (n=121) no symptoms 6.1% (n=8) residual pain 1.5% (n=2) had surgery for shoulder osteonecrosis			
				Primary Clinical efficacy	OR (95% CI) for residual symptoms after one HBOT session vs time between symptom onset and recompression (hrs)	≤24hrs: Reference 24-96 hrs: 2.24 (0.75-6.65) 96-240 hrs: 3.31 (1.08-10.13) ≥240 hrs: 23.84 (2.45-231.43)			
Xu 2012	Retrospective cohort study	n= 5278 DCI cases (male commercial fishery divers) treated at hyperbaric facilities in China between	All patients treated with one of 4 recompression schedules (summarised in the paper). Depth range 30-70m Treatment time 233-1870	Primary Clinical efficacy	% Complete or incomplete recovery vs delay between symptom onset and treatment	Hours delay vs %Complete/incomplete recovery 1-6hrs (n=2559) 93.8%/5.3% 6-12hrs (n=1802) 87.6%/12.0% 12-24hrs (n=555) 85.2%/14.4% 24-36hrs (n-234)	4	Direct	Outcomes (complete recovery, incomplete recovery, improvement or ineffectiveness) not defined. Retrospective classification into post-hoc subgroups; should be treated with caution Some tables have missing numbers of subjects not accounted for Analysis not clearly described; there does not appear to have been adjustment for confounders Unclear whether all patients had hyperbaric oxygen

Draft for consultation

		2000 and 2010 Classified into mild (n=3831), moderate (n=1124) or severe (n=323) DCI based on symptoms and whether decompression omitted. Mild= skin symptoms, mild to moderate MSK pain, non-specific symptoms without omitted decompression Moderate= severe MSK pain, mild cardiopulmonary symptoms, focal limb numbness, + 'mild' with omitted decompression Severe= mod to severe cardiopulmonary, peripheral nerve, audiovestiibular, CNS, + 'moderate' with omitted decompressi	min. Compression medium was air; oxygen administered via face mask. It was unclear whether all patients received hyperbaric oxygen. Hyperbaric oxygen was 'recommended' for all severe and for mild to mod patients who recovered incompletely after first recompression (schedule described). Patients who received additional HBOT were: 62 mild 39 moderate ?51 severe (unclear)			80.8%/18.4% >36hrs (n=119) 75.6%/24.4% Total (n=5269) 89.8%/9.5% Rate of complete recovery vs delay chi^2=114.27, p<0.0001 (Note: small numbers of patients including those who died are missing from these figures)			with their initial recompression. Interventions and outcomes in patients who received additional HBO not described clearly; not tabulated, making it difficult to tell how many patients in which groups received additional HBO and what their outcomes were. Symptoms of oxygen toxicity reported in 0.17% of patients on initial recompression. After oxygen breathing was suspended, then recommenced, the symptoms did not recur. There was no information about whether any patients had longer term adverse effects. It seems reasonable to conclude that outcomes are related to symptom severity despite the methodological problems of this study. There appears to have been no adjustment for confounders so the relationship between treatment delay and outcomes is unclear. The treatment tables used were developed in a Chinese recompression facility and not all appear to have included HBOT; they are unlikely to be relevant to the current UK context. The authors' conclusion that adjuvant HBO was 'critical' for some patients is not demonstrated by the data as outcomes for this group were not clearly presented, not all patients with sequelae after first treatment appear to have received additional HBO, and most who did not receive additional HBO also appear to have improved.
				Primary Clinical efficacy	Complete recovery, improvement or ineffectiveness after initial recompression for mild, moderate or severe DCI	Mild (n=3831): 92.2% complete, 7.8% improvement, 0% ineffectiveness Moderate (n=1124): 81.3% complete, 18.5% improvement, 0.2% ineffectiveness Severe (n=314): 48.7% complete, 39.5% improvement, 4.1% ineffectiveness Total (n=5269) 87.3% complete 12% improvement 0.3% ineffectiveness Rate of complete recovery after initial therapy vs severity Chi^2=539.93, p<0.001 Rate of ineffectiveness after initial therapy vs severity Chi^2=175.81, p<0.001			
				Primary Clinical	Complete recovery, improvement,	Mild (n=3831): 93.8% complete,			

Draft for consultation

		on		efficacy	ineffectiveness or death at discharge for mild, moderate or severe DCI Outcomes for patients receiving additional HBOT included in these figures but not shown separately	6.2% improvement, 0% ineffectiveness 0% death Moderate (n=1124): 84.8% complete, 15.0% improvement, 0.2% ineffectiveness 0% death Severe (n=314): 58.9% complete, 30.6% improvement, 2.9% ineffectiveness 7.6% death Total (n=5269) 89.8% complete 9.5% improvement 0.2% ineffectiveness 0.5% death Rate of complete recovery at discharge vs severity Chi^2=425.48, p<0.001 Rate of ineffectiveness at discharge vs severity Chi^2=114.51, p<0.001			
				Secondary Safety	Number of patients developing symptoms of oxygen toxicity (n=5269 receiving recompression therapy, but it was unclear whether this included hyperbaric oxygen for all patients)	5 (0.09%) suspected to have developed CNS oxygen toxicity (including one patient with seizures) 4 (0.08%) presented with early symptoms of oxygen toxicity Oxygen breathing was suspended for 30-60 minutes then resumed, after which none had any recurrence of symptoms.			

