

NHS England

**Evidence review: Hyperbaric oxygen therapy
for diabetic lower limb ulceration refractory
to best standard care**



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1. Introduction

- People with diabetes mellitus are at increased risk of foot ulceration. The ulcers are multifactorial, often caused or exacerbated by diabetic peripheral neuropathy and angiopathy. Diabetic neuropathy diminishes perception of pain, so that minor trauma, such as localised pressure caused by unsuitable shoes, abnormal biomechanical stress or open wounds, is often not noticed. This makes early treatment difficult and promotes the development of a foot ulcer. Poor circulation because of diabetic vessel damage leads to faster tissue breakdown and impairs resistance to infection, and ulcer healing (Schaper et al 2012).
- Ulcer care is responsible for a large proportion of the cost of health care for people with diabetes. Foot ulcers restrict mobility and diminish quality of life. They are sometimes slow to resolve, requiring professional time and materials to promote healing. Their most serious consequence is amputation, for instance in the forefoot area (minor amputation) or through the metatarsals or of part of the leg (major amputation) (Schaper et al 2012).
- The annual incidence of foot ulcers among people with diabetes has been estimated at between 2.5% and 10.7%, and the annual incidence of amputation is 0.25% to 1.8% (Boulton 2008).
- Standard treatment of diabetic foot ulcers requires a multidisciplinary team comprising a podiatrist, an orthotist, a specialised nurse and a diabetologist. Treatment options include close monitoring, intensive systemic antibiotic therapy, wound dressings and debridement of dead tissue. Revascularisation is also usually considered (National Institute for Health and Care Excellence 2015).
- Hyperbaric oxygen therapy (HBOT) involves the inhalation of pure oxygen at a pressure higher than normal atmospheric pressure, usually 2 to 3 atmospheres absolute (ATA). During HBOT, the patient is in a pressure chamber, and when used for the treatment of diabetic foot ulcers, this is usually for 45 to 120 minutes on most days for several weeks.
- Inhaling oxygen at increased pressure is intended to improve oxygen supply to the ulcer. Nearly all the oxygen in the blood is bound to haemoglobin; under normal pressure, saturation in the arterial blood is 97%. The remaining oxygen is dissolved in the blood plasma; this proportion can be increased by higher ambient pressure and the associated increase in the partial pressure of oxygen. In this way, tissue structures that would be hypoxic under normal conditions may receive a more adequate supply of oxygen, which may in turn improve cell function and promote wound healing. This might occur because of enhanced neutrophil killing ability, angiogenesis, fibroblast activity and/or collagen synthesis.
- The National Institute for Health and Care Excellence recommends that hyperbaric oxygen should not be used to treat diabetic foot ulcers, except as part of a clinical trial (National Institute for Health and Care Excellence 2015). This was because of the "*very low quality of the evidence*".
- NHS England does not commission HBOT for diabetic foot ulcers.

2. Summary of results

- This evidence review found four randomised controlled trials and one cost-utility analysis.
- Two trials compared HBOT plus standard care with standard care only, and two compared HBOT plus standard care with sham HBOT plus standard care.

- They reported results in three categories: amputation or the emergence of indications for amputation, partial or complete ulcer healing and adverse effects of treatment.
- The most reliable randomised trial was double-blind and used air at slightly above atmospheric pressure as a sham alternative to HBOT (Fedorko et al 2016). Its authors reported no effect of HBOT on rates of meeting criteria determined by a vascular surgeon for major amputation (95% CI 0.37 to 2.28, $p = 0.846$) or of recommendation of major or minor amputation (95% CI 0.52 to 2.43, $p = 0.771$) among their 103 participants. Major amputation was defined as a procedure below the knee or at the level of the metatarsals; minor amputations were at the level of the toes.
- Fedorko et al (2016) reported that compared to the control group who received air at 1.25 atmospheres, there was no significant effect of HBOT at 2.5 atmospheres on wound size, the rate at which the wound edge advanced, the results of a wound assessment tool or the proportion of wounds that healed at 3 months follow up.
- In another double-blinded study, Löndahl et al (2010) randomised 94 participants between HBOT and hyperbaric air, both at 2.5 atmospheres. The authors reported rates of complete healing of the index ulcer of 52% in the HBOT group and 29% in the placebo group ($p = 0.03$) at one year follow up. The authors also reported rates of death and major (above the ankle) and minor amputation, but without testing the statistical significance of differences.
- By contrast, Duzgun et al's (2008) unblinded trial with 100 participants did not use a placebo treatment. These authors reported that more participants treated with HBOT had ulcers that healed (66% vs 0%, $p < 0.05$) or were treated with a graft or flap (8% vs 0%, $p < 0.05$), while fewer had an amputation (distal: 8% vs 48%, $p < 0.05$; proximal: 0% vs 34%, $p < 0.05$).
- Ma et al (2013) reported a smaller, less reliable, unblinded study, with only 36 participants. They reported the same rates of completed ulcer healing with and without HBOT. Ulcer size was reported as reducing faster after HBOT, though not to the extent that significantly more ulcers had healed by the end of the study.
- Participants who underwent HBOT in Fedorko et al's (2016) trial reported 24 adverse events which had not been specifically solicited by the researchers, significantly more than the five events reported by the participants who had a sham treatment. Rates of reporting of solicited adverse events were similar in the two groups. Löndahl et al (2010) reported similar rates of adverse events in the two arms of their trial. The most common adverse events in these two trials included barotrauma, inability to equalise middle ear pressures and episodes of hypo- or hyper-glycaemia. Ma et al (2013) reported no adverse events in either arm of their trial.
- The most reliable trial, Fedorko et al (2016), reduced the risk of observer bias by the use of a placebo treatment with hyperbaric air, and double-blinding. The pressure of the air (1.25 ATA) was too low to be likely to have an adverse effect, a conclusion supported by the higher rate of adverse reactions in the intervention arm, so this trial can be viewed as truly placebo-controlled. The randomisation resulted in different proportions of participants with potential confounders in each arm: for example, the HBOT group participants had had their index ulcer for less time than those in the control group, but had had diabetes for longer. Any potential for biases operated in both directions and does not call into question the trial's reliability. These authors reported no benefit from HBOT.
- Löndahl et al (2010) also used a double-blind design, with control participants receiving hyperbaric air. Randomisation in this trial resulted in no important differences between participants allocated to the two arms. However, the pressure of the hyperbaric air in the control arm (2.5 ATA) was twice that in Fedorko et al's (2016) trial, high enough to create a risk of adverse effects; these were reported at similar rates in the two arms.
- The reason for the different ulcer-healing results of these two otherwise reliable trials is

