Adjunctive hyperbaric oxygen treatment for necrotising soft-tissue infections: A systematic review and meta-analysis

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Key words
Evidence; Necrotizing infections; Systematic review

Abstract
(Hedetoft M, Bennett MH, Hyldegaard O. Adjunctive hyperbaric oxygen treatment for necrotising soft-tissue infections: A systematic review and meta-analysis. Diving and Hyperbaric Medicine. 2021 March 31;51(1):34–43. doi: 10.28920/dhm51.1.34-43. PMID: 33761539.)
Introduction: Surgical intervention, broad-spectrum antibiotics and intensive care support are the standard of care in the treatment of necrotising soft-tissue infections (NSTI). Hyperbaric oxygen treatment (HBOT) may be a useful adjunctive treatment and has been used for almost 60 years, but its efficacy remains unknown and has not been systematically appraised. The aim was to systematically review and synthesise the highest level of clinical evidence available to support or refute the use of HBOT in the treatment of NSTI.
Methods: The review was prospectively registered (PROSPERO; CRD42020148706). MEDLINE, EMBASE, CENTRAL and CINAHL were searched for eligible studies that reported outcomes in both HBOT treated and non-HBOT treated individuals with NSTI. In-hospital mortality was the primary outcome. Odds ratio (ORs) were pooled using random-effects models.
Results: The search identified 486 papers of which 31 were included in the qualitative synthesis and 21 in the meta-analyses. Meta-analysis on 48,744 patients with NSTI (1,237 (2.5%) HBOT versus 47,507 (97.5%) non-HBOT) showed in-hospital mortality was 4,770 of 48,744 patients overall (9.8%) and the pooled OR was 0.44 (95% CI 0.33–0.58) in favour of HBOT. For major amputation the pooled OR was 0.60 (95% CI 0.28–1.28) in favour of HBOT. The dose of oxygen in these studies was incompletely reported.
Conclusions: Meta-analysis of the non-random comparative data indicates patients with NSTI treated with HBOT have reduced odds of dying during the sentinel event and may be less likely to require a major amputation. The most effective dose of oxygen remains unclear.

Introduction

Necrotising soft-tissue infections (NSTI) are a heterogeneous group of infections characterised by a rapidly progressive clinical course with necrosis of any layer of the soft-tissues.[1] NSTI encompasses a series of diseases including necrotising fasciitis, Fournier's gangrene and gas gangrene in which the conditions may differ due to different microbiological aetiology or anatomical site of infection; however, the clinical approaches to diagnosis and overall treatment remains identical. The annual incidence of NSTI varies considerably but is often reported at approximately four per 100,000 in developed countries.[2,3] Mortality rates highlight the severity of disease with a 90-day mortality of 18% reported in a multicentre study including more than 400 patients.[4]

The initial event in the onset of NSTI is the introduction of bacteria into the soft tissues through trauma (accidental or surgical) or spontaneously without a defined portal of entry (cryptogenic infection).[5] Rapid bacterial proliferation and endotoxin release cause a cascade of pathophysiological reactions including platelet-leukocyte aggregation, endothelial damage, capillary leakage and progressive occlusion of blood vessels that results in tissue hypoxia, oedema and necrosis.[5–8]

NSTI can be rapidly fatal. Early and radical surgery, broad-spectrum antibiotics and intensive care support remain the cornerstone of treatment.[9] Hyperbaric oxygen treatment (HBOT) might improve outcome when employed as an adjunct to conventional treatment and has been used in NSTI for almost 60 years.[10] Despite this, the use of HBOT remains controversial. It is not standard of care in many centres and a registry study in the USA suggested only 0.88% of cases received HBOT.[11]

HBOT involves the inhalation of 100% oxygen at pressures above 101.3 kPa (one atmosphere absolute [atm abs]). The precise protocol for NSTI varies among centres but

usually consists of one to two sessions of 60–120 minutes at 202.6–303.9 kPa (2–3 atm abs) within the first 24 hours. Thereafter, one to two daily sessions for several days or until further necrosis is no longer evident is a common protocol. The markedly increased serum partial pressure of oxygen during treatment results in a wide variety of biochemical effects which theoretically could improve the outcome of patients with NSTI.

The clinical evidence for the effectiveness of HBOT in these infections is sparse and of generally low quality. A Cochrane review highlighted the absence of randomised controlled trials (RCTs) in this area.[12] While a systematic review on the effectiveness of HBOT for NSTI has recently been published,[13] the combination of both newly published material and missing historical studies in that review have prompted this new and comprehensive systematic review with meta-analysis.

