

# Hyperbaric Oxygenation in the Treatment of Fournier's Gangrene: A Systematic Review

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## Keywords

Fournier's gangrene · Hyperbaric oxygenation

## Abstract

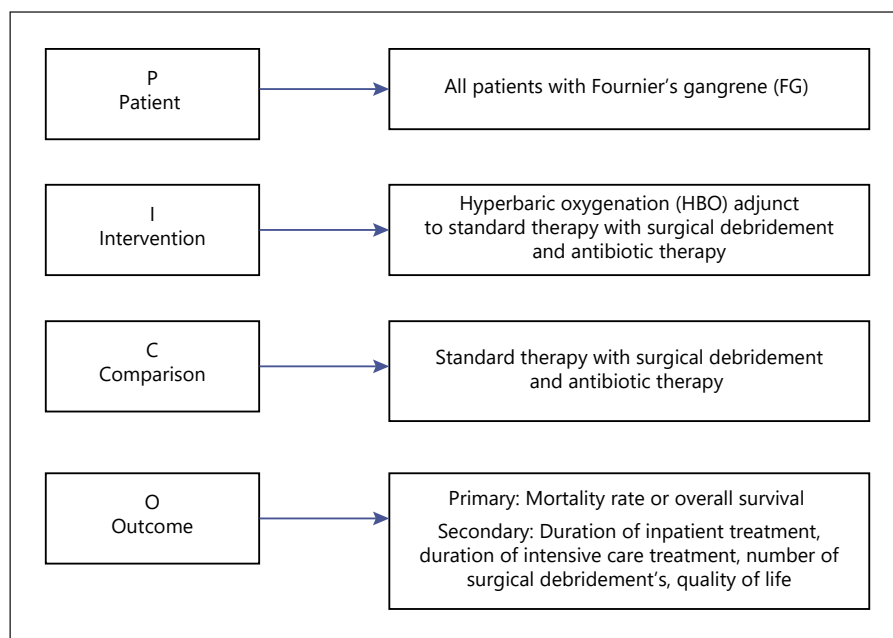
**Introduction:** Fournier's gangrene (FG) is a sporadic, life-threatening, necrotizing infection affecting the perineum, perineal region, and genitals. Hyperbaric oxygenation (HBO) improves tissue perfusion and promotes angiogenesis and collagen synthesis. Despite these positive effects of HBO, the indication and the effects on outcome as adjunct therapy in FG remain controversial. Consequently, we decided to perform a systematic review to compare the treatment of FG with or without the use of HBO as an adjunct therapy. **Materials and Methods:** We performed a systematic review following the recommendations provided in the Cochrane Handbook of systematic Reviews and the PRISMA reporting guidelines. Due to the paucity of data and a suspected lack of randomized controlled trials, we considered all the available information for this systematic review. **Results:** The literature search for primary studies yielded 79 results. Finally, 13 studies were considered, which included a total of 376 patients with FG, of whom 202 received HBO therapy. Five of these studies had a retrospective case-control design. How-

ever, these 5 studies included a total of 319 patients; 145 of these patients were treated with adjunct HBO therapy. Overall, this leads to a mortality rate of 16.6% in the HBO group and 25.9% in the non-HBO group. Overall, risk of bias was assessed as moderate to high. **Conclusions:** We conclude that despite the risk of bias, HBO has potential as an adjunct in FG treatment, but it is challenging to carry out further studies, mainly due to the rareness of FG and availability of HBO.

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## Introduction

Fournier's gangrene (FG) is a sporadic, life-threatening, necrotizing infection affecting the perineum, perineal region, and genitals [1–3]. As the incidence is low, most of the limited knowledge about FG arises from retrospective single-institutional studies with very small patient cohorts [1, 4–16]. Unfortunately, FG also has a poor prognosis. Early studies of FG reported a 20–88% mortality rate [1, 2, 17–19], but 2 studies from 2017 calculated a mortality rate of 25–26% [3, 12], which is still worrisome. Furthermore, Kranz et al. [1] reported in 2018 that the



**Fig. 1.** Illustration of the PICO question for this systematic review. PICO, Patient Intervention Comparison and Outcome.

situation of FG patients is alarming since outcome of this disease failed to improve over the last 10 years despite more intensive critical care therapy.