uncertain but could be due to the control treatment in Löndahl et al's (2010) study (air at 2.5 atmospheres) not being an inert placebo, a concern that was also raised by Fedorko et al (2016). This is because the pressure of air used for the control patients was the main difference between the two study protocols and the pressure used in Londahl et al's (2010) study was at a level that is well above what would be experienced during usual care. The effect of this level of air pressure is not understood and it is possible that it may have impaired ulcer healing. For this reason, the Löndahl et al (2010) study is considered somewhat less reliable than Fedorko et al (2016). Other minor differences between the studies, that may have had some impact on the differing ulcer healing results, were the longer follow up and larger number of treatment sessions in the study by Londahl et al (2010) (57% received at least 40 sessions in Londahl et al and 69% received at least 30 sessions in Fedorko et al).

- The other two trials reported benefit from HBOT. However, both were at material risk of bias because the participants and the researchers were aware of whether HBOT had been used; this is a plausible explanation for their discrepant results.
- There are some additional concerns about Duzgun et al (2008). The authors appear to suggest that there may have been significant confounding, though the nature, extent and impact of this are not reported.
- Furthermore, none of 50 control participants' ulcers in Duzgun et al's (2008) trial were healed after 92 weeks of treatment. This is inconsistent with the other trials, despite the participation of people with Wagner grade 2 ulcers in all trials, and calls into question the effectiveness of standard care in this trial. Poor standard care would make this trial not generalisable to the NHS.
- Adverse events appear more common after HBOT.
- We found one cost-utility study. Chuck et al (2008) reported that HBOT was both more effective and less expensive than standard care.
- Chuck et al's (2008) analysis is of limited relevance and reliability.
- It used estimates of the effectiveness of HBOT from a study published in 2003 (Guo et al 2003), which predates the three randomised trials in this rapid evidence review. The model's assumptions about the effectiveness of HBOT are incompatible with this more recent evidence, which is derived from more reliable studies. Chuck et al (2008) themselves noted that the clinical data that they used were "*limited*". The costs are based on the Canadian health care system in 2008, and may be materially different from those in the NHS. The authors admitted that their data were not "*of high quality*." They went on to note "*Cost data for HBOT were based on data from only a few centers, and reporting was not standardized*".
- There is insufficient evidence that HBOT is effective in the treatment of diabetic foot ulcers. Taken together, the evidence does not support HBOT's introduction to the NHS for this indication. Two of the trials reporting benefit were at risk of placebo effects and observer bias because they were unblinded; they are unreliable. Of the two double-blind trials, one reported no benefit from HBOT and a second, which is less reliable due to concern that the control intervention may not have been inert, reported benefit.
- There would be value in a further double-blind trial of HBOT for this indication, with a control similar to that used in Fedorko et al (2016).

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 for the topic (see section 9 for PICO).
- The PICO was used to search for relevant publications in EMBASE, MEDLINE and the Cochrane Library (see section 10 for search strategy).
- The search dates for publications were between 1 January 2007 and 2 May 2017.
- 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. The study by Löndahl et al (2010) was added following a request from NHS England.
- 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 below).
- The body of evidence for individual outcomes identified in the papers was graded and recorded in grade of evidence tables (see section 8 below).

4. Results

Four randomised trials were identified (Fedorko et al (2016), Ma et al (2013), Löndahl et al (2010) and Duzgun et al (2008)). Two trials compared HBOT plus standard care with standard care only. Two (Fedorko et al (2016) and Löndahl et al (2010)) concealed treatment allocation from researcher and participants by the use of sham HBOT, reporting a comparison of HBOT plus standard care with sham HBOT plus standard care. The studies were small, including in total 333 participants.

Participants were adults with diabetes and an ulcer of at least Wagner grade¹ 2 (deep ulcer with tendon or joint involvement) of at least four weeks duration. HBOT regimes varied, but all four included at least 20 daily 90-minute sessions at a pressure of at least 2 ATA. Session numbers were 20 in Ma et al (2013), 30 in Fedorko et al (2016), 40 in Löndahl et al (2010) and 30 to 45 in Duzgun et al (2008).

One cost-utility study was identified. It modelled the costs and effectiveness of HBOT for diabetic foot ulcers, based on Canadian cost data and an effectiveness review published in 2003.

In the patient populations of interest, what is the effect of adding HBOT to the standard management pathways on the specified outcomes?

Clinical efficacy outcomes reported in the studies included freedom from major and minor amputation, freedom from meeting criteria for amputation, rates of ulcer healing or other clinical

¹ The Wagner classification of diabetic foot ulceration:

Grade 0 - No open ulcer, high risk

Grade 1 - Superficial ulcer with subcutaneous involvement

Grade 2 - Deep ulcer with tendon or joint involvement

Grade 3 - Deep ulcer with bone involvement

Grade 4 - Wet or dry gangrene (forefoot), without cellulitis

Grade 5 - Generalized (whole foot) gangrene

outcomes, reductions in ulcer size, improvements in wound assessment scores and adverse effects.

Freedom from major and minor amputation

Three studies reported this outcome. In a double-blind trial, Fedorko et al (2016) reported no differences between HBOT and a sham procedure to mimic HBOT in the proportions of participants undergoing major amputation or meeting criteria determined by a vascular surgeon for such a procedure (odds ratio (OR) 0.91, 95% CI 0.37 to 2.28, $p = 0.85$); participants in this trial all received standard care. Löndahl et al (2010) reported three major (above the ankle) amputations in the HBOT group and one in the control group, along with four minor amputations in each group; no significance test was reported. Duzgun et al's (2008) unblinded trial reported significant differences between standard care with and without HBOT in the proportions of patients who underwent distal amputation (HBOT 4/50 (8%), control 24/50 (48%), $p < 0.05$) and proximal amputation (HBOT 0/50 (0%), control 17/50 (34%), $p < 0.05$).

Freedom from meeting criteria for amputation

Fedorko et al (2016) reported no difference in the proportion of participants receiving a recommendation in favour of major or minor amputation (OR for HBOT vs control groups 1.12, 95% CI 0.52 to 2.43, $p = 0.77$).