Within the field there is an understanding that a large RCT is required to properly define any place for the use of HBOT in these infections. The present aim was to synthesise the highest current level of clinical evidence in order to provide the best basis upon which to plan a subsequent multicentre RCT.

Methods

Eligibility criteria were agreed based on the formulation of a focused clinical question (Table 1). We included all trials reporting adult patients treated for NSTI and where the trial compared the effect of a regimen including HBOT with any treatment not including HBOT. HBOT was defined as 100% oxygen administered in a compression chamber between pressures of 152.0 and 405.2 kPa (1.5–4.0 atm abs) over treatment times from 30 to 120 minutes at least daily.

Table 1
PICO (population, intervention, comparison, outcome) criteria of included studies. HBOT – hyperbaric oxygen treatment; NSTI – necrotising soft tissue infection

Population	Adults with NSTI based on surgery
Intervention	HBOT
Comparison	HBOT versus Non-HBOT (sham or no treatment)
Outcome	***Primary*:** Mortality (In-hospital and 30-day) ***Secondary*:** Mortality (6 month and 1-year) Major amputation rate (above ankle/wrist or above) Number of surgical debridements Hospital length of stay Ventilator days Cost of therapy Functional outcomes (e.g., Quality of Life score) Adverse effect of all therapies

The primary outcomes were mortality during the sentinel admission and at 30 days from admission. The secondary outcomes were mortality at six months and one year, major amputation rate (above mid-foot), the number of surgical debridements, intensive care and hospital length of stay, mechanical ventilation days, the cost of therapy, quality of life scores and any adverse events of treatment (Table 1).

A comprehensive search of MEDLINE, EMBASE, CENTRAL and CINAHL was conducted, from inception to 20 April 2020. Citations in the included studies were searched for further comparative trials as were all previous relevant reviews available[12,13] and the US National Library of Medicine trials registry.[14] Authors of potentially eligible studies were contacted to provide any required data that would allow inclusion. The search strings used appear in Appendix 1*. Relevant journals and conference proceedings published since 1980 were hand searched (see Appendix 2*). No language restrictions were applied.

One author (MH) screened all identified citations by title and abstract. Potentially relevant studies were examined in full-text and independently reviewed by two authors (MH and MB) for compliance with eligibility criteria. Disagreements on eligibility were resolved by consensus. All studies where the full text was appraised were either accepted into the review or a reason given for rejection (Figure 1). Findings were reported in accordance with the "*Meta-analysis of Observational Studies in Epidemiology, (MOOSE)*"–guidelines (Appendix 3*).[15] This study was registered at the International Prospective Register of Systematic Reviews (PROSPERO), registration number CRD42020148706.

