

NHS England

**Evidence review: Hyperbaric oxygen therapy
for necrotising soft tissue infections**



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Prepared by: Solutions for Public Health on behalf of NHS England Specialised Commissioning

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1. Introduction

- Necrotising soft tissue infections (NSTIs) are rapidly progressive infections which can be highly aggressive in destroying skin, fascia and surrounding tissue. Organisms infiltrate and migrate along the superficial and deep fascial planes, causing vascular occlusion, ischaemia and tissue necrosis. This can lead to systemic sepsis and multiple organ dysfunction (Devaney et al 2015).
- There is no clear definition of NSTIs, nor is there a system of classification. They are a collection of heterogenous conditions, the outcome of which is in many instances significantly influenced by early diagnosis. The term necrotising fasciitis is broadly synonymous with NSTI. Fournier's gangrene is a necrotising fasciitis of the perineum; it most commonly occurs in elderly men and in people affected by diabetes, excessive alcohol consumption or immune-compromise (Li et al 2015).
- NSTIs are rare. Between 500 and 1,500 cases of NSTIs are recorded annually in the United States, although clinicians suggest that the total number greatly exceeds this figure (Hakkarainen et al 2014).
- NSTIs carry a risk of mortality of about 30%. They also cause long-term disability from limb and tissue loss (Hakkarainen et al 2014).
- The standard treatment for NSTIs is surgical debridement, intensive medical support and antibiotics (Hakkarainen et al 2014).
- Hyperbaric oxygen therapy (HBOT) has been suggested as an adjunct in the treatment of NSTIs. 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, usually for 45 to 120 minutes at least once daily.
- Inhaling oxygen at increased pressure is intended to improve oxygen supply to the infected tissue. Nearly all the oxygen in the blood is bound to haemoglobin; under normal pressure, saturation of haemoglobin in the arterial blood is around 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 that would be rendered hypoxic by the disease process may receive a more adequate supply of oxygen, and this in turn may improve cell function, the immune response and wound healing. This might occur because of enhanced neutrophil killing ability, angiogenesis, fibroblast activity and/or collagen synthesis (Li et al 2015).
- If HBOT is effective, the infection would spread more slowly and the patient will require fewer or less extensive debridements and/or less support with ventilation, inotropes and vasopressors.
- HBOT carries potential hazards, including respiratory distress, pneumothorax and barotrauma.
- We found no guidance from the National Institute for Health and Care Excellence on the use of HBOT in NSTIs.

2. Summary of results

- We found two uncontrolled studies and eight controlled but unrandomised studies. None of the controlled studies concealed treatment allocation from participants or researchers, creating a risk of bias.
- The studies were varied. In the larger studies covering many hospitals, the HBOT and control participants were treated in different hospitals with different regimes, introducing bias. No

study matched participants in HBOT and controls arms.

- Participants were adults with NSTIs; two smaller studies (one uncontrolled) included only people with Fournier's gangrene (Li et al 2015 (n=28), Rosa et al 2015 (n=34)).
- HBOT regimes varied: five reported regimes consistent with the PICO (Krenk et al 2007 (n=19), Rosa et al 2015, Li et al 2015, Bosco et al 2015 (n=34) and George et al 2009 (n=78)), while the other five provided no information on the regime but were included because of their large size and their inclusion of controls (Soh et al 2012 (n=45,913), Mulla et al 2007 (n=216), Devaney et al 2015 (n=341), Psinos et al 2013 (n=56,527) and Shaw et al 2014 (n=1583)).
- Two controlled studies (Soh et al 2012 and Mulla et al 2007) attempted to adjust fully for the differences between the participants who underwent HBOT and those that did not; this is the most reliable approach. Another three studies (Devaney et al 2015, Shaw et al 2014 and George et al 2009) undertook multivariate adjustment but only of some results – mortality in all three studies and complications in the case of Shaw et al 2014. They also used fewer variables in the adjustment than the first two studies and so are not as sound. The other controlled studies and the unadjusted results from these three studies are at much higher risk of confounding; we do not consider them reliable.
- The trials all compared HBOT plus standard care with standard care only.
- Nine studies reported mortality. Three of the five more reliable studies reported lower mortality with HBOT (Soh et al 2012 adjusted odds ratio (OR) 0.45, 95% confidence interval (CI) 0.29 to 0.83, $p = 0.008$; Shaw et al 2014 control participants' multivariate OR 10.6, 95% CI 5.2 to 25.1, (i.e. control participants at higher risk of death); Devaney et al 2015 HBOT 33/275 (12%), control 16/66 (24%), $p = 0.01$). Two reported mortality rates with and without HBOT that were not significantly different (Mulla et al 2007 multivariate relative risk (RR) 0.48, 95% CI 0.09 to 2.56, $p = 0.39$; George et al 2009 OR 0.98, 95% CI 0.18 to 5.42).
- Li et al 2015 reported mean curative time, but did not define this outcome measure. In an unadjusted analysis, it was shorter with HBOT (HBOT 15.4 days, control 25.5 days, $p < 0.05$).
- Four studies reported, without adjustment, the mean number of debridements, of which three reported more debridements with HBOT (Devaney et al 2015 HBOT 4.8, control 3, $p < 0.001$; Krenk et al 2007 HBOT 3.36, control 0.5, $p < 0.002$; George et al 2009 HBOT 3.3, control 2.4, $p = 0.03$). The discrepant result is from Li et al 2015, reporting fewer debridements with HBOT (HBOT 1.32, control 2.17, $p < 0.05$).
- Krenk et al 2007 reported, without adjustment, no significant difference in the mean number of incision and drainage procedures with HBOT (HBOT 4.63, control 2.13, $p > 0.05$).
- Devaney et al 2015 reported, without adjustment, no significant difference in the mean number of amputations with and without HBOT (HBOT 21/275 (7.6%), control 10/66 (15.2%), $p = 0.095$ calculated by SPH).
- The same authors reported without adjustment more intensive care admissions in those treated with HBOT (HBOT 210/275 (76%), control 37/66 (64%), $p = 0.05$). George et al 2009 reported similar durations of intensive care with and without HBOT (HBOT 5.7 days, control 4.7 days, $p = 0.95$).
- George et al 2009 also reported similar mean durations of antibiotic use with and without HBOT (HBOT 18 days, control 20 days, $p = 0.97$).
- Shaw et al 2014 reported a multivariate analysis indicating there were fewer complications with HBOT (HBOT 45%, control 66%, $p < 0.01$).
- Six studies reported length of stay. Of the more reliable adjusted analyses, Soh et al 2012 reported that this was longer with HBOT (HBOT 14.3 days, 95% CI 13 to 16; control 10.7

days, 95% CI 10 to 11; $p < 0.001$), while Mulla et al 2007 reported no association between treatment and length of stay (regression coefficient¹ 0.112, 95% CI -0.332 to 0.556, $p = 0.62$).