Rates of ulcer healing or other clinical outcomes

Fedorko et al (2016) reported no difference in the proportion of participants whose ulcers healed by 12 weeks (OR 0.90, 95% CI 0.35 to 2.31, $p = 0.823$).

Löndahl et al (2010) reported complete healing of the index ulcer at one year in 25 of 48 participants (52%) in the HBOT group and 12 of 42 (29%) in the placebo group ($p = 0.03$).

Ma et al (2013) also reported no difference in the proportion of participants whose ulcers healed by two weeks (none in either arm of their unblinded trial).

Reductions in ulcer size

Fedorko et al (2016) reported no difference between the two groups in reduction in manually measured ulcer size after 12 weeks (mean difference between HBOT and control groups -0.12cm, 95% CI -0.46 to 0.22, $p = 0.491$), reduction in digitally measured ulcer area after 12 weeks (mean difference between the groups of 0.037 cm², 95% CI -1.11 to 1.19, $p = 0.949$), linear advancement of the ulcer edge in the first six weeks of the trial (mean difference -0.002 cm/week, 95% CI -0.016 to 0.013, $p = 0.817$) or in the second six weeks (mean difference -0.0003 cm/week, 95% CI -0.012 to 0.015, $p = 0.97$).

Ma et al. (2013) reported larger reductions in ulcer area in participants who underwent HBOT (an absolute difference of 24.3%, $p < 0.05$). The authors did not report the change in ulcer size in absolute terms.

Improvements in wound assessment scores

Fedorko et al (2016) reported no differences in results from the Bates-Johnson wound assessment tool² after 12 weeks (mean difference between HBOT and control groups in the change over 12 weeks 0.53, 95% CI -2.58 to 3.64, $p = 0.735$). This tool assesses 13 wound

² The Bates-Jenson wound assessment tool assesses 13 wound characteristics, with each item scored on a 1–5 scale (maximum score 65). The individual scores are summated for a total score. The higher the total score, the more severe the wound status.

characteristics, with each item scored on a 1 to 5 scale.

Adverse effects

Fedorko et al (2016) reported a higher number of reported unsolicited adverse events from participants who had undergone standard care plus HBOT compared with standard care plus sham treatment (HBOT 24, control 5, $p = 0.02$). These included inability to equalise middle ear pressures, anxiety, chest pain, nausea, hypo- and hyperglycaemia, wound infection, pain after tympanic membrane rupture and congestive heart failure. Reported numbers of the adverse events about which the researchers specifically enquired were similar (HBOT 9, control 6, $p = 0.44$). These included acute respiratory distress, pneumothorax, convulsion/seizure, barotrauma and visual changes.

Löndahl et al (2010) reported similar rates of adverse events in the two arms of their trial. One participant in the HBOT group and three in the placebo group died during the first year after randomisation. Amputations are reported in the outcomes section above. The authors do not report tests of significance on these results. Symptomatic hypoglycaemia occurred in two and four patients in the HBOT and placebo groups respectively (not significant). One patient in the HBOT group had barotraumatic otitis, and a further four patients, two in each group, required myringotomy with tube placement. In the HBOT group, treatment-related dizziness was seen in one patient and the worsening of cataracts in another.

Ma et al (2013) reported no adverse events in either arm of their trial.

Is there evidence for greater improvements in treatment outcomes for patients who receive 30 or more hyperbaric oxygen treatments?

No. We found no evidence comparing HBOT regimes of different durations, nor was there any tendency among the three trials for regimes with 30 or more sessions to be reported as more effective.

What is the cost effectiveness for HBOT as an adjunctive treatment for diabetic patients with refractory ulcers of the lower limb?

We do not know. We found no reliable cost utility studies.

5. Discussion

The four randomised trials that were included report inconsistent results.

Fedorko et al (2016) is a high-quality study, the authors of which enhanced the reliability of their results by using a sham HBOT treatment as a placebo control. They report the widest range of outcomes of the three trials, and their results show no suggestion of a benefit from HBOT.

Löndahl et al (2010) also included several measures to minimise the risk of bias, improving its reliability. Like Fedorko et al (2016), the authors used pressurised air in control patients to ensure their trial was double-blind. However, the pressure of the hyperbaric air in the control arm (2.5 ATA) was twice that in Fedorko et al's (2016) trial, much higher than what would be experienced during usual care and high enough to create a risk of adverse effects; these were reported at similar rates in the two arms. Although the effects of hyperbaric air at these pressures are not well understood, the pressures used for control patients by Löndahl et al (2010) mean that we cannot regard Löndahl et al's (2010) control treatment as an inert placebo, raising the possibility that their results, which indicated better ulcer healing at one year after HBOT with 100% oxygen compared to hyperbaric air, arise at least in part from impaired ulcer healing in the control arm due to the control intervention. There were other differences between these two studies (longer follow up

and a larger number of treatment sessions in the study by Londahl et al (2010) (57% received at least 40 sessions in Londahl et al and 69% received at least 30 sessions in Fedorko et al). However, these differences are minor and less likely to be the reason for the discrepancy in the results between the two studies.

The trials by Ma et al (2013) and Duzgun et al (2008) are methodologically inferior. They both lacked a placebo control and were in consequence unblinded. They both report benefit from HBOT, with better ulcer healing and fewer amputations. The apparent confounding differences between participants in the two arms and poor results from standard care in Duzgun et al (2008) further limit that trial's reliability and generalisability to the NHS.

This pattern of results indicates that the discrepancy in results may be because of a placebo effect and/or observer bias producing unreliable results from the two unblinded trials, along with potential toxicity from high-pressure air in Londahl et al (2010) (the other differences between Londahl et al and Fedorko et al's studies were relatively minor). This leads us to accept Fedorko et al's (2016) conclusion that

"HBOT does not offer an additional advantage to comprehensive wound care in reducing the indication for amputation or facilitating wound healing in patients with chronic [diabetic foot ulcers]."

It is certainly not possible to reach a conclusion in favour of HBOT in the light of Fedorko et al's results.

Apart from the 2.5atm of hyperbaric air used for the comparator group in the Londahl et al(2010) study, standard care was apparently similar in the four trials. There were some differences in ulcer severity between the trials, with fewest severe ulcers in Ma et al (2013) and most in Duzgun et al (2008). However, this would not explain why the results of Fedorko et al (2016) differ from those of the other two trials.

Fedorko et al (2016) also report higher rates of adverse events after HBOT.