Key points for the successful treatment of FG are immediate surgical debridement, accompanied by forced antibiotic therapy and, usually, intensive medical management [20]. However, hyperbaric oxygenation (HBO) was first used by Boerema, who was a Dutch cardiovascular surgeon. He observed that when surgery was performed in an environment filled with pressure, vessels could be contracted for a longer time, resulting in cardiac repair [21, 22]. Additionally, HBO improves tissue perfusion, promotes angiogenesis and collagen synthesis, increases oxygen levels in tissues, and inhibits the production of toxins. Therefore, HBO therapy is widely used to treat mixed infections [20, 23, 24]. Despite these positive effects of HBO, the indication and the effects on outcome as adjunct therapy in FG remain controversial [21].

Consequently, we decided to perform a systematic review to compare the treatment of FG with or without the use of HBO as an adjunct therapy. To enunciate our question we used the PICO scheme (Patient Intervention Comparison and Outcome), illustrated in Figure 1. The primary aim of this review was to summarize the current evidence for HBO use in patients with FG and thereof knowledge for planning further clinical studies, especially prospective evaluations, which are warranted [1].

## Material and Methods

We followed the recommendations provided in the Cochrane Handbook of systematic Reviews [25] and the PRISMA reporting guidelines [26].

### *Criteria for considering Studies for This Review*

#### Types of Studies

Due to the paucity of data and a suspected lack of randomized controlled trials (RCTs) in this disease, we considered all the available information for this systematic review. Thus, all types of study designs were included: randomized and quasi-randomized studies (if available), comparative studies (e.g., cohorts, case and control), and non-comparative studies (e.g., case series or case reports); the only exclusion were made for narrative reviews. Full-text articles and abstracts were considered. No exclusions were made by publication date. We only included German and English publications.

#### Types of Participants

All patients diagnosed with FG were included in this systematic review.

#### Types of Outcome Measures

Measurement of outcomes assessed in this review will not be used as an eligibility criterion. The primary outcomes were mortality rate or overall survival. Secondary outcomes were accepted reporting of duration of inpatient treatment, duration of intensive care treatment, number of surgical debridements, and quality of life.

### *Search Methods for Identification of Studies*

A combination of electronic and manual searches for the identification of studies was conducted.

### Electronic Searches

We searched the following databases: MEDLINE via PubMed from 1946 to 2020 (search strategy: “fournier gangrene”[MeSH Terms] OR (“fournier”[All Fields] AND “gangrene”[All Fields]) OR “fournier gangrene”[All Fields] OR (“fournier’s”[All Fields] AND “gangrene”[All Fields]) OR “fournier’s gangrene”[All Fields]) AND (“hyperbaric oxygenation”[MeSH Terms] OR (“hyperbaric”[All Fields] AND “oxygenation”[All Fields]) OR “hyperbaric oxygenation”[All Fields]). Last search was conducted on April 2020. The electronic searches were complemented by searching the World Health Organization International Clinical Trials Registry Platform Search Portal (WHO ICTRP) and ClinicalTrials.gov by using the term “Fournier’s gangrene” (MeSH) to identify possible completed or ongoing trials.

### Searching Other Resources

The reference lists of included studies were hand-searched for additional references. Conference proceedings of 8 journals (*European Urology*, *European Urology Supplements*, *European Urology Focus*, *The Journal of Urology*, *British Journal of Urology International*, *World Journal of Urology*, *Urologia Internationalis*, *Central European Journal of Urology*) were hand-searched as well from the year 2010 onwards.

### Selection of Studies

Citavi 6.0 (Swiss Academic Software, Wädenswil, Switzerland) was used to manage the bibliographic references. Two review authors (L.S. and J.K.) independently screened title and abstracts to determine which studies should be assessed further. Two review authors (L.S. and J.K.) have assessed all potentially relevant records as full texts, mapped records to studies, and classified studies as included studies, excluded studies, studies awaiting classification, or ongoing studies in accordance with the criteria for each provided in the *Cochrane Handbook for Systematic Reviews of Interventions*[25]. Discrepancies will be resolved through consensus or consultation of a third review author (P.A.).

### Data Extraction and Management

For studies that fulfilled the inclusion criteria, 2 review authors (L.S. and J.K.) have independently extracted the following information: Study dates and settings, participant details, grade of evidence SIGN (Scottish Intercollegiate Guideline Network), definitions of relevant outcomes, method and timing of outcome measurement, and any relevant subgroups (Table 1).

### Measures of Treatment Effect

We extracted outcomes data relevant to this systematic review as needed for calculation of summary statistics and measures of variance. For dichotomous outcomes, we attempted to obtain numbers of events and totals for population of a 2 × 2 table, as well as summary statistics with corresponding measures of variance. For continuous outcomes, we attempted to obtain means and standard deviations or data necessary to calculate this information. For time-to-event outcomes, we attempted to obtain hazard ratios with corresponding measures of variance or data necessary to calculate this information.