- Three studies reported the cost of treatment. One of the fully adjusted analyses reported that HBOT was more expensive than standard treatment (Soh et al 2012 HBOT US\$52,205 (£40,500), control \$45,464 (£35,200), $p < 0.001$), while the other, Mulla et al 2007, reported no association between treatment and cost (regression coefficient 0.131, 95% CI -0.355 to 0.616, $p = 0.60$). Shaw et al 2014's univariate analysis also reported higher costs with HBOT (HBOT \$35,808 (£27,600), control \$27,504 (£21,300), $p < 0.01$).
- We found no studies reporting adverse effects of treatment.
- We found no cost effectiveness studies.
- The lack of high quality evidence and discrepancies between studies limit what can be concluded from this research. However, the more reliable studies suggest, but by no means prove, that HBOT might reduce mortality, shorten lengths of stay and increase costs in people with NSTIs. It may also prevent complications, though there is less evidence of this. Confidence in the studies' results is limited by the uncorrected influence of confounders not used in multivariate adjustment, such as differences in the quality of care of participants who did and did not receive HBOT.
- We found no analysis of whether the extra costs of HBOT are justified by any health benefits it produces.

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.
- 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).

¹ A regression coefficient is a measure of the association between two variables, with a positive value indicating that as one rises, the others tends to rise also.

4. Results

We found 44 studies within the scope of the literature search's terms, many of which were small, uncontrolled and/or did not describe the HBOT regime used. We consulted NHS England and agreed to include either studies which were clearly within the scope of the search, including the HBOT regime, or studies which were controlled, had more than 100 participants and were not clearly outwith the scope.

We found five studies in the first category which reported regimes consistent with the PICO (a maximum inspired partial pressure of oxygen between 200 and 314 kPa lasting between 60 and 150 minutes up to three times within the first 24 hours, then treatment with a maximum inspired partial pressure of oxygen between 200 and 253 kPa and lasting between 60 and 120 minutes up to twice each subsequent day until the infection is no longer spreading and the overall clinical condition of the patient is improving); two were uncontrolled (Bosco et al 2016 (n=34) and Rosa et al 2015 (n=34)) and three controlled (Li et al 2015 (n=28), George et al 2009 (n=78) and Krenk et al 2007 (n=19)). We found five controlled but unrandomised studies in the second category which provided no information on the regime: (Devaney et al 2015 (n=341), Shaw et al 2014 (n=1583), Psinos et al 2013 (n=56,527), Soh et al 2012 (n=45,913) and Mulla et al 2007 (n=216)). None of the controlled studies concealed treatment allocation from participants or researchers. There was overlap between participants in Psinos et al 2013 and Soh et al 2012.

Participants were adults with NSTIs; two studies (Rosa et al 2015 and Li et al 2015) included only people with Fournier's gangrene.

We found no cost effectiveness studies, though two studies reported treatment costs.

In the patient populations of interest, what is the effect of adjunctive HBOT in addition to standard treatment of necrotising fasciitis for the specified outcomes?

Clinical efficacy outcomes reported in the studies included mortality, clinical outcome (full recovery, survived with amputation, died), curative time (not defined), number of debridements, number of incision and drainage procedures, number of amputations, intensive care admissions, days of intensive care unit stay, days of antibiotic use, incidence of complications and length of hospital stay.

Mortality

Nine studies reported this outcome. Four reported lower mortality after HBOT; two of these had multivariate adjustment. Four other studies, one with multivariate adjustment, reported similar mortality and one study was uncontrolled.

Devaney et al 2015 reported lower mortality with HBOT (HBOT 33/275 (12%), control 16/66 (24%), $p = 0.01$). Shaw et al 2014's multivariate analysis reported that control participants were at higher risk of death (OR 10.6, 95% CI 5.2 to 25.1). Soh et al 2012's multivariate analysis reported that HBOT was associated with a lower risk of death (OR 0.45, 95% CI 0.29 to 0.83, $p = 0.008$). Krenk et al 2007 reported lower mortality with HBOT (HBOT 0/11 (0%), control 6/8 (75%), $p < 0.001$), but their study was seriously confounded by differences in other aspects of treatment between the two groups.

Li et al 2015 reported similar mortality with and without HBOT (HBOT 2/16 (13%), control 4/12 (33%), significance not reported but Yates' χ^2 calculated by SPH as 0.747, $p = 0.39$). Psinos et al 2013's multivariate analysis reported no significant difference in mortality with and without HBOT (OR 0.57, 95% CI 0.26 to 1.26) and George et al 2009's multivariate analysis reported similar mortality with and without HBOT (OR 0.98, 95% CI 0.18 to 5.42). Mulla et al 2007's

multivariate analysis also showed no statistically significant effect of HBOT on mortality (relative risk (RR) 0.48, 95% CI 0.09 to 2.56. $p = 0.39$).

Rosa et al 2015 reported from an uncontrolled study that 19/24 participants (79%) were discharged alive and 5/24 (21%) died. There were no results on another 10 participants.

Clinical outcome (full recovery, survived with amputation, died)

Bosco et al's uncontrolled study reported the following results: in perineal fasciitis, 19/20 participants (95%) had full recovery and 1/20 (5%) died; in cervical fasciitis, 8/8 (100%) had full recovery; and in gas gangrene, 6/8 (75%) had full recovery and 2/8 (25%) had an amputation.

Curative time

Li et al 2015 do not define this outcome measure, but may have used the term for the period from admission to the disappearance of all signs and symptoms of infection. For patients treated with HBOT, it was 15.4 days, and in control participants it was 25.5 days ($p < 0.05$).

Number of debridements

Four studies reported this outcome.