Chuck et al's (2008) cost utility review is unreliable, being based on earlier and less robust effectiveness studies and patchy cost data of uncertain relevance to the NHS.

6. Conclusion

There is insufficient evidence that HBOT is effective in the treatment of diabetic foot ulcers. Taken together, the evidence does not support HBOT's introduction to the NHS for this indication. Two of the trials reporting benefit were at risk of placebo effects and observer bias because they were unblinded; they are unreliable. Of the two double-blind trials, one reported no benefit from HBOT and a second, which is less reliable due to concern that the control intervention may not have been inert, reported benefit.

There would be value in a further double-blind trial of HBOT for this indication, with a control similar to that used in Fedorko et al (2016).

7. Evidence Summary Table

Use of HBOT plus best practice wound care Vs. best practice wound care to treat diabetic foot ulcers									
Study reference	Study Design	Population characteristics	Intervention	Outcome measure type	Outcome measures	Results	Quality of Evidence Score	Applicability	Critical Appraisal Summary
Fedorko et al 2016	P1 – randomised controlled trial 1 hospital in Canada	103 people with diabetes (96 (93%) type 2), aged at least 18 years, referred to a community-based specialised wound-care and hyperbaric treatment clinic for the treatment of a lower-limb wound (Wagner grade ³ 2, 3, or 4) persisting for a minimum of 4 weeks. Wagner grades: grade 2 n=46, grade 3 n=51, grade 4 n=6. 49 randomised to and received HBOT, 54 randomised to and	A computerised block randomisation schedule with a multiple block size of four was used. Intervention: HBOT oxygen for 90min at 244 kPa, with 5-min intervals of breathing air for every 30 min of oxygen, 5 days per week for 6 weeks (30 sessions) (Monoplace chambers (Pan-America Hyperbarics	Primary Clinical effectiveness	Freedom from major amputation and from meeting the criteria for major amputation (defined as below-knee or metatarsal level amputation) at 12 weeks, based on the following criteria for amputation: 1. Lack of significant progress in wound healing over the follow-up	Meeting the criteria for major amputation at 12 weeks: HBOT 11/49 (23%), control 13/54 (24%), odds ratio (OR) 0.91, 95% CI 0.37 to 2.28, p = 0.846.	9	Direct	Clinical and research personnel and participants were blinded to treatment allocation, reducing the risk of bias. Randomisation was uneven: HBOT group participants had had diabetes for longer than those in the control group (19.1 vs. 12.4 years, respectively) and were more likely to have type 1 diabetes (12% vs. 2%). The mean number of days with the index wound was 235 days in the HBOT group and 336 days in the control group. The mean index ulcer surface area at randomisation was reported as 5.1 cm ² and 6.1cm ² in the HBOT and control groups respectively in the text, with different figures for digital wound area of 3.8 cm ² and 3.6 cm ² given in Table 1. The authors report no tests of statistical significance on these differences. These differences do not cast doubt on the trial's reliability. Intention to treat analyses reported.

³ The Wagner classification of diabetic foot ulceration:
The Wagner classification of diabetic foot ulceration:
Grade 0 - No open ulcer, high risk
Grade 1 - Superficial ulcer with subcutaneous involvement
Grade 2 - Deep ulcer with tendon or joint involvement
Grade 3 - Deep ulcer with bone involvement
Grade 4 - Wet or dry gangrene (forefoot), without cellulitis
Grade 5 - Generalized (whole foot) gangrene

		<p>received control treatment.</p> <p>Study duration 12 weeks. Patients were followed for 6 weeks after the end of hyperbaric sessions and returned to the clinic every week for assessment.</p> <p>Mean age 61 years, 67% male.</p>	<p>Inc., Richardson, TX), plus standard care (SC) (weekly outpatient wound assessment and treatment for 12 weeks, including comprehensive wound care, infection control, debridement, offloading devices and advanced wound care dressings.</p> <p>Control: Sham sessions of breathing air at 125 kPa (equivalent to breathing 27% oxygen by face mask) on the same schedule as intervention. This minimum pressure was <i>“required to create a sensation of being pressurized and depressurized identical to the active treatment group to keep the patients blinded to the allocation”</i>, plus SC.</p>		<p>period, which indicated a risk of severe systemic infection related to the wound</p> <ol style="list-style-type: none"> 2. Persistent deep infection involving bone and tendons (antibiotics and hospitalisation required, pathogen involved) 3. Inability to bear weight on the affected limb 4. Pain causing significant disability. 				
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				Secondary Clinical effectiveness	Recommendation in favour of major or minor amputation	By 12 weeks: HBOT 25/49 (51%), control 26/54 (48%), OR 1.12, 95% CI 0.52 to 2.43, p = 0.771.			
				Secondary Clinical effectiveness	Wound size, measured weekly manually and by computerised analysis of wound surface area and perimeter from high-resolution calibrated digital photographs. The authors also calculated the linear advancement of the wound edge (LAWE). All measurements at 12 weeks	Manually measured mean width reduction at 12 weeks: HBOT 0.57cm (SD 0.13), control 0.69cm (SD 0.12), difference in mean width reduction-0.12cm, 95% CI -0.46 to 0.22, p = 0.491. Reduction in digital surface area at 12 weeks: HBOT 1.9 cm ² , control 1.8 cm ² , difference in reduction in mean area 0.037 cm ² , 95% CI -1.11 to 1.19, p = 0.949. LAWE between weeks 0 and 6: difference in mean rate of LAWE -0.002 cm/week, 95% CI -0.016 to 0.013, p = 0.817. LAWE between weeks 6 and 12: difference in mean rate of LAWE -0.0003 cm/week, 95% CI -0.012 to 0.015, p = 0.97.			
				Secondary Clinical effectiveness	The Bates-Jensen wound assessment tool ⁴ was used weekly to measure progress of ulcer healing.	Mean change in score between 0 and 12 weeks: HBOT -7.0 (SD 1.13), control -7.5 (SD 1.08), difference in mean change in score 0.53, 95% CI -2.58 to 3.64, p = 0.735.			
				Secondary Clinical effectiveness	Proportion of ulcers healed (i.e. Wagner grade* 0 or 1) at 12 weeks	At 12 weeks: HBOT 20%, control 22%, OR 0.90, 95% CI 0.35 to 2.31, p = 0.823.			

⁴ The Bates-Jensen wound assessment tool assesses 13 wound characteristics, with each item scored on a 1–5 scale (maximum score 65). The individual scores are summated for a total score. The higher the total score, the more severe the wound status.