We resolved any disagreements by discussion, or, if required, by consultation with a third review author (P.A.). We attempted to contact authors of included studies to obtain key missing data as needed.

### Assessment of Risk of Bias in Included Studies

We have attempted to assess the risk of bias by using the Cochrane risk of bias tool for RCTs and quasi-RCTs [25], the SIGN tool for cohort studies, case-control studies, and case series [27].

### Assessment of Study Heterogeneity and Data Synthesis

Due to the different study designs of included studies and their different end points, we could finally not perform a synthesis of results, and therefore no meta-analysis was performed.

## Results

The literature search for primary studies yielded 79 results. Finally, 13 studies were considered, which included a total of 376 patients with FG, of whom 202 (53.7%) received HBO therapy (Fig. 2) [20, 21, 28–38]. We could only identify retrospective studies for this review. At the time of this review, 1 prospective study was registered at WHO ICTRP or ClinicalTrials.gov, named “Prognosis and treatment of Necrotizing Soft Tissue Infections: A Prospective Cohort Study” from Copenhagen University Hospital (Denmark). This study is completed but not yet published. Table 1 shows the main characteristics, interventions, end points, and main results of the 13 included studies.

The included studies are very heterogeneous, especially in terms of the administration of the HBO therapy. However, Table 2 gives a specification of administration of HBO in the included studies. Due to this heterogeneity, we were not able to perform a meta-analysis of the data.

On the whole, 12 of the included studies concluded that adjunct HBO to standard treatment of FG has positive effects, especially in terms of mortality rate, and further investigations are reasonable. In contrast, Mindrup et al. [31] reported that the data do not support routine HBO in the treatment of FG. There was a trend towards higher baseline morbidity in the HBO group, suggesting that more severely ill patients were selected for HBO treatment.

Furthermore, 5 of the 13 included studies had a retrospective case-control design [20, 21, 28, 31, 33]. Mortality rate in these studies ranged from 0 to 26.9% in the HBO groups. All authors reported a significant lower mortality rate in the HBO group except Mindrup et al. [31] (12.5% non-HBO vs. 26.9% HBO). Interestingly, Creta et al. [28] identified surgical debridement and HBO as independent predictors for lower mortality in multivariate analysis. Additionally, Li et al. [21] indicated that the difference in the number of surgical debridements, indwelling drainage tube time, and curative time were significantly lower

**Table 1.** Overview and characterization of all included studies (*n* = 13)

Reference	Study design	Evidence	Participants	Intervention	End points	Main result	Authors conclusion
Creta et al. [28]	Retrospective multi-institutional observational case-control study	SIGN: 2+	A total of 161 patients with FG; 72 of them underwent HBO	Patients received surgical debridement and/or standard antibiotic therapy alone or in combination with HBO	Mortality rate	Mortality due to FG was observed in 32 (44.7%) without HBO, in 14 (19.4%) with HBO treatment ( <i>p</i> = 0.01); at multivariate analysis, surgical debridement and HBO were independent predictors for lower mortality	HBO and surgical debridement are independent predictors of reduced FG-related mortality
Anheuser et al. [20]	Multi-institutional, retrospective observational study	SIGN: 2-	62 patients in 2 groups: without HBO (group A, <i>n</i> = 45) and with HBO therapy (group B; <i>n</i> = 17)	Patients received surgical debridement and/or standard antibiotic therapy alone or in combination with HBO	Influence of HBO on outcome and prognosis of FG	No significant difference regarding demographic data between the groups; wound debridement frequency and hospitalization stay were significantly greater in group B; mortality was 0% in group B and 4.5% in group A	Despite poorer baseline findings with comparable risk factors, mortality was 0% in the HBO group. The analysis of a larger patient cohort is desirable to increase significance of the results
Li et al. [21]	Retrospective observational study	SIGN: 2-	28 cases of FG in a single institution from January 2004 to December 2013; 12 patients treated without HBO and 16 with HBO	Patients received surgical debridement and/or standard antibiotic therapy alone or in combination with HBO	Outcome and mortality rate	Mortality was lower in the HBO group 12.5 versus 33.3%; difference in number of surgical debridement, indwelling drainage tube time and curative time were significantly lower in HBO group	The preliminary research results suggest that the effect of combining HBO with conventional therapy offers considerable advantage in the management of FG; further multi-institutional studies are warranted
Zagli et al. [29]	Case report	SIGN: 3	2 patients in septic shock due to FG	Patients were treated with surgical debridement, protective colostomy, HBO and broad-spectrum antibiotic therapy followed by vacuum-assisted wound-closure	Description of outcome	Both patients survived and were discharged from intensive care unit after HBO	Author's experience suggest the consideration of HBO in life-threatening FG, more studies are needed
Yoshida et al. [30]	Case report	SIGN: 3	1 patient with FG after living donor liver transplantation	Patient was treated with surgical debridement, HBO and antibiotic therapy	Description of outcome	The patient successfully recovered within 2 months after initial surgery	HBO in FG has a positive effect on infection control and wound healing
Mindrup et al. [23]	Retrospective observational study	SIGN: 2-	A total of 42 patients, single institutional from 1993 to 2002; 16 without HBO and 26 of them treated with HBO	16 patients underwent surgical debridement and antibiotic therapy alone compared to 26 treated with additional HBO	Outcome and mortality rate	Disease specific mortality was 12.5% in the non-HBO group versus 26.9% in HBO group	The data do not support routine HBO in the treatment of FG; there was a trend toward higher morbidity in the HBO group, suggesting that the treatment was given to patients who were more ill
Korhonen et al. [32]	Retrospective observational study	SIGN: 3	33 patients, single institutional	Debridement, broad-spectrum antibiotics and HBO; urinary and fecal diversions when necessary	Morbidity and mortality	3 patients died (9%); HBO reduced systemic toxicity, prevented extension of the necrotizing infection and increased demarcation, thereby improving the overall outcome	HBO is both life and tissue saving. It is an important adjunct that prevents extension of necrosis and reduces systemic toxicity