Draft for consultation

Besser eau 2010	P1 Prospect ive cohort study Mainly descripti ve but includes univariat e and multivari ate analysis of factors associat ed with mortality/ sequelae including some treatmen t-related factors	n=125 6 (5%) lost to follow-up Patients with proven IGE treated in one unit in Paris from 1993-2004 Inclusion criteria: 1) clinical condition at risk for IGE; 2) at least one of coma, focal motor deficit, seizures, cardiac arrest, cardiovascul ar collapse, acute dyspnoea; 3) evidence of gas bubble entry in the systemic circulation during a surgical/ radiological procedure, or imaging evidence of gas bubbles in left heart cavities or cerebral arteries..	Identical HBO procedure used for all (described) lasting total of 168 min with 100% oxygen throughout. All but one patients had a single HBO session; one patient had 2 HBO sessions	Primary Clinical efficacy	Crude mortality at: ICU discharge Hospital discharge 6 months 1 year	12% (14/119) 16% (19/119) 17.6% (21/119) 21% (25/119)	4	Direct	Mainly descriptive Overall mortality was 12% at ICU discharge, 16% at hospital discharge, 17.6% at 6 months and 21% at 1 year A large number (34) of variables were examined in univariate analysis for association with mortality and sequelae in 3 patient subgroups: ie 102 different analyses reported. Those where p values were small were then examined in multivariate analyses. Out of these a worse outcome was found to be associated with a small number of variables. It is not clear whether analyses were planned beforehand or whether this represented data trawling (prior hypotheses were not stated). One patient (0.8%) experienced seizures during HBO, which resolved on shifting from pure oxygen to air. The conclusion that IGE is associated with high mortality and morbidity appears reasonable. The characteristics associated with worse outcomes were found as a result of analysis of a large number of variables and should be treated with caution. It is not clear to what extent treatment decisions about patients similar to those in this study would be influenced by knowledge of these characteristics The contribution of HBO treatments to the outcomes is not clear. The authors also reported that there was a significant association between whether patients had sequelae at 1 year, and the time delay between the incident and commencement of HBO treatment. However this outcome was not clearly reported in the paper, with no explanation of the units used.
				Primary Clinical efficacy	OR (95% CI) of crude 1-year mortality in ICU survivors (n=105) who had: Babinski sign Acute Renal Failure	6.58 (1.14-38.2) p=0.04 8.09 (1.28-51.21) p=0.03			
				Primary Clinical efficacy	OR (95% CI) of sequelae at 1 year in ICU survivors (n=105) who had: Babinski sign Focal motor deficit	6.76 (2.24-20.33) P=0.0007 12.78 (3.98-41.09) P<0.0001			
				Secondary Safety	Number of patients experiencing adverse events during HBO.	1/125 (0.8%) patient experienced seizures during HBO. Resolved on shifting from pure oxygen to air.			
Sayer et al 2009	S2 Retrospe ctive cohort study	2 cohorts: 1) 300 divers (ages 16-77, mean 35) treated for DCI at a	Recompressio n schedule chosen by clinician; related to severity of	Primary Clinical efficacy	Response to initial treatment (change in patient's relative condition) (cohort 2):		3	Direct	Data taken from different patient datasets; may be variability in definitions, approaches to assessment and treatment. Retrospective classification into post-hoc subgroups; should be treated with caution. Comparability of different treatment groups unclear