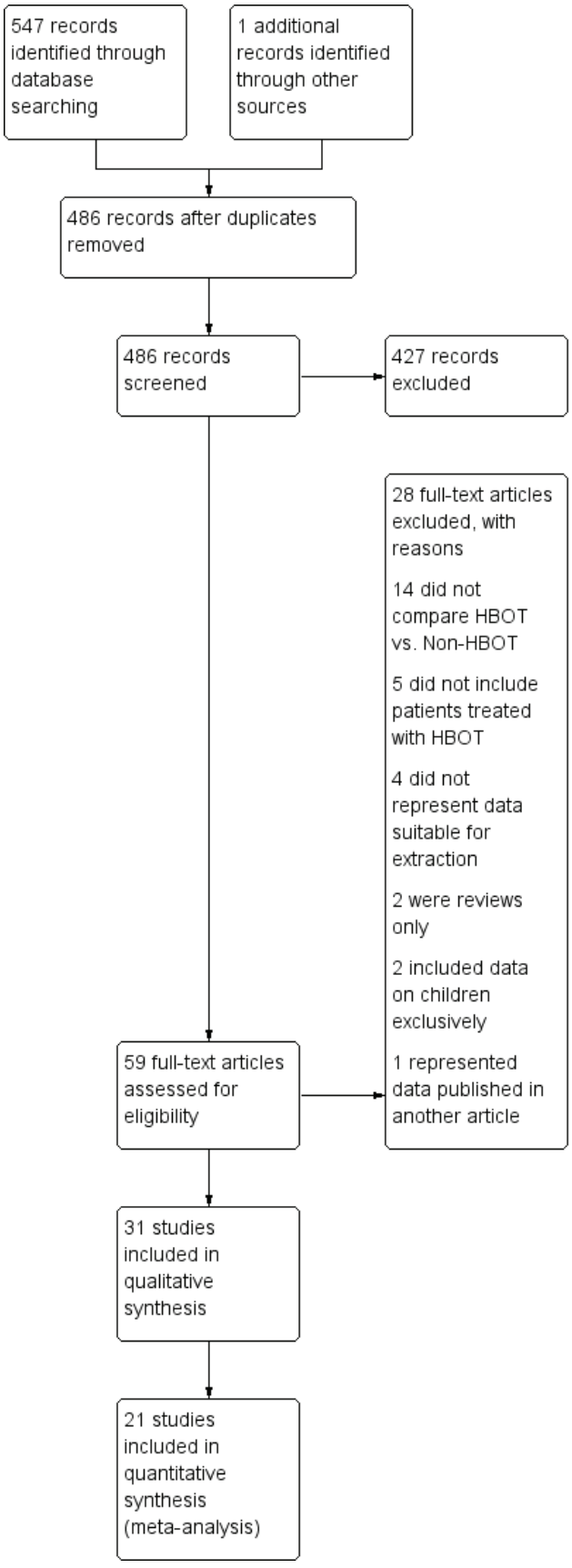
DATA EXTRACTION AND ANALYSIS

Two authors (MH and MB) independently extracted information into a pre-piloted data extraction form. Both the Newcastle-Ottawa Scale (NOS)[16] and the Cochrane-recommended ROBINS-I assessment[17] for non-random comparative trials were used (see Appendix 4*).

Review Manager 5.3 was used for pooled measures of treatment effect. Odds ratios (ORs) and 95% confidence intervals (95% CIs) were used for dichotomous outcomes. If there were no events in one arm an automatically fixed value of 0.5 of an event was applied to allow that study to contribute to analysis. If there were no events in either arm

Footnote: * Appendices 1–10 are available on DHM Journal's website: https://www.dhmjournal.com/index.php/journals?id=81

Figure 1
PRISMA flowchart for the review. HBOT – hyperbaric oxygen treatment



the study did not contribute to the analysis. For continuous data we used the mean difference (MD) between treatment and control groups in each trial and aggregated MDs using inverse variance weights to estimate an overall MD and 95% CI. A random-effect model was applied as clinical heterogeneity between studies was likely.

We considered clinical heterogeneity between studies and refrained from quantitative analysis where the heterogeneity was high. Statistical heterogeneity was assessed using the I^2 statistic and the appropriateness of pooling and meta-analysis was considered. Subgroup analysis based on the nature of the control group (historical versus contemporary), anatomical location (trunk versus peripheral), principal infecting organism and illness severity was also considered.

Sensitivity analyses for study quality were performed based on the inclusion and exclusion of those trials deemed to be at serious risk of bias. If inclusion of the latter did not substantially alter the result we chose to pool the two sub-groups. Studies at critical risk of bias were excluded from meta-analysis.

Results

The systematic search identified 486 studies. Of these, a total of 31 studies met the inclusion criteria (Figure 1).[11,18–47] All studies were retrospective observational studies and published between 1985 and 2020. Two (6%) of the included studies were written in languages other than English (German and Danish). Participant characteristics from all included studies are presented in Appendix 5*. Most included studies provided HBOT at 202.6–283.6 kPa (2.0–2.8 atm abs) for at least 90 minutes at different frequencies (Appendix 6*). Three (14%) of the included studies used historical non-HBOT controls, whereas 18 (86%) used contemporary non-HBOT controls. Study quality assessed by NOS and ROBINS-I are presented in Appendix 6*.