				Secondary Safety	<p>The researchers solicited information on acute respiratory distress, pneumothorax, convulsion/seizure, barotrauma and visual changes.</p> <p>They also recorded other adverse events as unsolicited. These included inability to equalise middle ear pressures, anxiety, chest pain, nausea, hypo- and hyperglycaemia, wound infection, pain after tympanic membrane rupture and congestive heart failure</p>	<p>Solicited adverse events: HBOT 9, control 6, p = 0.44.</p> <p>Unsolicited adverse events: HBOT 24, control 5, p = 0.02.</p>			
Löndahl et al (2010)	<p>P1 – randomised controlled trial</p> <p>1 hospital in Sweden</p>	<p>94 people with diabetes, at least one full-thickness wound below the ankle (Wagner grade 2, 3 or 4) for >3 months and adequate distal perfusion or non-reconstructable peripheral vascular disease.</p> <p>Wagner grades: grade 2 26%,</p>	<p>Randomisation was done in blocks of 10 using sealed envelopes.</p> <p>Intervention: compression in air for 5 minutes, then 100% oxygen at 2.5 atmospheres absolute (ATA) for 85</p>	<p>Primary Clinical effectiveness</p>	<p>Complete healing of the index ulcer (the ulcer with the largest area and a duration of at least three months at the time of randomisation)</p>	<p>At one year: HBOT 25/48 (52%), control 12/42 (29%), p = 0.03).</p>	7	Direct	<p>Clinical and research personnel and participants were blinded to treatment allocation, reducing the risk of bias.</p> <p>The authors used air pressurised to 2.5 atmospheres in control patients to ensure their trial was double-blind. This is high enough to create a risk of adverse effects; these were reported at similar rates in the two arms. The control treatment may not have been an inert placebo, raising the possibility that their results arise at least in part from impaired ulcer healing in the control arm.</p>
				Primary	Amputations: major (above	At one year: HBOT 3 major and 4 minor, control 1 major			

		<p>grade 3 56%, grade 4 18%.</p> <p>49 randomised to and received HBOT, 45 randomised to control treatment.</p> <p>Study duration 1 year</p> <p>Mean age 69 years, 81% male.</p> <p>Analysis by intention to treat.</p>	<p>minutes, then decompression for 5 minutes, plus standard care (SC) (treatment of infection, revascularization, debridement, off-loading, and metabolic control).</p> <p>Control: Identical to the intervention, except for the use of air, not 100% oxygen, for the 85 minute treatment phase, plus SC as above.</p>	<p>Clinical effectiveness</p>	<p>the ankle) and minor (all others)</p>	<p>and four minor, no significance test reported.</p>			<p>1, 2, 3, 6 and 9 month per protocol outcomes, rather than intention to treat outcomes, were reported in a graph in the paper. These are not reported here because they are per protocol rather than intention to treat and because they were published in a poorly labelled graph with no accompanying data. Comparison of per protocol outcomes with intention to treat outcomes is not valid. Intention to treat outcomes were only reported at 1 year.</p>
				<p>Secondary Safety</p>	<p>Adverse event</p>	<p>HBOT: 1 death from multiple organ failure 20 days after randomisation, 2 participants with hypoglycaemia (symptoms and blood-glucose < 3.0 mmol/l), 1 with barotraumatic otitis, 2 with myringotomy and tube placement, 1 with treatment-related dizziness, 1 with worsening of cataracts.</p> <p>Control: 1 patient lost consciousness after a treatment session, 4 participants with hypoglycaemia, 2 with myringotomy and tube placement, 1 patient had a fall and minor head injury in the chamber.</p> <p>The difference in rates of hypoglycaemia was not significant; statistical tests of the other results were not reported.</p>			
<p>Ma et al 2013</p>	<p>P1 – randomised controlled trial</p> <p>1 hospital in China</p>	<p>36 people with diabetes, at least one full-thickness wound below the ankle (Wagner grade 3 or less) for >3 months; history of receiving standard care for >2 months; normal palpation of arterial pulses at lower extremities; normal lower limb Doppler scan results; transcutaneous oxygen pressure >30 mm Hg at the dorsum of the foot, and no abnormal</p>	<p>Randomisation with random number table.</p> <p>Intervention: HBOT 100% oxygen, twice daily, for 90 minutes at 2.5 ATA, 5 days a week for 2 weeks, in a multi-person hyperbaric chamber (K018YX-10-8, XinYing, Hang Zhou City, China). Each HBO session included 15 minutes of</p>	<p>Primary Clinical efficacy</p>	<p>Healed by day 14</p>	<p>HBOT 0, control 0.</p>	<p>9</p>	<p>Direct</p>	<p>The study was unblinded, increasing the risk of bias. There were no reported significant baseline differences between the arms.</p> <p>Materially shorter follow-up than the other two trials.</p> <p>This was the only trial to use palpable peripheral pulses as an entry criterion.</p>