Draft for consultation

		single unit in Scotland between 1972 and 2007 2) 536 divers (ages 14-77, mean 34.4) treated for DCI at one of 4 units in Scotland between 1991 and 2003 151 subjects common to both datasets	initial illness. Patients received variable numbers of treatments. 4 main schedules used: RN T62 (50% cohort 1, 57% cohort 2) RN T62 + extension RNT62ext) (42% cohort 1, 33% cohort2) Air or helium oxygen saturation (Sat Tx) (4% cohort 2) RN T61 or HBO (6% cohort 2)		No symptoms at start and no change; Complete resolution; Major improvement; Moderate improvement; Slight/ no improvement	RNT62 16%; RNT62ext 3%; Sat Tx 0; RNT61/HBO 12% RNT62 55%; RNT62ext 42%; Sat Tx 15%; RNT61/HBO 15% RNT62 21%; RNT62ext 44%; Sat Tx 60%; RNT61/HBO 42% RNT62 5%; RNT62ext 7%; Sat Tx 15%; RNT61/HBO 18% RNT62 3%; RNT62ext 4%; Sat Tx 10%; RNT61/HBO 12%			No measures of significance of effects No definitions of 'Response to initial treatment' outcomes. Adjustment for confounders appears to have been limited and not clearly described. Results were not clearly tabulated The impact of initial condition on outcomes of different treatments is not clear. Data do not support the conclusion that RNT61 may produce worse outcomes as this group is very small, there is no description of how comparable the groups were, it is unclear to what extent confounders were adjusted for, and no measures of statistical significance. The conclusion that almost all (96%) patients had a good outcome seems reasonable but the contribution of recompression schedules/ HBOT to these outcomes is not clear. The significance of 'response to initial treatment' in relation to long term outcome is unclear. The authors stated that this measure did not necessarily relate to the outcome at discharge.
				Primary Clinical efficacy	Condition at discharge (cohorts 1 + 2): 'Good' (no symptoms or minor pain or sensory symptoms only) 'Poor' (any ataxia, motor weakness, cerebral dysfunction or presence of urinary catheter)	 96% of all patients 4% of all patients			
Koch et al 2008	S2 Retrospective cohort study	n=267 Patients treated for DCS-II at the German Naval Medical Institute between 1973-2006. Patients	Patients treated according to standardised German Navy Guidelines for diving accidents. Text refers to this being 'hyperbaric treatments'	Primary Clinical efficacy	Clinical outcome after completion of hyperbaric treatments (outcome score): Unchanged (0) Improvement (1) Full recovery (2)	Mean (+/- SD) outcome score: Type A (n=42): 1.39 +/- 0.56 Type B (n=225): 1.82 +/- 0.46 P<0.001	4	Direct	Classification into Types A and B and evaluation of outcomes done post-hoc using retrospective analysis of patient records which may have used inconsistent definitions or been incompletely documented. Classification into Types A and B was done by two independent assessors; evaluation of outcomes was not, so should be treated with caution. No definition of the clinical outcome groups, and clinical significance of mean outcome scores unclear Relationship between number of treatments and

Draft for consultation

		were classified into 2 types of DCS-II depending on neurological symptoms at initial presentation Type A criteria more severe, e.g. paralysis, incontinence Type B criteria less severe, e.g. paraesthesia, minor muscle weakness	but no further details given or referenced						outcomes unclear Details of treatment schedules not given or referenced and the German guidelines for the period covered by this study could not be found online. The conclusion that patients classified as Type A by two independent assessors (more severe symptoms) had worse outcome scores seems reasonable but the clinical significance of the outcome scores and the contribution of hyperbaric treatments is not clear.

Draft for consultation

8 Grade of evidence table[2]

Recompression with HBOT alone vs recompression with HBOT plus non-steroidal anti-inflammatory drug (NSAID) for treatment of DCI					
Outcome Measure	**Reference**	**Quality of Evidence Score**	**Applicability**	**Grade of Evidence**	**Interpretation of Evidence**
Recovery at discharge from hospital	Bennett et al 2012	5	Direct	C	Complete recovery at discharge from hospital was defined as' well, no symptoms or signs'. The overall rate of complete recovery of patients with DCI at discharge was 112/168 (67%). The clinical condition of the remaining 33% of patients at discharge was not clear. This analysis included patients recruited to both the intervention and control arms of a RCT designed to evaluate the addition of a NSAID to recompression treatment. No difference in outcomes was found with the addition of the NSAID. All patients received one or more sessions of recompression; 88% had recompression according to USN T6. The RCT was of reasonably good quality and data were collected prospectively. While two-thirds of patients with DCI had recovered at discharge, it is not possible to determine the contribution of recompression therapy with or without HBOT to recovery as there was no comparison with patients who did not receive recompression.
Recovery at 4-6 weeks	Bennett et al 2012	5	Direct	C	Complete recovery in patients with DCI at 4-6 weeks' follow up was defined as 'well, no symptoms or signs'. It was not stated whether follow up was 4-6 weeks after completion of treatment or after discharge. Overall 134/164 (82%) of all patients treated for DCI with one or more sessions of recompression (88% according to USN T6) were reported to have completely recovered at 4-6 weeks. Longer term outcomes for the remaining 18% are not described. This analysis included patients recruited to both the intervention and control arms of a RCT designed to evaluate the addition of a NSAID to recompression treatment. No difference in outcomes was found with the addition of the NSAID. The RCT was of reasonably good quality and data were collected prospectively. While over four-fifths of patients with DCI had recovered at 4-6 weeks, it is not possible to determine the contribution of recompression therapy with or without HBOT to recovery as there was no comparison with patients who did not receive recompression.
Adverse effects of initial recompression treatment	Bennett et al 2012	5	Direct	C	Problems during initial recompression were reported for six out of 179 patients (3.4%) with DCI treated with recompression (88% according to USN T6). Three complained of aural barotrauma, two developed premonitory signs of cerebral oxygen toxicity and one complained of nausea not resolved by removal from oxygen breathing at depth. This analysis included patients recruited to both the intervention and control arms of a RCT designed to evaluate the addition of a NSAID to recompression treatment. The RCT was of reasonably good quality and data were collected prospectively. There was no information on whether these adverse effects of initial recompression

[2] See list at the end of section 8 for definitions of abbreviations used in these tables

Draft for consultation

					had any longer-term impact or on the longer-term outcomes of patients who experienced adverse effects. From the evidence provided by this study it is not possible to determine the significance of adverse effects of initial recompression in patients with DCI.