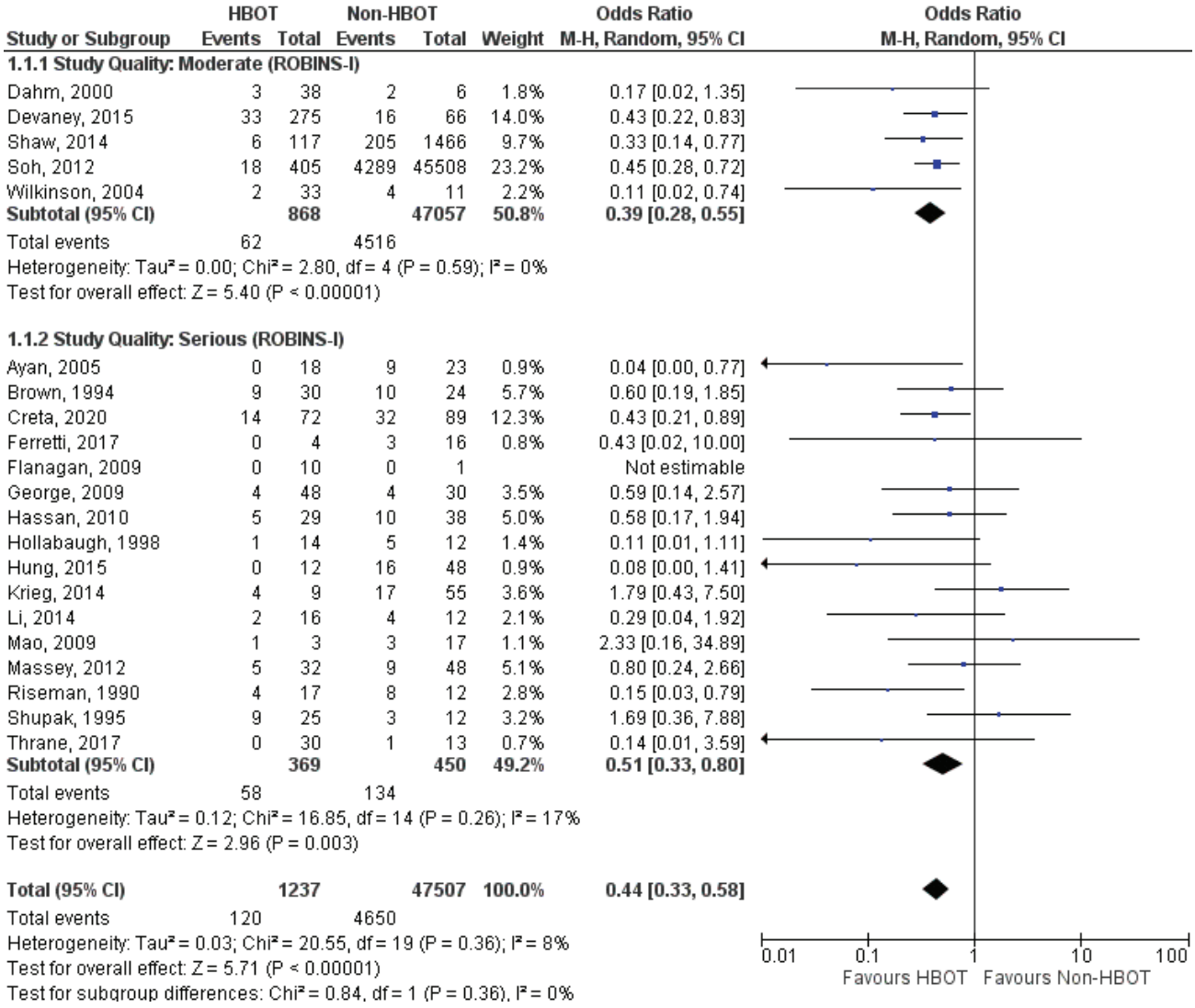
PRIMARY OUTCOMES

Mortality (31 reports)

No studies reported 30-day mortality. Reported mortality was interpreted as in-hospital mortality. Mortality was plotted chronologically and did not show any visual trend over time (see Appendix 7*).

Ten of the 31 studies were judged to be at critical risk of bias (ROBINS-I), and in line with Cochrane Collaboration recommendations were not included in the quantitative estimates.[48] Seven of these reported results in favour of HBOT.[18,19,28,32,40,42,43] The pooled estimates included 21 studies with a total of 48,744 participants and mean age from 43 to 67 years. Overall, the odds of dying after receiving

Figure 2
Forrest plot of the pooled effect of HBOT on in-hospital mortality. A random-effects model was used for meta-analysis



HBOT were lower, OR 0.44 (95% CI 0.33–0.58, I^2 = 8%, Figure 2). Sensitivity analysis for study quality did not substantially alter this estimate. One study[11] dominated the patient numbers, so a sensitivity analysis removing that study was performed. The results were not significantly affected: pooled OR 0.44 (95% CI 0.31–0.62).

Eighteen studies used contemporary controls and three historical controls. Subgroup analysis showed the pooled estimate was OR 0.24 (95% CI 0.03–1.87) for historical controls vs. OR 0.45 (95% CI 0.35–0.59) for contemporary controls (See Appendix 8*).

The possibility of publication bias was evaluated using visual assessment of the funnel plot (Figure 3). There is some suggestion of bias in favor of HBOT, with a paucity of smaller studies in the bottom right of the graph (smaller studies less favourable to HBOT are missing).