Li et al 2015 reported fewer debridements in the group receiving HBOT (HBOT 1.32, standard deviation (SD) 0.48; control 2.17, SD 0.72; $p < 0.05$). Conversely, the other three studies reported more debridements in the HBOT group: Devaney et al 2015 (HBOT 4.8 (SD 3.4), control 3 (SD 2.1), $p < 0.001$), George et al 2009 (HBOT 3.3 (SD 2.4), control 2.4 (SD 2.2), $p = 0.03$) and Krenk et al 2007 (HBOT 3.36, control 0.5, $p < 0.002$).

Number of incision and drainage procedures

Krenk et al 2007 reported no significant difference in the number of incision and drainage procedures with HBOT (HBOT 4.63, control 2.13, $p > 0.05$).

Number of amputations

Devaney et al 2015 reported rates of amputation with and without HBOT that were not significantly different (HBOT 21/275 (7.6%), control 10/66 (15.2%), significance not reported but Yates' χ^2 calculated by SPH as 2.79, $p = 0.095$).

Intensive care admission

Devaney et al 2015 reported more intensive care admissions in those treated with HBOT (HBOT: 210/275 (76%), control 37/66 (64%), $p = 0.05$). This was despite participants receiving HBOT having lower APACHE III scores, indicating less severe illness (51.2 vs. 68.8, p -value not reported).

Days of intensive care unit stay

George et al 2009 reported similar durations of intensive care with and without HBOT (HBOT 5.7 (SD 9.1), control 4.7 (SD 6.7), $p = 0.95$).

Days of antibiotic use

George et al 2009 reported similar durations of antibiotic use with and without HBOT (HBOT 18 (SD 12), control 20 (SD 17), $p = 0.97$).

Incidence of complications

Two studies reported this outcome. Neither specified the complications, though in the case of Psinos et al 2013 they were complications of NSTIs rather than of HBOT.

Shaw et al 2014 reported fewer complications with HBOT (multivariate analysis: HBOT 45%, control 66%, $p < 0.01$). Psinos et al 2013 reported similar rates in the two groups (OR 0.82, 95%

CI 0.57 to 1.18).

Length of hospital stay

Six studies reported this outcome. Four reported longer length of stay after HBOT; two of these had multivariate adjustment. Two other studies, one with multivariate adjustment, reported similar lengths of stay.

Shaw et al 2014 reported longer length of stay with HBOT (HBOT 16 days, control 14 days, $p < 0.05$), as did Soh et al 2012's adjusted analysis (HBOT 14.3 days, 95% CI 13 to 16; control 10.7 days, 95% CI 10 to 11; $p < 0.001$). Psinos et al 2013 also reported longer length of stay with HBOT (adjusted regression coefficient 3.47, 95% CI 1.11 to 5.84), along with Krenk et al 2007 (HBOT 30.8 days, control 15.3 days, $p < 0.02$). George et al 2009 reported similar lengths of stay in the two groups (HBOT 22.6 (SD 15.4), control 20.1 (SD 18.6), $p = 0.15$), and so did Mulla et al 2007's multivariate analysis: regression coefficient 0.112, 95% CI -0.332 to 0.556, $p = 0.62$).

What is the clinical effectiveness of adjunctive HBOT for patients whose disease has continued to progress, or has failed to resolve, despite appropriate antibiotics, surgery and medical support (any regime) prior to treatment with hyperbaric oxygen therapy?

We found no evidence specific to this group of patients.

What is the cost effectiveness of HBOT for the treatment of necrotising soft tissue infections?

We found no cost effectiveness studies.

We found three studies which reported the cost of treatment.

Two studies reported HBOT to be more expensive than standard treatment: Shaw et al 2014 (HBOT \$35,808 (£27,600), control \$27,504 (£21,300), $p < 0.01$) and Soh et al 2012 (HBOT US\$52,205 (£40,500), control \$45,464 (£35,200), $p < 0.001$). Mulla et al 2007 reported no relationship between treatment and cost (multivariate analysis: regression coefficient 0.131, 95% CI -0.355 to 0.616, $p = 0.60$). None of these studies included costs after discharge.

5. Discussion

The more reliable studies that we found indicate, but by no means prove, that HBOT may reduce mortality, increase lengths of stay and increase costs in people with NSTIs, although this result needs to be interpreted with caution.

The studies that we found ranged from uncontrolled studies, through controlled studies affected by serious confounding and others with less apparent confounding, to those with statistical adjustment of varying quality for differences in the two groups. None were randomised and none had made an attempt to conceal treatment allocation from researchers or participants, so all remain affected by a material risk of reporting bias. The HBOT regime varied and was not always fully described. In Devaney et al 2015, the regime used is not completely clear, but was probably 2.8 ATA three times in the first 24 hours, twice in the second 24 hours, and then daily as required. This is a slightly higher pressure than specified in the PICO after 24 hours.

The studies did not reach the same conclusion for any of the outcomes. There are several likely explanations for this: some were small and underpowered, the participants had different diagnoses in different proportions, there may have been differences in standard of care and in

HBOT regimes and some outcomes may have been differently defined. Specifically, if the participants allocated to HBOT were more seriously ill and/or received more intensive treatment, this rather than HBOT might explain some results. Their longer lengths of stay and more frequent debridements and admissions to intensive care support this explanation.

An important cause of discrepancy and bias is the differences between the participants who did and did not receive HBOT. For example, in Devaney et al 2015, all the participants who received HBOT also received three antibiotics, compared with 70% of the controls ($p=0.0010$); 28% received intravenous immunoglobulin compared with 19% of controls ($p=0.03$). Devaney et al 2015 report reasons for not using HBOT such as the presence of arrhythmias, a requirement for mechanical ventilation and expected futility of treatment, all of which might result in worse prognosis in the control group and bias results in favour of HBOT. Few studies described how participants were allocated to treatment. Most reported potentially important differences between the two groups which would bias the comparison and render the results hard to interpret. Furthermore, many of the larger studies which used multivariate adjustment provided no information on the HBOT regimes that they used. This makes it impossible to use their findings to shape policy and practice. Differences in results might be due to differences in HBOT regimes between studies.