Recompression with or without HBOT for treatment of DCS, DCI or IGE. No comparator.					
Outcome Measure	**Reference**	**Quality of Evidence Score**	**Applicability**	**Grade of Evidence**	**Interpretation of Evidence**
Outcome immediately after a single HBOT session	Lee et al 2015	4	Direct	C	Outcome after a single HBOT session (US Navy Table 5 or Table 6) (USN T5 or T6)) was described as either complete recovery or residual symptoms in patients with Type I DCS. Residual symptoms were reported 'according to the patient's statement'; there were no further details on how these were assessed. Overall 33% (n=64) of patients were reported to be completely recovered from Type I DCS and 67% (n=131) to have residual symptoms immediately after treatment. From the evidence provided by this study it is not possible to determine the contribution of a single session of HBOT to recovery immediately after treatment in patients with Type I DCS as there was no comparison with patients who did not receive HBOT. In addition, complete recovery and residual symptoms were assessed retrospectively and were not defined. The clinical significance of residual symptoms immediately after treatment and their relationship to longer term outcomes is unclear.
Adverse effects of initial recompression treatment	Xu et al 2012	4	Direct	C	Out of 5259 divers with DCI receiving recompression therapy, five were suspected to have developed CNS oxygen toxicity and four presented early symptoms of oxygen toxicity. All had been treated with recompression in air with oxygen breathing via face mask, although it was not clear how many of the cohort had received hyperbaric oxygen. Oxygen breathing was suspended for 30-60 minutes then resumed, after which all were reported to have no recurrence of symptoms. Overall 0.17% of patients in this large cohort were thought to have experienced oxygen toxicity but no longer-term sequelae were reported. The treatment schedules used were developed in a Chinese recompression facility and are unlikely to be relevant to the current UK context. Out of 125 patients with IGE, one (0.8%) experienced seizures during HBO, which resolved on shifting from pure oxygen to air.
	Bessereau et al 2010	4	Direct	C	
Outcome at discharge from hospital	Xu et al 2012	4	Direct	C	Outcomes were described as complete recovery, improvement, ineffectiveness or death at discharge from hospital in 5269 Chinese divers with DCI treated with recompression, of whom around 150 also had additional sessions of HBOT (Xu et al 2012). Complete recovery at discharge was reported in 89.8% (n=4732) of all patients, improvement in 9.5% (n=502), ineffectiveness in 0.2% (n=11) and death in 0.5% (n=24).
	Sayer et al 2009	3	Direct	C	These findings should be treated with caution as the outcomes were assessed retrospectively and were not defined. It is not possible to determine the contribution

Draft for consultation

					of recompression with or without HBOT to recovery at discharge in patients with DCI as there was no comparison with patients who did not receive recompression. The treatment schedules used were developed in a Chinese recompression facility and not all appear to have included HBOT; they are unlikely to be relevant to the current UK context.
Outcome one month after treatment with a single HBOT session	Lee et al 2015	4	Direct	C	Self-reported outcomes for patients with Type I DCS who had reported residual symptoms immediately after treatment with one session of HBOT were collected by telephone interview one month after treatment. Overall, of 131 patients with Type I DCS, 92.3% (n=121) reported no symptoms, 6.1% (n=8) residual pain and 1.5% (n=2) having had surgery for shoulder osteonecrosis. The findings should be treated with caution as no symptoms and residual pain were not defined and there were no objective measures of these outcomes. It is not possible to determine from this evidence what the contribution of a single session of HBOT was to recovery one month after treatment in patients with Type I DCS as there was no comparison with patients who did not receive HBOT.
Crude mortality	Bessereau et al 2010	4	Direct	C	Crude mortality was defined as the proportion of patients who had died at a specified time point after treatment. In a study of 125 patients with iatrogenic gas embolus (IGE) treated with a single session of HBOT, data were collected prospectively and outcomes were reported for 119 patients (6 were lost to follow-up). Crude mortality was 12% (14/119) at Intensive Care Unit (ICU) discharge, 16% (19/119) at hospital discharge, 17.6% (21/119) at 6 months and 21% (25/119) at one year. This study demonstrates significant mortality in patients with IGE with some deaths occurring more than 6 months after treatment. However it is not possible to determine the impact of HBOT on mortality up to 1 year in patients with IGE as there was no comparison with patients who did not receive HBOT.
Response to initial recompression for patients with mild, moderate and severe DCI	Xu et al 2012	4	Direct	C	Complete recovery, improvement or ineffectiveness after initial recompression were reported for 5269 Chinese divers with mild, moderate or severe DCI, which was defined, based on symptoms and whether decompression had been omitted. Complete recovery was reported in 92.2%, 81.3% and 48.7% of mild, moderate and severe patients respectively, with a significant association between severity and complete recovery after initial therapy, $p<0.001$. Ineffectiveness was reported in 0%, 0.2% and 4.1% of mild, moderate and severe patients respectively, with a significant association between severity and ineffectiveness after initial therapy, $p<0.001$. The analysis was not clearly described and it is not clear whether there was any adjustment for confounders. From the evidence provided in this study it is not possible to determine what the contribution of initial recompression with or without HBOT was to outcomes after recompression as there was no comparison with patients who did not receive recompression. Patients with more severe disease were reported to have had worse outcomes, but these findings should be treated with caution because severity and outcomes were classified retrospectively, and the outcome groups were not defined. It is also not clear to what extent other confounding factors might have contributed. The treatment tables used were developed in a Chinese recompression facility and not all appear to have included HBOT; they are unlikely to be relevant to the current UK context.