SECONDARY OUTCOMES

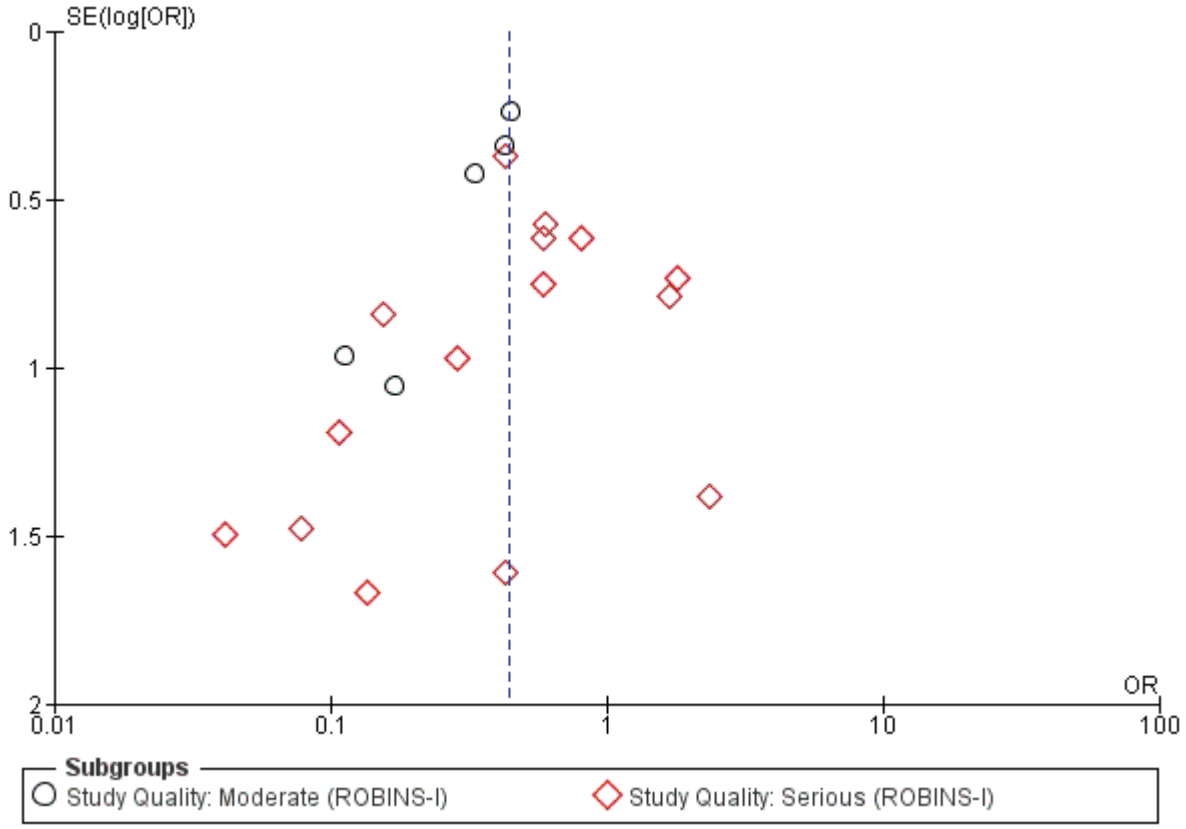
Major amputation (5 reports)

For the pooled estimate a total of five studies reported a total of 45,632 participants; three studies were of moderate quality.[11,23,37] Overall, the odds of requiring a major amputation with HBOT were 0.60 (95% CI 0.28–1.28, I^2 = 54%, P = 0.07. Figure 4).

Number of surgical debridements (11 reports)

Only one study[23] judged at low or moderate risk of bias could be included in this outcome and five studies judged at serious risk of bias were also included (see below). As the estimate of Devaney et al.[23] was very different to the other five, a combined estimate of effect is not provided (See Appendix 9*). Devaney et al.[23] enrolled 341 patients,

Figure 3
Funnel plot on primary outcome; in-hospital mortality



275 of whom received HBOT (81%). Analysis suggested there were more debridements in the HBOT group (mean 4.8 versus 3.0 per patient, difference 1.8 (95% CI 1.15–2.45), $P < 0.001$).

Five studies[21,24,26,29,35] were pooled and any effect of HBOT in these studies was unclear (MD 0.63 more debridements per patient with HBOT [95% CI -0.49–1.75], $I^2 = 90\%$). The high chance of important heterogeneity suggests this estimate should be treated with great caution.

Five further studies reported on this outcome but could not be included in the quantitative analysis. One[19] was judged at a critical risk of bias and reported a mean of 13.3 debridements in the HBOT groups compared to 4.8 in the non-HBOT group. Another[37] reported non-parametric data (median of 5 (IQR 1–16) debridements in the HBOT group and 1 (IQR 1–4) in the non-HBOT group. The third[39] included only one patient in one arm. The fourth[25] only reported the number of debridements in a sub-group of participants, and the last[34] did not provide standard deviations.