The only way to eliminate this bias is randomisation. The next best approach is comprehensive adjustment for all potential confounding variables. The most methodologically reliable controlled studies are Soh et al 2012 and, to a lesser extent, Mulla et al 2007 and Psinos et al 2013. These studies attempted to adjust fully for the differences between the participants who underwent HBOT and those that did not, with Soh et al 2012's approach being more comprehensive. Devaney et al 2015, Shaw et al 2014 and George et al 2009 undertook multivariate adjustment, but used fewer variables and only adjusted some of their results; they are not as sound. The remaining controlled studies (Li et al 2015 and Krenk et al 2007) are at much higher risk of confounding – we do not consider them reliable.

One of the three more reliable studies (Soh et al 2012) reported lower mortality with HBOT, while the other two (Mulla et al 2007 and Psinos et al 2013) reported no significant difference in mortality. This indicates, but by no means proves, that HBOT may reduce mortality. However, given the low overall quality of the studies, this should be interpreted with caution.

One of the more reliable studies (Shaw et al 2014) reported an adjusted analysis showing fewer unspecified complications with HBOT.

Two of the more reliable studies (Soh et al 2012 and Psinos et al 2013) reported longer lengths of stay associated with HBOT, while Soh et al 2012 also reported higher costs; Mulla et al 2007 reported no differences in either measure.

The other outcomes were not reported by any of the more reliable studies and so are affected by continuing uncertainty. No conclusions can be drawn with respect to them.

The clinical and cost effectiveness of HBOT for NSTIs remain uncertain due to the insecurity of available research and the lack of health economic evidence. Further research is required to address this uncertainty, which can only be resolved by a randomised trial with health economic evaluation.

6. Conclusion

The lack of high quality evidence and discrepancies between studies limit what can be concluded

from this research. However, the more reliable studies that we found indicate, but by no means prove, that HBOT may reduce mortality, increase lengths of stay and increase costs in people with NSTIs, although this result needs to be interpreted with caution. HBOT may also prevent complications, though there is less evidence of this. Further research is needed to reduce the current uncertainty.

We found no analysis of whether the extra costs of HBOT are justified by any health benefits it produces.

7. Evidence Summary Table

Use of HBOT plus standard care Vs. standard care to treat necrotising soft tissue infections									
Study reference	Study Design	Population characteristics	Intervention	Outcome measure type	Outcome measures	Results	Quality of Evidence Score	Applicability	Critical Appraisal Summary
Li et al 2015	P1 – Controlled unrandomised study	28 people with Fournier's gangrene 1 hospital in Changsa, China Mean age 47 years, 100% male.	HBOT: 2.5 ATA for 90 to 120 minutes twice daily for 5 to 7 days, plus standard care (SC) (antibiotics, debridement and incision drainage) Control: SC only	Primary Clinical efficacy	Mortality	HBOT 2/16 (13%), control 4/12 (33%), significance not reported but Yates' χ^2 calculated by SPH as 0.747, $p = 0.39$.	5	Direct	No description of how participants were allocated to HBOT or control. Participants receiving HBOT were younger with less severe gangrene, though differences were not significant. Study at risk of bias and confounding. Apparently shorter curative time did not result in shorter length of stay. Most patients declined admission to intensive care "due to financial constraints", reducing generalisability to the NHS.
				Primary Treatment	Mean number of debridements	HBOT: 1.32, standard deviation (SD) 0.48; control 2.17, SD 0.72; $p < 0.05$			
				Primary Clinical efficacy	Mean curative time (not defined)	HBOT: 15.4 days, SD 4.8; control 25.5 days, SD 9.6; $p < 0.05$			
Devaney et al 2015)	P1 – Controlled unrandomised study	341 people with necrotising fasciitis (perineum 34%, leg 30%, trunk 18%, other sites 18%). 1 hospital in Melbourne, Australia Mean age not stated but about 54 years, 61% male.	HBOT: regime not completely clear, but probably 2.8 ATA three times in the first 24 hours, twice in the second 24 hours, and then daily as required. This is a slightly higher pressure than specified in the PICO after 24 hours. Mean of 8 sessions with mean of 2 in first 14 hours, plus SC	Primary Clinical efficacy	Mortality	HBOT 33/275 (12%), control 16/66 (24%), $p = 0.01$	7	Direct	No description of how participants were allocated to HBOT or control, though reasons for not using HBOT included the presence of arrhythmias, a requirement for mechanical ventilation and expected futility of treatment, all of which might result in worse prognosis in the control group and bias results in favour of HBOT. Participants receiving HBOT were younger (52.2 vs. 55.7 years) and were less likely to be male (58% vs. 76%) and to be obese (35 vs. 42%); the authors do not report the statistical significance of these differences. Participants receiving HBOT had lower APACHE III scores, indicating less severe illness (51.2 vs. 68.8, p -value not reported), were more likely to receive triple antibiotics (275/275 (100%), vs. 46/66 (70%), $p = 0.001$) and more likely to receive intravenous immunoglobulin (75/275 (28%) vs. 12/66 (19%), $p = 0.03$). They were also more likely to be admitted to intensive care (210/275
				Primary Treatment	Intensive care admission	HBOT 210/275 (76%), control 37/66 (64%), $p = 0.05$.			
				Primary Treatment	Number of debridements	HBOT 4.8 (SD 3.4), control 3 (SD 2.1), $p < 0.001$.			
				Primary Clinical efficacy	Number of amputations	HBOT 21/275 (7.6%), control 10/66 (15.2%), significance not reported but Yates' χ^2 calculated by SPH as 2.79, $p = 0.095$.			