Draft for consultation

Condition at discharge for patients with mild, moderate and severe DCI.	Xu et al 2012	4	Direct	C	Complete recovery, improvement, ineffectiveness or death at discharge were reported in 5269 Chinese divers with mild, moderate or severe DCI treated with recompression, of whom around 150 had additional sessions of HBOT. Mild, moderate and severe DCI were defined, based on symptoms and whether decompression had been omitted. Complete recovery was reported in 93.8%, 84.8% and 58.9% of mild, moderate and severe patients respectively, with a significant association between severity and complete recovery at discharge, p<0.001. Ineffectiveness was reported in 0%, 0.2% and 2.9% of mild, moderate and severe patients respectively, with a significant association between severity and ineffectiveness at discharge, p<0.001. The analysis was not clearly described and it is not clear whether there was any adjustment for confounders. From the evidence provided in this study it is not possible to determine what the contribution of recompression with or without HBOT was to outcomes at discharge as there was no comparison with patients who did not receive recompression. The relationships between outcome after initial therapy, condition at discharge and long term outcome were not clear. Patients with more severe disease were reported to have had worse outcomes, but these findings should be treated with caution because severity and outcomes were classified retrospectively, and the outcome groups were not defined. It is also not clear to what extent other confounding factors might have contributed. The treatment tables used were developed in a Chinese recompression facility and not all appear to have included HBOT; they are unlikely to be relevant to the current UK context.
Clinical outcome after completion of treatment for patients with more severe or less severe Type II DCS	Koch et al 2008	4	Direct	C	Clinical outcome (unchanged, improvement or full recovery) after completion of hyperbaric treatments was reported in 267 patients with Type II DCS.. The patients were grouped retrospectively by two independent assessors into Type A (more severe) and Type B (less severe) DCS-II according to defined diagnostic criteria. Each outcome group was given a score (unchanged 0, improvement 1, full recovery 2) for the analysis. The mean (+/- SD) outcome score for patients with Type A (n=42) was 1.39 +/-0.56, significantly worse than for patients with Type B (n=225) which was 1.82 +/-0.46 (p<0.001). While a statistical association was demonstrated between patients with more severe Type II DCS and worse outcome scores, it is not possible to comment on the clinical significance of this difference in outcome scores. In addition the findings should be treated with caution as the outcome groups were classified retrospectively and were not defined. Details of treatment schedules were not given or referenced, and it is not known whether patients received HBOT. From the evidence provided in this study it is not possible to determine what the contribution of recompression with or without HBOT was to outcomes after completion of treatment for patients with Type II DCS.
Outcomes at one year in relation to patient and treatment factors	Bessereau et al 2010	4	Direct	C	The odds ratios (OR) of having neurological sequelae and of crude mortality at one year in relation to various patient and treatment factors were reported in patients with IGE treated with a single HBO procedure. Data were collected prospectively in 105 patients who survived ICU. Neurological sequelae were not defined but a number of examples were given, such as focal motor deficits, restriction of visual field, and seizures. A significant association on multivariate analysis was found between patients having a positive Babinski sign (p=0.0007) or focal motor deficit (p<0.0001) at presentation

Draft for consultation

					and neurological sequelae at one year. A significant association was also found between patients having a positive Babinski sign at presentation (p=0.04) or acute renal failure (p=0.03) and mortality at one year. However these came from initial analysis of 34 variables in 102 analyses so should be treated with caution. It is not clear whether analyses were planned beforehand (prior hypotheses were not stated). The clinical relevance of these findings is uncertain as it is not clear to what extent treatment decisions about patients similar to those in this study would be influenced by knowledge of these characteristics. All patients received HBOT and it is not possible from the evidence provided by this study to determine the impact of HBOT on neurological sequelae or mortality at one year in patients with IGE as there was no comparison with patients who did not receive HBOT.
Response to initial treatment with different treatment tables	Sayer et al 2009	3	Direct	C	Response to initial treatment, compared to treatment table used, was reported for 536 patients treated for DCI with various treatment schedules. Patients were retrospectively allocated to one of five outcome groups: no symptoms at start, complete resolution, major improvement, moderate improvement, slight or no improvement. Outcomes were reported for four main groups of treatment schedules, which were used for varying proportions of patients: Royal Navy Table 62 (RN T62) (57% of patients), RN T62 with extension (33%), air or helium oxygen saturation (Sat Tx) (4%), and RN T61 or HBO (6%). A higher proportion of the 90% of patients treated with RN T62 were reported to have a better response than those treated with Sat Tx or RN T61/HBO. . However there were no measures of the significance of differences between treatment groups. It was unclear how comparable the treatment groups were and to what extent adjustments were made for potential confounders. The outcome groups were not defined and the clinical significance of the outcomes in the immediate or longer term was also not clear; the response to initial treatment was reported to not necessarily relate to outcomes at discharge. From the evidence provided in this study it is not possible to determine the contribution of recompression with or without HBOT, or of recompression using different treatment schedules, to outcomes after initial treatment for patients with DCI.
Recovery 10-14 days after treatment with different treatment tables more than 48 hours after surfacing	Hadanny et al 2015	4	Direct	C	No improvement, partial recovery or complete recovery were reported 10-14 days after treatment of divers with DCS who received recompression with USN T6 (n=46) or 2ATA (n=27) more than 48 hours after surfacing. In patients receiving USN T6 3% had no improvement, 13% partial recovery and 84% complete recovery. In patients receiving 2ATA 14.8% had no improvement, 18.5% partial recovery and 66.7% complete recovery. There was no significant difference between the two treatment groups (p=0.07). A multivariate analysis of clinical outcome for all divers compared with patient and treatment variables was reported to find more favourable outcomes for patients treated with USN T6 (p=0.009). However no further details of this analysis were provided, so it is not possible to judge its reliability or the implications for treatment. The clinical significance of outcomes at 10-14 days and their relationship to longer term outcomes was not described. The findings of this study should be treated with caution as it is not clear how similar