		<p>x-ray findings that may be indicative of chronic bone infection.</p> <p>Wagner grades: grade 1 n=9, grade 2 n=10 grade 3 n=17.</p> <p>18 randomised to and received HBOT (of whom 23 had type I diabetes), 18 randomised to and received control treatment (of whom 2 had type I diabetes).</p> <p>Study duration 2 weeks</p> <p>Mean age 60.1 years, 64% male.</p>	<p>compression time, three 30-minute HBOT periods with two 5-minute intervals in room air, and a 15-minute decompression period, plus standard care (SC) (admitted to hospital for 2 weeks for offloading, footwear, non-weight-bearing of the affected foot, oral antibiotics, drug sensitivity test of ulcer tissue, blood glucose levels monitoring and maintenance at <8 mmol/L with subcutaneous insulin injections if necessary, daily dressing changes with silver-impregnated dressings used in infected ulcers and absorptive cotton in uninfected ulcers, daily wound curettage or debridement of necrotic tissue and surrounding callus.</p>						
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			Control: SC only						
				Primary Clinical efficacy	Average reduction in ulcer area by day 14	HBOT 42.4% standard deviation (SD) 20.0%, control 18.1% SD 6.5%, p <0.05.			
				Secondary Safety	Adverse events: death, amputation, barotraumatic otitis, dizziness, seizures, and pneumothorax	HBOT 0, control 0.			
Duzgun et al 2008	P1 – randomised controlled trial 1 hospital in Ankara, Turkey	100 people with diabetes (86% insulin-dependent) at least 18 years of age with a foot wound that had been present for at least 4 weeks despite appropriate local and systemic wound care. Wagner grades: grade 2 n=18, grade 3 n=37, grade 4 n=45. 50 participants randomised to each arm. Mean duration of follow-up was 92 weeks. Mean age 60 years, 64% male	Randomisation with a random number table, allocating patients to a treatment group depending on whether the number was even or odd. Intervention: HBOT with maximum working pressure of 20 ATA, using a unichamber pressure room (Patterson Companies, Inc., St. Paul, MN), employing a volume of 10 m ³ at 2 to 3 ATA for 90 minutes, once or twice daily on alternate days for 20 to 30 days, plus	Primary Clinical efficacy	Clinical outcome, one of the following 6: Healed (complete closure without debridement in the operating room), graft or flap (graft or flap closure required), distal amputation (amputation distal to metatarsophalangeal joints), proximal amputation (amputation proximal to the metatarsophalangeal joints), debridement (standard therapy wound or operative debridement), no change (failure to heal	Healed: HBOT 33/50 (66%), control 0/50 (0%), p < 0.05. Graft or flap: HBOT 4/50 (8%), control 0/50 (0%), p < 0.05. Distal amputation: HBOT 4/50 (8%), control 24/50 (48%), p < 0.05. Proximal amputation: HBOT 0/50 (0%), control 17/50 (34%), p < 0.05. Debridement: HBOT 0/50 (0%), control 9/50 (18%), p < 0.05. No change: HBOT 9/50 (18%), control 0/50 (0%), p < 0.05.	8	Direct	The study was unblinded. It is surprising that none of 50 control participants' ulcers were healed after 92 weeks of treatment. This is inconsistent with the other trials, despite the participation of people with Wagner grade 2 ulcers in all trials, and calls into question the effectiveness of standard care in this trial. Poor standard care would make this trial not generalisable to the NHS. The randomisation produced uneven results, with HBOT participants more likely to be male, obese and smokers and with less severe ulceration at the trial's outset. This may have influenced the outcome. The authors report <i>"Although all of these findings were statistically significant when nonparametric null hypothesis tests were calculated, the association with the risk factor variables changed considerably (>10%) when univariate and multiple variable logistic regression equations were computed for ulcer grade and HBOT, indicating confounding between these variables (results not shown)."</i> The implications of these remarks are unclear, but suggest the trial's results

			standard care (SC) (daily wound care, including dressing changes and local debridement at bedside or in the operating room, and amputation when indicated). Control: SC only.		during the course of treatment).				may be materially undermined by confounding.
Chuck et al (2008)	Health economic modelling using previously published data Alberta, Canada	Modelling of costs and outcomes for a 65-year old with a diabetic foot ulcer. Time horizon 12 years	HBOT plus standard care (SC) vs SC alone. HBOT was assumed to range from thirty to forty sessions of 2 to 2.5 hours in duration.	Cost utility	Costs, outcomes (major amputation, healed with or without a minor amputation, unhealed) and the utility of these outcomes	Probabilities in year 1: healed HBOT 0.56, SC 0.24; minor amputation and healed ulcer HBOT 0.27, SC 0.16; unhealed ulcer HBOT 0.06, SC 0.28; major amputation HBOT 0.11, SC 0.33. Costs: HBOT C\$40,695 (£23,400), SC C\$49,786 (£28,600). Utilities: HBOT 3.64 quality-adjusted life-years (QALYs), SC 3.01 QALYs. HBOT plus SC was deemed the dominant strategy, with better outcomes and lower costs.	6	Direct	The model has limited relevance and reliability: <ul style="list-style-type: none"> The estimates of the effectiveness of HBOT are from a study published in 2003 (Guo et al 2003), which predates the three randomised trials in this rapid evidence review. The model's assumptions about the effectiveness of HBOT are incompatible with this more recent evidence, which is derived from more reliable studies. For example, the model assumes absolute risk differences between HBOT and SC of 22% and 32% for major amputation and healing respectively, whereas the most reliable trial that we found, by Fedorko et al (2016), found no significant differences with respect to either of these outcomes. The authors' sensitivity analysis included too small an adjustment to these assumptions to align them with more reliable evidence. The authors noted that "the clinical data supporting the effectiveness of adjunctive HBOT for [diabetic foot ulcers] remains limited. Good quality studies are required to confirm the comparative benefits of

									<p>this technology.” They expected that Fedorko et al’s trial, already underway in Canada when they published their analysis, would “<i>help meet this need</i>”. If, as that trial reported, “<i>HBOT does not offer an additional advantage to comprehensive wound care in reducing the indication for amputation or facilitating wound healing in patients with chronic [diabetic foot ulcers]</i>”, then HBOT cannot be cost-effective.</p> <ul style="list-style-type: none"> • The costs are based on the Canadian health care system in 2008, and may be materially different from those in the NHS. The authors admit “<i>The data (notably cost data) upon which the variables in the economic model were based, are not of high quality.</i>” They went on “<i>Cost data for HBOT were based on data from only a few centers, and reporting was not standardized.</i>”
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8. Grade of evidence table

Use of HBOT plus best practice wound care Vs. best practice wound care to treat diabetic foot ulcers					
Outcome Measure	Reference	Quality of Evidence Score	Applicability	Grade of Evidence	Interpretation of Evidence
Freedom from major and minor amputation or meeting the criteria for major amputation	Fedorko et al 2016	9	Direct	B	<p>Freedom from major amputation or meeting the criteria for major amputation (defined as below-knee or metatarsal level amputation) at 12 weeks, was based on not having any of the following criteria for amputation:</p> <ol style="list-style-type: none"> 1. Lack of significant progress in wound healing over the follow-up period, which indicated a risk of severe systemic infection related to the wound 2. Persistent deep infection involving bone and tendons (antibiotics and hospitalisation required, pathogen involved) 3. Inability to bear weight on the affected limb 4. Pain causing significant disability. <p>This is a subjective judgement of the presence of indications for amputation, made by a single surgeon, blinded to the participant's treatment allocation.</p> <p>Only Fedorko et al. (2016) reported this outcome measure. They reported no effect of HBOT on this outcome in a high quality double-blind trial with 103 participants. They reported that 23% of HBOT and 24% of controls met criteria for major amputation over the 12 weeks of the study.</p> <p>This result suggests that HBOT had no effect on this outcome.</p> <p>The result provides an indication of whether HBOT reduces the risk of a below-knee or metatarsal-level amputation. This would be of major benefit, but the results provide no reason to believe HBOT has this effect.</p>
Recommendation in favour of major or	Fedorko et al 2016	9	Direct	B	<p>This is a subjective judgement of the presence of indications for amputation, made by a single surgeon, blinded to the</p>