			(not described but included debridement and amputation) Control: SC only						<p>(76%) vs. 37/66 (64%), $p = 0.05$). All these could influence prognosis, biasing the study in favour of HBOT.</p> <p>The authors attempted to correct their study's confounding by multivariate analysis of mortality, adjusting only for age and ICU admission (a proxy for illness severity). HBOT was then associated with a lower probability of death (odds ratio (OR) 0.45, 95% confidence interval (CI) 0.20 to 0.99, $p = 0.05$), a difference which just reached statistical significance.</p> <p>However, the absence of randomisation and of adjustment for other variables which might plausibly influence outcome undermines the reliability of this study. It remains at material risk of bias and confounding.</p>
Shaw et al 2014	P1 – Controlled unrandomised study	1,583 people with NSTIs, of whom 117 (7%) were treated with HBOT. Fournier's gangrene 69%, necrotising fasciitis 17%, gas gangrene 14%. 14 HBOT-capable university hospitals in the United States. Mean age 55 years, 66% male.	HBOT: regime not described, plus SC (not described) Control: SC only	Primary Clinical efficacy	Mortality	Multivariate analysis: control participants OR 10.6, 95% CI 5.2 to 25.1, p -value not reported (i.e. control participants at higher risk of death).	6	Direct	<p>No description of how participants were allocated to HBOT or control.</p> <p>There were material differences between those who did and did not receive HBOT. Twenty-two percent of the HBOT cohort had major severity of illness², compared to 45% of controls ($p = 0.01$), but 66% of the HBOT group had extreme severity of illness compared to 46% of controls ($p = 0.03$). There were also fewer Medicare³ patients in the HBOT group than in the control group (16% vs. 33%, $p = 0.04$). The HBOT group had more medical co-morbidities than the control group (5 vs. 3; $p = 0.03$).</p> <p>Among participants with minor, moderate or major severity of illness, there was no difference between HBOT and control groups in length of stay, costs, complications and mortality. Only among those with extreme severity of illness did the HBOT group have fewer complications (45% vs. 66%, $p < 0.01$) and fewer deaths (4% vs. 23%, $p < 0.01$).</p> <p>The authors attempted to correct their study's confounding by multivariate analysis, and adjusted mortality for patient demographics, insurance status, co-morbid conditions, and severity of illness. This approach is still at</p>
				Primary Clinical efficacy	Complications (not defined)	Multivariate analysis: HBOT 45%, control 66%, $p < 0.01$.			
				Primary Resource utilisation	Length of stay	Unadjusted analysis: HBOT 16 days, control 14 days, $p = 0.049$.			
				Primary Resource utilisation	Cost	Unadjusted analysis: HBOT \$35,808 (£27,600), control \$27,504 (£21,300), $p < 0.01$.			

² The University Health Consortium severity of illness score weights patient variables such as co-morbid conditions, age and diagnoses in the context of patient illness. Its validity is unclear.

³ Medicare is a publicly funded healthcare funding scheme for older US citizens.

									material risk of bias because of the presence of unknown or uncorrected confounders such as possible differences in other aspects of care provided.
Psoinos et al 2013	P1 – Controlled unrandomised study	56,527 weighted admissions with NSTI, of whom 707 (1.3%) were treated with HBOT. Mean age not reported, about 65% male. Hospitals in the United States	HBOT: regime not described, plus SC (not described) Control: SC only.	Primary Clinical efficacy	Mortality	Adjusted HBOT vs. controls OR 0.57, 95% CI 0.26 to 1.26	8	Direct	<p>No description of how participants were allocated to HBOT or control.</p> <p>The number of admissions was estimated from a sample of the Nationwide Inpatient Sample (NIS), a database of inpatient care in the United States. The NIS is a 20% stratified sample of all acute care hospital admissions, containing about 8 million admission records per year. The estimated were calculated using the NIS survey weights and sampling frame.</p> <p>The study was designed to examine trends in incidence, treatment, and outcomes for NSTIs, not to estimate the effectiveness of HBOT. The authors did not report how those who received HBOT differed from those who did not. Psoinos et al 2013 adjusted their model for year of treatment, age group, sex, race, insurance, and Elixhauser index, a co-morbidity score. The models for mortality and LOS also included total major complications. The model for LOS included only those patients who survived hospitalisation.</p>
				Primary Clinical efficacy	Any complication	Adjusted HBOT vs. controls OR 0.82, 95% CI 0.57 to 1.18			
				Primary Resource utilisation	Median length of stay	Adjusted regression coefficient ⁴ 3.47, 95% CI 1.11 to 5.84. This indicates longer length of stay associated with HBOT.			
Soh et al 2012	P1 – Controlled unrandomised study	45,913 people admitted with NSTI, of whom 405 (0.9%) were treated with HBOT. Mean age 54 years, about 65% male. Hospitals in the United States	HBOT: regime not described, plus SC (not described). Control: SC only	Primary Clinical efficacy	Mortality	Adjusted HBOT vs. controls OR 0.49, 95% CI 0.29 to 0.83, p = 0.008	8	Direct	<p>No description of how participants were allocated to HBOT or control.</p> <p>The number of admissions was estimated from a sample of the Nationwide Inpatient Sample (NIS), a database of inpatient care in the United States. The authors' sample overlaps almost completely with that of Psoinos et al 2013, but Soh et al 2012 adjusted their results using a propensity score which adjusted for gender, discharge, type and size of hospital, comorbidity, source and type of admission, site and aetiology of NSTI.</p>
				Primary Resource utilisation	Median length of stay	Adjusted analysis: HBOT 14.3 days, 95% CI 13 to 16; control 10.7 days, 95% CI 10 to 11; p < 0.001			
				Primary Resource utilisation	Median cost	Adjusted analysis: HBOT US\$52,205 (£40,500), control \$45,464 (£35,200), p < 0.001.			

⁴ A regression coefficient is a measure of the association between two variables, with a positive value indicating that as one rises, the others tends to rise also.