Draft for consultation

					the treatment groups were and whether any adjustments were made in this analysis for confounders. The outcomes were assessed retrospectively and were not defined. Around half of all patients received additional HBOT sessions but there was no information on the number, significance or impact on outcomes. It is not possible to determine the contribution of recompression with or without HBOT, or of recompression using different treatment schedules, to outcomes 10-14 days after treatment for patients with DCS.
Recovery immediately after a single HBOT session in relation to time to treatment	Lee et al 2015	4	Direct	C	The odds ratio (OR) of residual symptoms immediately after treatment with one session of HBOT, in relation to the time between developing symptoms and receiving treatment, was reported for 195 patients with Type I DCS Patients who received HBOT up to 24 hours after developing symptoms were treated as the reference group, and in multivariable logistic regression analysis, the OR (95% CI) for residual symptoms by time from symptoms to recompression was: 24-96 hours: 2.24 (0.75-6.65); 96-240 hours: 3.31 (1.08-10.13); ≥240 hours: 23.84 (2.45-231.43). This analysis therefore suggests that patients receiving recompression more than 96 hours after the development of symptoms had a significantly greater chance of residual symptoms immediately after treatment than patients treated within 24 hours. However the clinical significance of residual symptoms immediately after treatment and their relationship to longer term outcomes is unclear. In addition the findings should be treated with caution because patients were allocated retrospectively to outcome groups, which were undefined.
Recovery at discharge in relation to time to treatment	Xu et al 2012	4	Direct	C	Complete or incomplete recovery at discharge, compared with the time between onset of symptoms and receipt of recompression treatment, was reported in 5269 Chinese divers with DCI. A significant association was reported between a longer time between symptom onset and treatment, and higher rates of incomplete recovery ($p<0.0001$). The proportions of patients receiving treatment within different times from symptom onset who had complete/incomplete recovery were: 1-6hrs (n=2559) 93.8%/5.3%; 6-12hrs (n=1802) 87.6%/12.0%; 12-24hrs (n=555) 85.2%/14.4%; 24-36hrs (n=234) 80.8%/18.4%; >36hrs (n=119) 75.6%/24.4%. The evidence from this study suggests that there were worse outcomes at discharge for patients who had a longer time between symptom onset and treatment. However the findings should be treated with caution as complete and incomplete recovery were assessed retrospectively and were not defined. In addition it is not clear to what extent the analysis was adjusted for confounders as details of the analysis were not described. The treatment tables used were developed in a Chinese recompression facility and not all appear to have included HBOT; they are unlikely to be relevant to the current UK context.

Draft for consultation

Recovery 10-14 days after treatment with early or delayed recompression	Hadanny et al 2015	4	Direct	C	No improvement, partial recovery and complete recovery 10-14 days after treatment were reported for 204 divers with DCS who received recompression less than 48 hrs from surfacing (early recompression) or more than 48hrs after surfacing (delayed recompression). In early recompression (n=128), 78% had complete recovery, 15.6% partial recovery and 6.2% no improvement. In delayed recompression (n=76) 76% had complete recovery, 17.1% partial recovery and 6.6% no improvement. There was no significant difference between the two groups (p=0.955). In the delayed treatment group 70% had symptom onset within 12 hrs of surfacing. The evidence provided in this study suggests that delay in treatment has no effect on outcome at 10-14 days in patients with DCS. However the findings should be treated with caution as the outcomes were assessed retrospectively and were not defined, and it is not clear how similar the treatment groups were and whether any adjustments were made in this analysis for confounders. The clinical significance of outcomes at 10-14 days and their relationship to longer term outcomes was not described.