Hospital length of stay (6 reports)

Three studies[24,29,44] reported this outcome in 68 participants, MD -1.98 days (95% CI -9.93–5.97, $I^2 = 47\%$) (see Appendix 10*).

Additionally, three studies[11,23,38] reported non-parametric data with length of stay as medians with interquartile ranges. One study[23] demonstrated a median of 21.8 days (IQR 9–36.7) in the HBOT group and 24 days (IQR 10–39) in the non-HBOT group. The second[11] reported a median of 14.3 days (IQR 13–16) in the HBOT group and 10.7 days (IQR 10–11) in the non-HBOT group. The third[38] reported a median of 16 days (IQR 11–23) in the HBOT group and 14 days (IQR: 8–23) in the non-HBOT group.

Ventilator days (3 reports)

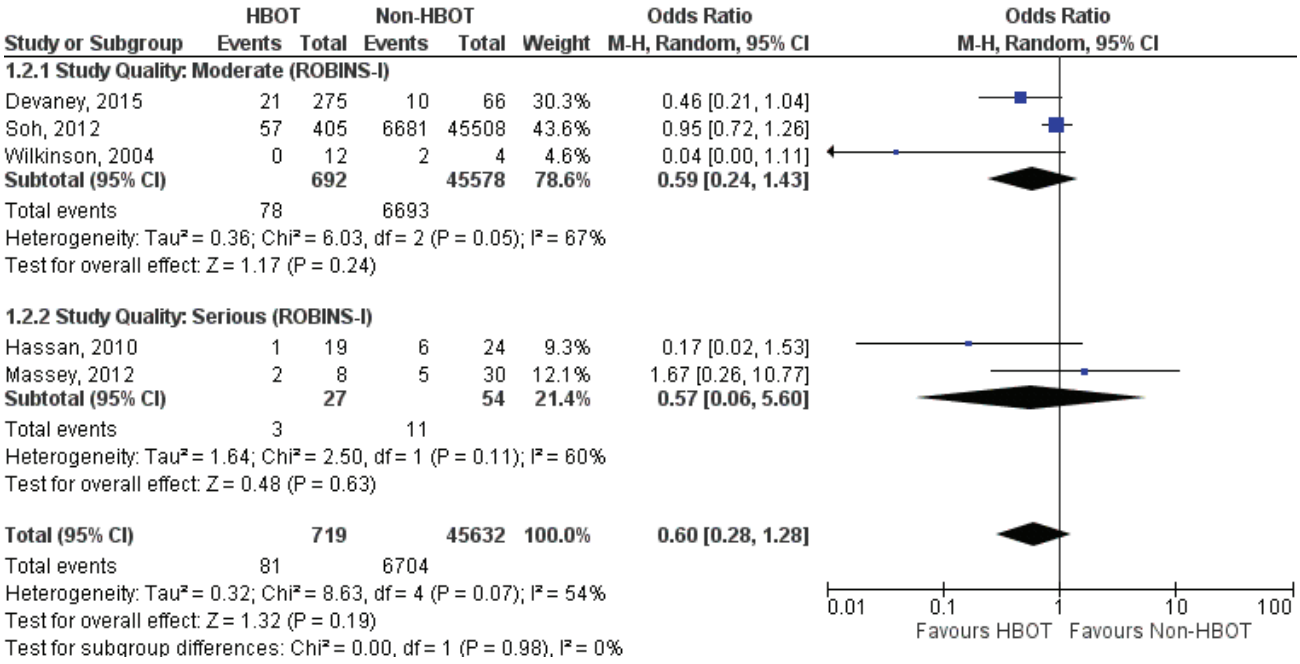
One study[21] reported ventilator days with a mean of 7.3 (SD 7.1) and 3.5 (SD 6.2) days in the HBOT and non-HBOT groups respectively. Another two studies[23,33] reported non-parametric data with medians of 4.9 in the HBOT groups and 2.6 and 2 in the non-HBOT groups, respectively.

Cost of therapy (3 reports)

Three studies[11,33,38] provided data on cost of therapy, but not in a uniform way to allow pooling the results. One[38] reported the cost of therapy was US$35,808 (IQR 23k–65k) in the HBOT group compared to US$27,504 (IQR 14k–51k) in the non-HBOT group. Another[11] reported US$107,000 in the HBOT group and US$86,000 in the non-HBOT group but

Figure 4

Forrest plot of the pooled effect of HBOT on risk of major amputation. A random-effects model was used for meta-analysis



the study didn't provide standard deviations of the reported means. The third[33] reported a median cost of US$63,199 (range 31,858–256,741) with HBOT and US$51,185 (range 8,691–427,283) without HBOT.