George et al 2009	P1 – Controlled unrandomised study	78 people admitted with NSTI, of whom 48 (62%) were treated with HBOT. Mean age 50 years, 63% male. 2 hospitals in Minnesota, United States.	HBOT: 3 ATA of 100% oxygen for 90 minutes 3 times in the first 24 hours, then twice daily until infection was controlled, plus SC (not described, but included antibiotics and debridement)	Primary Clinical efficacy	Mortality	HBOT 4/48 (8%), control 4/30 (13%), p = 0.48 Multivariate analysis: OR 0.98, 95% CI 0.18 to 5.42.	6	Direct	Whether participants were allocated to HBOT or control depended on the hospital to which they presented. The two groups differed. More of the participants who did not receive HBOT had undergone a solid organ transplant before developing an NSTI (5 vs. 1, p = 0.01). In the HBOT group, mean white blood cell count on admission was higher (15.5 x 10 ⁹ /l vs. 10.9 x 10 ⁹ /l, p = 0.01). The influence of these differences on outcome is unclear. Multivariate analysis included adjustment for age, hypotension, truncal involvement, clostridial infection and immunosuppression. The authors note that their study was underpowered to detect a difference in mortality rates of 5%. They also note that their study may be confounded by differences in patient characteristics such as wound care, general health, socioeconomic status and the organisms causing infection.
			Control: SC only	Primary Treatment	Days of antibiotic use	HBOT 18 (SD 12), control 20 (SD 17), p = 0.97.			
				Primary Treatment	Number of debridements	HBOT 3.3 (SD 2.4), control 2.4 (SD 2.2), p = 0.03			
				Primary Resource utilisation	Days of intensive care unit stay	HBOT 5.7 (SD 9.1), control 4.7 (SD 6.7), p = 0.95			
				Primary Resource utilisation	Days of hospital stay	HBOT 22.6 (SD 15.4), control 20.1 (SD 18.6), p = 0.15			
Mulla et al 2007	P1 – Controlled unrandomised study	216 people with necrotising fasciitis, of whom 19 (8.8%) were treated with HBOT. Age not reported, but 73% were > 42 years old. 51% male. 87 hospitals in Florida, United States.	HBOT: regime not described, plus SC (not described) Control: SC only	Primary Clinical efficacy	Mortality	Multivariate analysis: relative risk (RR) 0.48, 95% CI 0.09 to 2.56, p = 0.39	7	Direct	The authors analysed a discharge dataset of discharge summaries from all non-federal Florida hospitals except state tuberculosis and state mental health hospitals. Multivariate analysis for age (0 to 43 years versus older), gender, ethnicity (White non-Hispanic vs. other), insurance status (commercial insurance payer vs. other), infection with group A streptococcal, excisional debridement and diabetes.
				Primary Resource utilisation	Length of hospital stay	Multivariate analysis: regression coefficient 0.112, 95% CI -0.332 to 0.556, p = 0.62			
				Primary Resource utilisation	Total patient charges	Multivariate analysis: regression coefficient 0.131, 95% CI -0.355 to 0.616, p = 0.60			
Krenk et al 2007	P1 – Controlled unrandomised study	19 people with cervico-cranial	HBOT: 2.8 ATA for 90 minutes three times in the	Primary Clinical efficacy	Mortality	HBOT 0/11 (0%), control 6/8 (75%), p < 0.001	7	Direct	Authors compared outcomes before and after a change in treatment protocol which comprised more extensive surgical debridement, a new antibiotic regime, intravenous gamma globulin

		necrotising fasciitis, of whom 11 (58%) were treated with HBOT. Age not reported but about 57 years old. 26% male. 1 hospital in Copenhagen, Denmark.	first 24 hours and twice daily thereafter until no evidence of necrosis, plus SC (not described). Control: SC only	Primary Resource utilisation	Mean length of hospital stay	HBOT 30.8 days, control 15.3 days, $p < 0.02$			and HBOT. It is unclear the extent to which each of these contributed to the results; the extent of the change in treatment regime means that we cannot attribute differences in outcomes to the effect of HBOT. The authors state "It has not been possible to differentiate the entities in the new guideline, and the revolutionary survival in the HBO group must be the result of the combined effect of [the new regime's components]."
				Primary Treatment	Mean number of debridements	HBOT 3.36, control 0.5, $p < 0.002$			
				Primary Treatment	Mean number of incision and drainage procedures	HBOT 4.63, control 2.13, $p > 0.05$			

Use of HBOT plus standard care to treat necrotising soft tissue infections (studies with no comparator group)									
Study reference	Study Design	Population characteristics	Intervention	Outcome measure type	Outcome measures	Results	Quality of Evidence Score	Applicability	Critical Appraisal Summary
Bosco et al 2016	P1 – Uncontrolled study	34 people with NSTIs (20 perineal fasciitis, 8 cervical fasciitis, 6 gas gangrene) 1 hospital in Padua, Italy No reporting of age or gender	HBOT of 254 to 284 kPa daily for "several weeks". Participants inhaled 100% oxygen from a demand-regulated mask for three 25-minute periods; conscious unventilated participants had two 5-minutes	Primary Clinical efficacy	Clinical outcome (full recovery, survived with amputation, died)	Perineal fasciitis: 19/20 (95%) full recovery, 1/20 (5%) died. Cervical fasciitis: 8/8 (100%) full recovery. Gas gangrene: 6/8 (75%) full recovery, 2/8 (25%) amputation.	9	Direct	An uncontrolled study which provides no information on whether the clinical outcome is altered by HBOT.

			breaks. Participants also received antibiotics, surgical debridement or drainage, fasciotomies and/or myringotomies.						
Rosa et al 2015	P1 – Uncontrolled study	34 people with Fournier's gangrene 1 hospital in Lisbon, Portugal Mean age 53.7 years, 94.1% male	HBOT: 2.8 ATM for 90 minutes twice daily until the infection is controlled. Until 2011, the protocol was 90 minutes of HBOT at 2.5 ATM twice daily. In both time periods, this was followed by daily HBOT sessions at 2.5 ATM for 75 minutes until the condition is fully resolved. Participants also received antibiotics and surgical debridement.	Primary Clinical efficacy	Mortality	19/24 (79%) were discharged alive and 5/24 (21%) died. There was no information on the other 10.	7	Direct	An uncontrolled study which provides no information on whether mortality is altered by HBOT. The large proportion (29%) with no information on outcome reduces the reliability of the result.