Abbreviations

2ATA	2 atmospheres absolute	MSK	Musculoskeletal
AGE	Arterial gas embolus	NSAID	Non-steroidal anti-inflammatory drug
CI	Confidence intervals	OR	Odds ratio
CX30	Comex 30	RCT	Randomised controlled trial
DCI	Decompression illness	RN T61	Royal Navy table 61
DCS	Decompression sickness	RN T62	Royal Navy table 62
DCS-I	Decompression sickness Type I	RN T62 ext	Royal Navy table 62 with extension
DCS-II	Decompression sickness Type II	Sat Tx	Saturation treatment
HBOT	Hyperbaric oxygen therapy	SD	Standard deviation
ICU	Intensive care unit	USN T5	US Navy table 5
IGE	Iatrogenic gas embolus	USN T6	US Navy table 6

Draft for consultation

9 Literature Search Terms

Search strategy *Indicate all terms used in the search*	
P – Patients / Population Which patients or populations of patients are we interested in? How can they be best described? Are there subgroups that need to be considered?	Adults or children suffering from decompression illness, decompression sickness or gas embolism arising from circumstances such as: decompression after breathing gas in an environment at pressure greater than one atmosphere, such as while diving for commercial, military or recreational purposes, working at pressure in a tunnel, chamber or caisson; actual or simulated submarine escape decompression to sub-atmospheric pressures, such as in air crew during altitude training or during high-altitude flight in an unpressurised cabin; space-walk by an astronaut iatrogenic gas embolism following invasive clinical procedures including cannulation of the arterial or venous system and intermittent positive pressure ventilation (IPPV) Symptoms of decompression illness include, but are not limited to: 1. Limb Pain 2. Pain presenting in a thoracolumbar dermatomal distribution (Girdle Pain) 3. Subjective or objective Neurological deficit 4. Audio-vestibular symptoms or signs 5. Cardio-pulmonary symptoms or signs 6. Cutaneous symptoms or signs (pruritus, rash, discoloration) 7. Lymphatic symptoms or signs (painful or swollen lymph nodes, regional oedema) 8. Constitutional symptoms or signs (such as headache, fatigue, malaise, nausea, vomiting and anorexia) severe enough to affect quality of life or function. Symptoms of gas embolism include, but are not limited to: 1. Subjective or objective Neurological deficit 2. Cardio-pulmonary symptoms or signs In order to make the diagnosis of decompression illness or gas embolism, the patient must have a history of an event that could cause gas to arise in the blood or other tissues and has a temporal relation to the onset of clinical manifestations, and all alternative diagnoses that can reasonably be ruled out have been excluded. Suggested search terms: Decompression illness Decompression sickness Caisson disease The bends Arterial gas embolism venous gas embolism arterial embolism gas embolism iatrogenic and/or anaesthesia and/or IPPV or ventilation Diver

Draft for consultation

	Diving Submarine escape Tunneller Caisson
I – Intervention Which intervention, treatment or approach should be used?	Initial hyperbaric treatment within 7 days of causative event and up to 10 repeat treatments if resolution of symptoms is incomplete. The patient is subjected to increased ambient pressure and is given oxygen at a partial pressure greater than is found in air. The inspired partial pressure of oxygen can vary from less than 50 kPa up to 304 kPa and the ambient pressure can be as high as 608 kPa. There is a range of hyperbaric treatment schedules but the most common is one that delivers oxygen at a maximum inspired partial pressure of 284 kPa lasting between 4.75 and 8 hours (e.g. Royal Navy Table 62 or US Navy Table 6) US Navy Table 6 is described at page 17-44 in the US Navy Diving Manual which can be downloaded from: http://www.navsea.navy.mil/LinkClick.aspx?fileticket=FvvZRd7DaAw%3d&tabid=20538&portalid=103&mid=48858 If resolution is incomplete, repeat treatments are indicated. These treatments sometimes use a lower partial pressure of oxygen, are usually of shorter duration, are administered once or twice every 24 hours and are repeated until: i. the signs resolve completely ii. there is no change after a treatment iii. it is clear that there is no sustained improvement when the patient's status immediately prior to several consecutive treatments is compared (even if there has been a temporary improvement immediately after one or more of those treatments) iv. the patient is mentally competent and declines further treatment The Undersea and Hyperbaric Medical Society recommends that an independent clinician should formally review progress after 10 treatments. The hyperbaric treatment is administered in conjunction with supportive care. Suggested search terms: Recompression Decompression Therapeutic recompression Therapeutic decompression Hyperbaric chamber Recompression chamber Decompression chamber Omitted decompression hyperbaric and oxygen hyperbaric oxygen therapy all combined with population/patient terms
C – Comparison What is/are the main alternative/s to	Any including best supportive care and the management of symptoms

Draft for consultation

compare with the intervention being considered?	
O – Outcomes What is really important for the patient? Which outcomes should be considered? Examples include intermediate or short-term outcomes; mortality; morbidity and quality of life; treatment complications; adverse effects; rates of relapse; late morbidity and re-admission; return to work, physical and social functioning, resource use.	Critical to decision-making: Clinical effectiveness: Mortality Morbidity Short term, long term outcomes including resolution of symptoms Neurological (e.g. cerebral) impairment Ability to walk unaided Dysbaric osteonecrosis Organ (e.g. cardiac) impairment Functional impairment Activities of Daily Living Quality of Life Adverse events Important to decision-making: Cost effectiveness,

Assumptions / limits applied to search

Inclusion criteria

Goodman, M. W., and R. D. Workman. 1965. Minimal-recompression, oxygen breathing approach to treatment of decompression sickness in divers and aviators. U.S. Navy Experimental Diving Unit Report No. 5-65, Washington, D.C., November. Available from: http://archive.rubicon-foundation.org/3342

Plus

Peer reviewed studies published in the last 10 years including:

Peer reviewed studies published in the last 10 years including:

Systematic review with or without meta-analysis

Randomised Controlled Trials

Prospective or retrospective cohort studies.