Discussion

To our knowledge, this is the most comprehensive analysis to date of the effect of HBOT for patients with NSTI. With data from 21 non-randomised studies including 48,744 patients, this meta-analysis indicates patients with NSTI treated with HBOT have reduced odds of dying during the sentinel hospital admission. This suggests a number needed to treat of approximately 19 patients with HBOT in order to prevent one death (calculated from OR).[49] Patients treated with HBOT may also be at a lower risk of major amputation (OR 0.6). Data on ventilator days and cost of therapy were not appropriate for meta-analysis. Both length of stay and the days on a ventilator may be affected by many factors, such as differences in the severity of illness and the use of intensive treatment regimens, but both may also simply reflect longer survival. The cost of therapy was rarely reported, and all studies that did so were from the United States. Caution is needed in extrapolating these costs to other systems where the cost of treatment is likely to be lower.

While there is some indication of a publication bias in favour of HBOT on inspection of the funnel plot, this is by no means established and the analysis suggests those reports at a lower risk of bias show a greater benefit with HBOT than those judged at higher risk of bias. A sensitivity analysis excluding the largest study[11] did not substantially affect the pooled estimate, indicating the overall result was not biased by the inclusion of this study and increasing confidence in the overall pooled estimate of effect.

Many older studies with poor methodology were identified, however a chronological assessment of the OR over time did not suggest an historical bias and the overall estimate of benefit with HBOT has been stable over time.

Most of the identified studies used a HBOT protocol of 90 minutes at 202.6–283.6 kPa (2.0–2.8 atm abs). However, treatment frequency varied greatly from once daily[20] to more aggressive treatment regimens with three sessions within 24 hours and thereafter twice daily.[24,34,37] Nine studies failed to provide any information on the treatment table used or frequency of treatment (Appendix 6*).

Treatment of NSTI requires a multidisciplinary approach including surgery, broad-spectrum antibiotics and intensive care treatment. Detailed information on the standard of care (e.g., type and dosage of antibiotics, number of surgical debridements and treatment interventions performed in the intensive care unit) is key when evaluating potential adjuncts to NSTI treatment. However, these were in general incompletely reported in the included studies. NSTI encompasses a variety of diseases (e.g., necrotising fasciitis, Fournier's gangrene and clostridial myonecrosis). While these diseases all produce widespread necrosis and require similar treatment, they differ substantially in aetiology, microbiology and anatomical site, and are a likely cause of clinical heterogeneity between included studies. Incomplete reporting meant we were unable to perform

any of our planned sub-group analyses to investigate the influence of clinical heterogeneity, including the dose of oxygen, anatomical location, principal infecting organisms and illness severity.

We have found limited data on which to base our estimates for all planned outcomes. While mortality was universally reported, the times from onset to death were not. Our own experience leads us to assume mortality here was for the sentinel event admission. Only the minority of the included studies reported comparable outcomes for our secondary endpoints. Future studies need to address endpoints with clear and reproducible definitions.

Pooled analysis of data from non-randomised studies remains controversial. Indeed, it has been suggested that pooling estimates in this area would be susceptible to high uncertainty and misinterpretation.[13] Critics have suggested that when meta-analyses include low-quality studies, fundamental errors will be transferred into the meta-analyses – the 'garbage in, garbage out' metaphor.[50] While we agree a meta-analysis can be misleading when confounders are not adequately addressed in the trial design and analysis, there is also a counter argument. Avoiding formal data synthesis and simply listing all the trials and their individual characteristics for the reader to interpret is unsatisfactory. It leaves the reader free to continue in their own biased interpretation and avoids a clear statement of the most likely consequences of adopting a particular treatment. Linked with sound interpretations of the implications for both practice and research, we believe meta-analysis can be justified. If the purpose of a systematic review is to inform the reader of the best evidence and also to inform future triallists of the most appropriate treatment and outcomes to include in any future study, then the calculation of an overall estimate of effect may do more good than harm.

A potential advantage of including non-randomised trials into systematic reviews is that they are more likely to include the full spectrum of patients and therefore be more generalisable to the population at large.[51] The inclusion criteria of the present systematic review are broad in order to reflect the variety of different aetiologies, pathogenic agents and anatomical locations. All are united by requiring the same multidisciplinary approach.