8. Grade of evidence table

Use of HBOT plus standard care Vs. standard care to treat necrotising soft tissue infections					
Outcome Measure	Reference	Quality of Evidence Score	Applicability	Grade of Evidence	Interpretation of Evidence
Mortality	Li et al 2015	5	Direct	A	<p>Mortality is the proportion of participants who die during the study.</p> <p>Soh et al 2014 reported lower mortality with HBOT (adjusted OR 0.45, 95% CI 0.29 to 0.83, $p = 0.008$). This study is more reliable than Psinos et al (2013) because of more comprehensive multivariate adjustment.</p> <p>This study indicates that HBOT may lower mortality, but is subject to bias due to uncontrolled confounding.</p> <p>Mortality reduction would be of high value to patients. Soh et al 2012's analysis suggests that this may be the case, though their study is not robust enough to make this conclusion reliable.</p>
	Rosa et al 2015	7	Direct		
	Devaney et al 2015	7	Direct		
	Shaw et al 2014	6	Direct		
	Psinos et al 2013	8	Direct		
	Soh et al 2012	8	Direct		
	George et al 2009	6	Direct		
	Mulla et al 2007	7	Direct		
	Krenk et al 2007	7	Direct		
Mean curative time (not defined)	Li et al 2015	5	Direct	C	<p>Li et al 2015 do not define this outcome measure, but it may be the period from admission to the disappearance of all signs and symptoms of infection.</p> <p>The authors report shorter curative time with HBOT (HBOT: 15.4 days, SD 4.8; control 25.5 days, SD 9.6; $p < 0.05$).</p> <p>These results suggest that HBOT might reduce the duration of illness by about 10 days.</p> <p>Faster cure would be of benefit to patients, though Li et al 2015 do not report shorter length of stay with HBOT (see below).</p>
Mean number of debridements	Li et al 2015	5	Direct	A	<p>The outcome measure reports the mean number of debridement procedures per participant.</p> <p>Devaney et al 2015 reported more debridements with HBOT: HBOT 4.8 (SD 3.4), control 3 (SD 2.1), $p < 0.001$. This study is more reliable than Krenk et al 2007 because of its multivariate adjustment.</p> <p>This indicates that HBOT is associated with more debridement procedures being carried out.</p> <p>Patients are materially disadvantaged if HBOT leads to more operative procedures being required, unless longer term outcomes are better as a result.</p>
	Devaney et al 2015	7	Direct		
	George et al 2009	6	Direct		
	Krenk et al 2007	7	Direct		

					However, Devaney et al 2015 was seriously confounded by differences between patient groups. Furthermore, the number of procedures may be a confounding variable that affects outcomes.
Mean number of incision and drainage procedures	Krenk et al 2007	7	Direct	B	<p>The outcome measure reports the mean number of incision and drainage procedures per participant.</p> <p>Krenk et al 2007 was the only study to report this outcome (HBOT 4.63, control 2.13, $p > 0.05$).</p> <p>This result does not suggest an effect of HBOT on the number of incision and drainage procedures.</p> <p>Patients are materially disadvantaged if HBOT leads to more operative procedures being required, unless longer term outcomes are better as a result. However, this result may plausibly be attributed to chance and is not conclusive. Furthermore, the number of procedures may be a confounding variable that affects outcomes.</p>
Number of amputations	Devaney et al 2015	7	Direct	B	<p>The outcome measure reports the mean number of amputations per participant.</p> <p>Devaney et al 2015 was the only study to report this outcome (HBOT 21/275 (7.6%), control 10/66 (15.2%), significance not reported but Yates' χ^2 calculated by SPH as 2.79, $p = 0.095$).</p> <p>This result does not suggest an effect of HBOT on the number of amputation procedures.</p> <p>Patients benefit greatly if HBOT leads to fewer amputations being required. However, this result does not support that conclusion.</p>
Intensive care admission	Devaney et al 2015	7	Direct	B	<p>The outcome measure reports the mean number of participants admitted to intensive care.</p> <p>Devaney et al 2015 was the only study to report this outcome (HBOT: 210/275 (76%), control 37/66 (64%), $p = 0.05$).</p> <p>This result suggests HBOT is associated with a higher number of intensive care admissions, although this result is of borderline statistical significance.</p> <p>Patients benefit if HBOT leads to fewer intensive care admissions being required. The participants in Devaney et al 2015 who received HBOT had lower APACHE III scores, indicating less severe illness. There are several possible explanations for this finding: HBOT patients were treated more aggressively overall, possibly because clinicians were unblinded or because they are treated by different groups of clinicians; APACHE III is a poor</p>

					indicator of illness severity in these patients, and those who received HBOT were in fact more seriously ill; HBOT leads to an increased need for intensive care. The study does not enable us to evaluate which of these is correct, though the authors cast doubt on the accuracy of APACHE III.
Days of intensive care unit stay	George et al 2009	6	Direct	C	<p>The outcome measure reports the mean number of days for which participants were admitted to intensive care.</p> <p>George et al 2009 was the only study to report this outcome (HBOT 5.7 days (SD 9.1), control 4.7 days (SD 6.7), $p = 0.95$).</p> <p>This result suggests HBOT has no effect on the duration of intensive care admissions.</p> <p>Patients benefit if HBOT leads to shorter intensive care admissions being required, and costs would be avoided, but there is no evidence from George et al 2009 that this is the case.</p>
Days of antibiotic use	George et al 2009	6	Direct	C	<p>The outcome measure reports the mean number of days on which participants received antibiotics.</p> <p>George et al 2009 was the only study to report this outcome (HBOT 18 (SD 12), control 20 (SD 17), $p = 0.97$).</p> <p>This result suggests HBOT has no effect on the duration of antibiotic treatment.</p> <p>Patients benefit if HBOT leads to shorter courses of antibiotic treatment, and costs would be reduced, but there is no evidence from George et al 2009 that this is the case.</p>
Incidence of complications	Shaw et al 2014	6	Direct	B	<p>The outcome measure reports the incidence of complications. Neither study specified the complications, though in the case of Psinos et al 2013 they were complications of NSTIs rather than of HBOT.</p> <p>Psinos et al 2013 was the higher quality study reporting this outcome (OR 0.82, 95% CI 0.57 to 1.18).</p> <p>This result suggests HBOT has no effect on the incidence of complications.</p> <p>Patients benefit if HBOT leads to fewer complications, but there is no evidence from Psinos et al 2013 that this is the case.</p>
	Psinos et al 2013	8	Direct		
Length of hospital stay	Shaw et al 2014	6	Direct	A	This outcome measure reports the duration of

	Psoinos et al 2013	8	Direct		<p>participants' admissions.</p> <p>The highest quality study was Soh et al 2012 (adjusted analysis: HBOT 14.3 days, 95% CI 13 to 16; control 10.7 days, 95% CI 10 to 11; $p < 0.001$). This study is more reliable than Psoinos et al (2013) because of more comprehensive multivariate adjustment.</p> <p>This study indicates longer length of stay with HBOT.</p> <p>Longer length of stay is disadvantageous to patients and more expensive, unless longer term outcomes are better as a result. Soh et al 2012 reported longer length of stay among survivors, indicating that the difference does not arise because of higher or earlier mortality without HBOT.</p>
	Soh et al 2012	8	Direct		
	George et al 2009	6	Direct		
	Mulla et al 2007	7	Direct		
	Krenk et al 2007	7	Direct		
Cost	Shaw et al 2014	6	Direct	A	<p>This outcome measure indicates the cost of all treatment, including HBOT where this was used.</p> <p>Soh et al 2012 reported costs as follows, in an analysis adjusted for severity of illness: HBOT US\$52,205 (£40,500), control \$45,464 (£35,200), $p < 0.001$.</p> <p>This indicated that treatment with HBOT is more expensive than treatment without.</p> <p>Higher treatment costs mean less funds are available for other patients' care. Soh et al 2012 is a study from the United States and costs in the NHS will differ.</p>
	Soh et al 2012	8			
	Mulla et al 2007	7			