Case series

The time frame of the original publications suggests that early publications may fall short of present day designs

Exclusion criteria

Work that is not available in the English language

Case reports; conference abstracts, grey literature, anecdotal

Unpublished evidence

Draft for consultation

10 Search Strategy

We searched PubMed, Embase, Cochrane Library, TRIP and NHS Evidence. Limiting the search to papers published in England from **1st January 2007 to 2 May 2017**. We excluded conference abstracts, commentaries, letters, editorials and case reports.

Search date: 2 May 2017
Embase search:

1	barotrauma/ or decompression sickness/
2	air embolism/ or gas embolism/
3	diving/ and decompression/
4	(decompression adj5 (sickness or illness or syndrome)).ti,ab.
5	(caisson* adj5 (disease* or sickness or illness or syndrome)).ti,ab.
6	"the bends".ti,ab.
7	((gas or air) adj2 embol*).ti,ab.
8	((diver? or diving or submarin* or tunneller?) adj5 (decompress* or recompress*)).ti,ab.
9	((decompress* or recompress*) adj2 (therap* or treatment)).ti,ab.
10	intermittent positive pressure ventilation/
11	(intermittent positive pressure ventilation or ippv).ti,ab.
12	airplane crew/
13	((air crew or pilots or airline staff* or aeroplane staff* or airline personnel or aeroplane personnel or flight staff flight personnel) and (altitude or decompress* or recompress*)).ti,ab.
14	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13
15	hyperbaric oxygen/
16	((hyperbaric adj2 (oxygen* or therap* or treatment)) or hbot or oxygen chamber* or barochamber*).ti,ab.
17	15 or 16
18	14 and 17
19	(exp animals/ or nonhuman/) not human/
20	conference*.pt.
21	19 or 20
22	18 not 21
23	limit 22 to (english language and yr="2007 -Current")

11 Evidence Selection

- Total number of publications reviewed: 37
- Total number of publications considered potentially relevant: 20
- Total number of publications selected for inclusion in this briefing: 7

Draft for consultation

12 References

Bennett MH, Lehm JP, Mitchell SJ, Wasiak J. 2012. Recompression and adjunctive therapy for decompression illness. Cochrane Database of Systematic Reviews. 2012; (5): Available from: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD005277.pub3/abstract.

Bennett M, Mitchell S, Dominguez A. 2003. Adjunctive treatment of decompression illness with a non-steroidal anti-inflammatory drug (tenoxicam) reduces compression requirement. *Undersea & Hyperbaric Medicine 30(3): 195–205.*

Bessereau J, Genotelle N, Chabbaut C, Huon A, Tabah A, Aboab J, Chevret S, Djillali A. 2010. Long-term outcome of iatrogenic gas embolism. *Intensive Care Medicine* 36(7):1180-7

Goodman MW, Workman RD. 1965. Minimal-recompression, oxygen breathing approach to treatment of decompression sickness in divers and aviators. *US Navy Experimental Diving Unit* Report No 5-64, Washington DC.

Hadanny A, Fishlev G, Bechor Y, Bergan J, Friedman M, Maliar A, Efrati S. 2015. Delayed recompression for decompression sickness: Retrospective analysis. *PLoS ONE* 10(4): e0124919. doi: 10.1371/journal.pone.0124919

Koch AE, Wegner-Brose H, Warninghoff V, Deuschl G. 2008. Viewpoint: the type A- and the type B-variants of Decompression Sickness. *Undersea & hyperbaric medicine: journal of the Undersea and Hyperbaric Medical Society*, Inc. 35(2):91-7.

Lee J, Kim K, Park S. 2015. Factors associated with residual symptoms after recompression in type I decompression sickness. *American Journal of Emergency Medicine.* 33; 363-366.

NHS England, 2017. Population, Intervention, Comparator and Outcomes (PICO) template, Hyperbaric Oxygen Therapy for Decompression Illness/ Gas Embolism.

Sayer MDJ, Ross JAS, Wilson CM. 2009. Analysis of two datasets of divers with actual or suspected decompression illness. *Diving and Hyperbaric Medicine* 39(3):126-32.

US Navy Department 2008. *US Navy Diving Manual*, Revision 6. Volume 5: Diving Medicine and Recompression Chamber Operations.

Xu W, Liu W, Huang G, Zou Z, Cai Z, Xu W. 2012. Decompression illness: Clinical aspects of 5,278 consecutive cases treated in a single hyperbaric unit. *PLoS ONE:* 7(11): e50079. doi: 10.1371/journal.pone.0050079

Draft for consultation