A good discussion of the potential mechanisms of action of HBOT highlights the importance of the controlled release of active oxygen and nitrogen species through the use of HBOT.[52] Several mechanisms have been proposed by which HBOT may achieve clinically important benefits in this group of infections. HBOT exposure at 222.9 kPa (2.2 atm abs) results in the achievement of gross arterial hyperoxia and a PaO_2 above 100 kPa is achievable with reasonable cardiorespiratory function.[53] Gross arterial hyperoxia results in vasoconstriction, increased oxygen diffusion distances, a reduction in leucocyte adherence, bacteriostasis and osmotic reduction in tissue oedema, all of which may be clinically important.

Hyperoxic vasoconstriction will maintain oxygen delivery while limiting or improving tissue oedema, extending the diffusion distance of oxygen and restoring local tissue oxygenation.[54,55] Elevated capillary oxygen tension will inhibit the adherence of neutrophils to damaged endothelium via a specific nitric oxide mediated pathway that inhibits β_2-integrin function. This prevents microvascular plugging and further tissue hypoxia without otherwise compromising neutrophil function.[56,57] The local release of reactive oxygen species in hypoxic tissues also has direct bacteriostatic effects, particularly against anaerobic bacteria, and enhances the antimicrobial effects of some antibiotics.[58–60] In addition, while biofilm formation in NSTI[61] protects bacteria utilising anaerobic metabolism from antibiotics in an hypoxic environment, HBOT may restore the susceptibility to antibiotics by inducing aerobic metabolism. This has been demonstrated in *Pseudomonas aeruginosa* and *Staphylococcus aureus* biofilm models.[60,62] Finally, HBOT may interrupt the pathology of NSTI by acting as an intravascular osmotic agent.[63]

HBOT carries a limited number of risks complicating the therapeutic process for patients with NSTI. Middle ear barotrauma occurs in about 2% of awake patients[64] but is avoided in unconscious patients by the use of trans-tympanic ventilation tubes.[65] Rarely, pulmonary barotrauma may occur during decompression in patients with airway obstruction;[64] however, to our knowledge pulmonary barotrauma has not occurred in a ventilated patient, where the airway is likely to remain open. Oxygen has toxic effects with both pulmonary and neurologic manifestations. Pulmonary toxicity requires prolonged exposure to hyperbaric doses and is not a practical problem,[64] while the incidence of oxygen seizures is approximately 0.01% of treatments with no evidence of long-term sequelae.[64,66]

Patients with NSTI are often critically unwell and unstable. Inter-hospital transportation may be inadvisable in some cases, preventing the application of this therapy if HBOT is unavailable at the treating hospital. In-hospital HBOT chambers with ICU-capabilities are essential for the safe delivery of HBOT,[64,67,68] particularly as HBOT may reduce mortality in the most critically ill patients.[38]

There are several limitations to our review. Mortality, co-morbidities, illness severity and co-interventions were all incompletely reported leading to some doubt these patients are directly comparable between studies. Additional important variables include geographical location and the year of reporting. Our results should be applied with caution to any single subset of NSTI.

The absence of randomised trials of HBOT for NSTI has been highlighted. We urge researchers to consider remedying

this. We emphasise such a study needs careful preparation including power calculations based on the data in this review, reliable randomisation with blinding of patient and investigators, uniform approaches to hyperbaric oxygen doses, antibiotic administration, intensive management and surgical approach, rigorous data collection and well-defined outcomes. Such a study cannot be achieved by any single clinical unit and will involve close co-operation across many centres.

Conclusions

Meta-analysis of the non-random comparative data indicates patients with NSTI treated with HBOT have reduced odds of dying during the sentinel event and may be less likely to require a major amputation. Other benefits are uncertain. The most effective dose of oxygen remains unclear in terms of treatment profile, the optimal interval between treatments and the total number of treatments required for the best outcome. A high quality RCT is justified.

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Acknowledgements

We would like to thank Dr John McKenzie for valuable help in translation of non-English literature.

Conflicts of interest and funding

No conflicts of interest were declared. MH was granted by Rigshospitalet's Research Foundation (grant no. R167-A7352-B3897), Knud and Edith Eriksen's Foundation, Wedellsborg Foundation and King Christian X's Foundation. Moreover, the study was supported by the projects of PERMIT (grant number 8113-00009B) funded by Innovation Fund Denmark and EU Horizon 2020 under the frame of ERA PerMed (project 2018-151) and PERAID (grant number 8114-00005B) funded by Innovation Fund Denmark and Nordforsk (project no. 90456).

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Submitted: 07 September 2020
Accepted after revision: 29 October 2020