Use of HBOT to treat necrotising soft tissue infections					
Outcome Measure	Reference	Quality of Evidence Score	Applicability	Grade of Evidence	Interpretation of Evidence
Mortality	Rosa et al 2015	7	Direct	B	<p>Mortality is the proportion of participants who die during the study.</p> <p>Rosa et al 2015 reported that 19/24 (79%) were discharged alive and 5/24 (21%) died. There was no information on the other 10 participants.</p> <p>These results provide an indication of mortality from one small study.</p> <p>Mortality reduction would be of high value to patients, but this uncontrolled study does not indicate whether it follows HBOT.</p>
Clinical outcome (full recovery, survived with amputation,	Bosco et al 2016	9	Direct	B	<p>The outcome measure enumerates three possible clinical outcomes.</p> <p>Only Bosco et al 2016 reported this outcome</p>

died)					<p>measure. They reported the following results from their uncontrolled study: perineal fasciitis: 19/20 (95%) full recovery, 1/20 (5%) died; cervical fasciitis: 8/8 (100%) full recovery; gas gangrene: 6/8 (75%) full recovery, 2/8 (25%) amputation.</p> <p>These results indicate the pattern of clinical outcomes from this study.</p> <p>A greater probability of full recovery would be of high value to patients, but because Bosco et al 2016 was uncontrolled, it provides no indication of whether HBOT makes this more likely.</p>
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9. Literature Search Terms

<p>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?</p>	<p>Patients with a diagnosis of necrotising soft tissue infection which can also be described as progressive bacterial gangrene; progressive bacterial synergistic gangrene; anaerobic crepitant or clostridial cellulitis; necrotizing fasciitis; Fournier's gangrene; synergistic necrotising cellulitis; non-clostridial streptococcal myositis / myonecrosis; ecthyma gangrenosum; gangrenous impetigo; pyoderma gangrenosum; erysipelas; gangrenous or necrotizing erysipelas; symbiotic gangrene; phagedena gemoetrica; hospital gangrene; suppurative fasciitis; Meleney's ulcer and haemolytic streptococcal gangrene.</p> <p>Ludwig's angina (cervical necrotizing fasciitis); Vincent's angina is an acute necrotic gingivitis. Lemierre's Syndrome is a septicaemia secondary to pharyngitis. Both can evolve into a necrotising fasciitis.</p> <p>One subgroup that should also be considered is that of patients whose disease has continued to progress, or has failed to resolve, despite appropriate antibiotics, surgery and medical support (any regime) prior to treatment with hyperbaric oxygen therapy.</p>
<p>I – Intervention Which intervention, treatment or approach should be used?</p>	<p>Hyperbaric treatment delivering a maximum inspired partial pressure of oxygen between 200 and 314 kPa lasting between 60 and 150 minutes (eg Royal Navy Table 60 or 61) up to three times within the first 24 hours, then treatment with a maximum inspired partial pressure of oxygen between 200 and 253 kPa and lasting between 60 and 120 minutes (eg Royal Navy Table 66) up to twice each subsequent day until the infection is no longer spreading and the overall clinical condition of the patient is improving. Management with antibiotics, surgical debridement and medical support (any regime) should continue in addition to HBOT which should be administered at intervals that do not interfere with any surgical interventions that are necessary.</p>
<p>C – Comparison What is/are the main alternative/s to compare with the intervention being considered?</p>	<p>Management with antibiotics, surgical debridement and medical support (any regime)</p>

<p>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.</p>	<ul style="list-style-type: none"> – Mortality – Morbidity – Cessation of spread of infection – Comparative healing and resolution times – Reduction in spread of disease or manifestation of resolution of disease within 48hrs – Requirement for amputation in survivors – Length of hospital stay for survivors – Surgical interventions for reconstruction / repair in survivors Psychological morbidity – Quality of Life scores – Activities of Daily Living – Adverse Drug Reactions and other side-effects of treatment – Cost effectiveness
<p>Assumptions / limits applied to search</p>	<p><u>Inclusion criteria:</u> Peer reviewed studies published in the last 10 years including: Systematic Reviews Meta-analyses Randomised Controlled Trials Cohort studies Case series Cost effectiveness studies</p> <p><u>Exclusion criteria:</u> Work that is not available in the English language Case reports Grey literature including conference reports, abstracts, letters, posters unpublished studies</p>

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 search:

Searches



- 1 *soft tissue infection/ or *skin infection/
- 2 necrosis/ or gangrene/ or necrotizing fasciitis/ or tissue necrosis/
- 3 erysipelas/ or fournier gangrene/
- 4 pyoderma gangrenosum/
- 5 cellulitis/
- 6 Ludwig angina/
- 7 Vincent stomatitis/
- 8 Lemierre syndrome/
- 9 muscle necrosis/
- 10 (necrosis or necroti*).ti,ab.
- 11 (fasciitis or cellulitis or myositis or myonecrosis).ti,ab.
- 12 gangren*.ti,ab.
- 13 erysipelas.ti,ab.
- 14 (meleney* ulcer* or ludwig* angina or vincent* angina or lemierre* syndrome).ti,ab.
- 15 ((soft tissue or skin) adj2 infection?).ti,ab.
- 16 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 or 14 or 15
- 17 hyperbaric oxygen/
- 18 ((hyperbaric adj2 (oxygen* or therap* or treatment)) or hbot or oxygen chamber* or barochamber*).ti,ab.
- 19 17 or 18
- 20 16 and 19
- 21 (exp animals/ or nonhuman/) not human/
- 22 conference*.pt.
- 23 21 or 22
- 24 20 not 23
- 25 limit 24 to (english language and yr="2007 -Current")

Searches



11. Evidence Selection

- Total number of publications reviewed: 54
- Total number of publications considered potentially relevant: 44
- Total number of publications selected for inclusion in this briefing: 10

12. References

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