minor amputation					<p>participant's treatment allocation.</p> <p>Only Fedorko et al. (2016) reported this outcome measure. They reported that 51% of HBOT and 48% of controls were judged to need major or minor amputation over the 12 weeks of the study.</p> <p>The result provides an indication of whether HBOT reduces the risk of a below-knee or metatarsal-level amputation, or a minor amputation of one or more toes. This would be of major benefit, but the results provide no reason to believe HBOT has this effect.</p>
Major or minor amputation	Löndahl et al (2010)	7	Direct	B	<p>Amputations above the ankle were defined as major and all others as minor.</p> <p>Only Löndahl et al (2010) reported this outcome. They reported 3 major and 4 minor amputations in the HBOT arm, and 1 major and four minor amputations in the control arm. No significance test was reported.</p> <p>The result provides an indication of whether HBOT reduces the risk of an above-ankle or below-ankle amputation. This would be of major benefit, but the results provide no reason to believe HBOT has this effect.</p>
Progress of ulcer healing over 12 weeks	Fedorko et al 2016	9	Direct	B	<p>Wound size was measured weekly manually and by computerised analysis of wound surface area and perimeter from high-resolution calibrated digital photographs. The authors also calculated the linear advancement of the wound edge. All measurements were made at 12 weeks.</p> <p>This is an assessment of the progress and extent of wound healing, made blind to the participant's treatment allocation.</p> <p>Only Fedorko et al. (2016) reported this outcome measure. They reported a difference in mean width reduction of -0.12cm, 95% CI -0.46 to 0.22, p = 0.491.</p> <p>This result suggests that HBOT had no effect on this outcome.</p> <p>Faster wound healing would be of major</p>

					benefit, but the results do not indicate that HBOT hastens this outcome.
Progress of ulcer healing by day 14	Ma et al 2013	9	Direct	B	<p>Average reduction in ulcer area by day 14 was assessed. Ulcer area was assessed by computerised examination of clinical photographs.</p> <p>Only Ma et al.'s (2013) unblinded randomised trial with 36 participants reported this outcome measure. In the HBOT arm, the average reduction in ulcer area was 42%, compared with 20% in the control arm (p<0.05).</p> <p>Faster wound healing would be of major benefit; the results suggest that HBOT may hasten this outcome.</p> <p>The assessment was made without blinding to the participant's treatment allocation, increasing the risk of bias.</p>
Ulcer healing at one year	Löndahl et al 2010	7	Direct	B	<p>The outcome is complete healing of the index ulcer (the ulcer with the largest area and a duration of at least three months at the time of randomisation).</p> <p>Only Löndahl's et al (2010) double-blind randomised trial with 94 participants reported this outcome measure. In the HBOT arm, healing rates were 25/48 (52%), compared with 12/42 (29%) in controls (p = 0.03).</p> <p>Faster wound healing would be of major benefit; the results suggest that HBOT may hasten this outcome.</p> <p>The authors used air pressurised to 2.5 atmospheres in control patients to ensure their trial was double-blind. This pressure is high enough to create a risk of adverse effects; these were reported at similar rates in the two arms. The effects of hyperbaric air are not well understood and this control treatment may not have been an inert placebo, raising the possibility that their results arise at least in part from impaired ulcer healing in the control arm due to the control intervention.</p>
Progress of ulcer healing as measured by the Bates-Jensen	Fedorko et al 2016	9	Direct	B	<p>The Bates-Jensen wound assessment tool was used weekly to measure progress of ulcer healing. This is an</p>

wound assessment tool					<p>assessment of the progress and extent of wound healing, made blind to the participant's treatment allocation. This tool assesses 13 wound characteristics, with each item scored on a 1 to 5 scale (maximum score 65). The individual scores are summated for a total score. The higher the total score, the more severe the wound status.</p> <p>Only Fedorko et al. (2016) reported this outcome measure. They reported a difference in mean change in score of 0.53, 95% CI -2.58 to 3.64, $p = 0.735$.</p> <p>This result suggests that HBOT had no effect on this outcome.</p> <p>Faster wound healing would be of major benefit, but the results do not indicate that HBOT hastens this outcome.</p>
Proportion of ulcers healed at 12 weeks	Fedorko et al 2016	9	Direct	B	<p>The proportion of ulcers healed (ie Wagner grade 0 or 1) was measured at 12 weeks. This is an assessment of the progress and extent of wound healing, made blind to the participant's treatment allocation. (The Wagner classification of diabetic foot ulceration is as follows: Grade 0 No open ulcer, high risk; Grade 1 Superficial ulcer with subcutaneous involvement; Grade 2 Deep ulcer with tendon or joint involvement; Grade 3 Deep ulcer with bone involvement; Grade 4 Wet or dry gangrene (forefoot), without cellulitis; Grade 5 Generalized (whole foot) gangrene.)</p> <p>Fedorko et al. (2016) reported this outcome measure. They reported that 20% of HBOT and 22% of controls had healed at 12 weeks.</p> <p>This result suggests that HBOT had no effect on this outcome.</p> <p>A higher likelihood of ulcer healing would be of major benefit, but the results do not indicate that HBOT hastens this outcome.</p>
Proportion of ulcers healed by day 14	Ma et al 2013	9	Direct	B	<p>Ulcer healed by day 14. This assessment of the completion of wound healing was made by examination of clinical photographs, without blinding to</p>

					<p>the participant's treatment allocation.</p> <p>Only Ma et al. (2013) reported this outcome measure. They reported no effect of HBOT on this outcome in an unblinded trial with 36 participants.</p> <p>Faster wound healing would be of major benefit, but the results do not indicate that HBOT hastens this outcome.</p>
Clinical outcome	Duzgun et al 2008	8	Direct	B	<p>This outcome measure enumerated how many participants were in each of six clinical categories at the completion of the trial. The categories were: healed (complete closure without debridement in the operating room), graft or flap (graft or flap closure required), distal amputation (amputation distal to metatarsophalangeal joints), proximal amputation (amputation proximal to the metatarsophalangeal joints), debridement (standard therapy wound or operative debridement), no change (failure to heal during the course of treatment).</p> <p>Only Duzgun et al. (2008) reported this outcome measure, in an unblinded trial with 100 participants.</p> <p>Faster wound healing would be of major benefit. The study suggests it may be more likely after HBOT, but was unblinded, so the results may be attributable to observer bias.</p> <p>It is surprising that none of 50 control participants' ulcers were healed after 92 weeks, indicating that the control intervention was ineffective. Since treatment without HBOT usually leads to ulcer healing, this result suggests the control treatment was not representative of normal care, reducing the generalisability of the trial's result.</p>
Cost utility	Chuck et al 2008	6	Direct	C	<p>This is a measure of costs, outcomes (major amputation, healed with or without a minor amputation, unhealed) and the utility of these outcomes. This result is intended to indicate the cost utility, or health value for money, of HBOT for diabetic foot ulcers.</p>

					<p>Only Chuck et al. (2008) reported this outcome. They used modelling based on a 2003 study of the effectiveness of HBOT (Guo et al. 2003) and Canadian healthcare cost data.</p> <p>Their modelling indicated that HBOT was more effective and less expensive than standard care.</p> <p>The unreliable assumptions used in this study's model undermine its usefulness to NHS policymakers. The estimates of the effectiveness of HBOT were based on unreliable and potentially obsolete studies, and not compatible with Fedorko et al's (2016) high-quality randomised trial. Also, the costs are based on the Canadian health care system in 2008, and may be materially different from those in the NHS.</p>
Incidence of adverse effects	Fedorko et al 2016	9	Direct	A	<p>This is an assessment of the incidence of adverse effects resulting from HBOT.</p> <p>Fedorko et al (2016) was the better study in that reports were made by participants blind to their treatment allocation. Participants reported the incidence of solicited adverse effects such as acute respiratory distress, pneumothorax, barotrauma, dizziness, convulsions or seizures, and visual changes. They also recorded other adverse events as unsolicited. These included inability to equalise middle ear pressures, anxiety, chest pain, nausea, hypo- and hyperglycaemia, wound infection, pain after tympanic membrane rupture and congestive heart failure.</p> <p>Fedorko et al. (2016) reported solicited adverse events in 9 HBOT and 6 controls (p=0.44), and unsolicited adverse events in 24 HBOT and 5 controls (p=0.02).</p> <p>This result indicates that HBOT causes a significant number of adverse effects. Safety of HBOT is important to patients.</p>
	Löndahl et al (2010)	7	Direct	A	
	Ma et al 2013	9	Direct	A	

9. Literature Search Terms

<p>P – Patients / Population</p> <p>Which patients or populations of patients are we interested in? How can they be best described? Are there subgroups that need to be considered?</p>	<p>Children, young people and adults with type 1 or type 2 diabetes who have foot ulcers (with or without soft tissue infection, osteomyelitis or gangrene) which have failed to improve, or continue to deteriorate, despite receiving standard ‘best practice’ treatment for 6 weeks or longer.</p> <p>One subgroup that should also be considered is that of patients who receive 30 or more hyperbaric oxygen treatments.</p>
<p>I – Intervention</p> <p>Which intervention, treatment or approach should be used?</p>	<p>20 or more hyperbaric treatments each delivering a maximum inspired partial pressure of oxygen between 200 and 304 kPa and lasting between 60 and 120 minutes (eg Royal Navy Table 66) administered 5 days each week. Hyperbaric oxygen therapy to be administered as adjunctive therapy to best practice wound care described below.</p>
<p>C – Comparison</p> <p>What is/are the main alternative/s to compare with the intervention being considered?</p>	<p>Best practice wound care in accordance with NICE Guideline 19 which recommends offering one or more of the following:</p> <ul style="list-style-type: none"> • Offloading. • Control of foot infection. • Control of ischaemia. • Wound debridement. • Wound dressings. <p>No time scale is specified for the duration of these treatments in the guideline</p>
<p>O – Outcomes</p> <p>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.</p>	<p>Critical to decision-making:</p> <p>Clinical effectiveness:</p> <ul style="list-style-type: none"> • Mortality • Major amputation • Minor amputation • Length of hospital inpatient stay • Quality of Life • Activities of Daily Living • Long term outcomes • Adverse events • Psychological morbidity • Proportion of patients achieving success criteria explicitly defined in study • Proportion of patients with healed ulcers at time points defined in studies • Time to healing • Fraction of wound bed epithelialised <p>Important to decision-making:</p> <ul style="list-style-type: none"> • Cost effectiveness

Assumptions / limits applied to search	<p>Inclusion criteria</p> <p>Peer reviewed studies published in the last 10 years including: Randomised Controlled Trials Systematic reviews with/without meta-analysis.</p> <p>Exclusion criteria</p> <p>Work that is not available in the English language Case series Case reports Non comparator studies Unpublished studies Studies in which HBOT is alternative rather than adjuvant therapy to standard best practice wound care Grey literature, letters, conference reports, abstracts etc</p>
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10. Search Strategy

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

Search date 2 May 2017

Embase

- | | |
|----|--|
| # | Searches |
| 1 | diabetic foot/ |
| 2 | *diabetic neuropathy/ |
| 3 | exp diabetes mellitus/ and (skin ulcer/ or foot ulcer/ or ulcer healing/) |
| 4 | ((foot or feet or forefoot or forefeet or toe or toes or leg or legs or lower limb? or lower extrem*) adj5 (ulcer* or sore? or wound?)).ti,ab. |
| 5 | (diabet* adj5 (ulcer* or sore? or wound?)).ti,ab. |
| 6 | diabet*.mp. and (ulcer* or sore? or wound?).ti. |
| 7 | 1 or 2 or 3 or 4 or 5 or 6 |
| 8 | hyperbaric oxygen/ |
| 9 | ((hyperbaric adj2 (oxygen* or therap* or treatment)) or hbot or oxygen chamber* or barochamber*).ti,ab. |
| 10 | 8 or 9 |
| 11 | 7 and 10 |
| 12 | (exp animals/ or nonhuman/) not human/ |
| 13 | conference*.pt. |
| 14 | 12 or 13 |

15 11 not 14

16 limit 15 to (english language and yr="2007 -Current")

11. Evidence Selection

- Total number of publications reviewed: 77
- Total number of publications considered potentially relevant: 26
- Total number of publications selected for inclusion in this briefing: 5

12. References

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