**Table 1** (continued)

Reference	Study design	Evidence	Participants	Intervention	End points	Main result	Authors conclusion
Hollabaugh et al. [33]	Retrospective observational study	SIGN: 2-	26 cases, single institutional, 14 of them received HBO as adjuvant therapy	All cases involved prompt surgical debridement with initiation of broad-spectrum antibiotics; multiple debridement's, orchiectomy, urinary diversion and fecal diversion when clinically indicated; 14 patients received HBO as adjuvant therapy	Outcome and mortality rate	Statistically significant difference regarding mortality rate with 7% mortality in the HBO group and 42% in the non-HBO group	This study shows significant improvement combining traditional surgical and antibiotic regimens with HBO
Pizzorno et al. [34]	Retrospective case series	SIGN: 3	11 patients, single institutional with FG and HBO therapy	All patients were treated with antibiotic therapy and HBO; 6 of these patients underwent surgical debridement of the wounds and 3 patients underwent delayed reconstructive surgery	Description of experience with HBO	Results obtained with HBO as an adjunctive measure for the treatment of FG were excellent, the mortality rate was 0%	The authors believe that their findings, although limited in number, underline the excellent results that can be obtained with HBO as an adjunct treatment in FG
Baykal et al. [35]	Case report	SIGN: 3	1 patient	Patient treated with broad-spectrum antibiotic therapy, wound debridement and additional HBO	Description of experience with HBO	Patient survived and on the 15th day it was possible to close the wound with primary sutures	In this patient, the addition of HBO therapy to surgical debridement and antibiotic therapy was successful in preventing further morbidity and possible mortality
Lucca et al. [36]	Case report	SIGN: 3	1 patient	Patient treated with broad-spectrum antibiotic therapy, wound debridement and additional HBO	Description of experience with HBO	Patient survived and was discharged in good condition on the 21st hospital day	Because of the use of HBO limited to this disease entity, the author's department has seen its role expand in the treatment of many hospitalized patients
Ziser et al. [37]	Case report	SIGN: 3	3 patients	Patients treated with broad-spectrum antibiotic therapy, wound debridement, and additional HBO	Description of experience with HBO	All 3 patients recovered from the infection, although 1 died later from renal and pulmonary complications	In the author's opinion, HBO should be started immediately after the diagnosis has been established, together with other modes of therapy. However, conclusive proof of its efficiency requires further documentation and prospective clinical trials
Riegels-Nielsen et al. [38]	Case report	SIGN: 3	5 patients	Patients treated with broad-spectrum antibiotic therapy, wound debridement and additional HBO	Description of experience with HBO	One patient died of septic shock without any response to the therapy, the 4 other patients were cured	It is proposed that the treatment of FG should be limited to centers capable of administering HBO. Evidence suggests a beneficial effect of HBO to FG

SIGN, Scottish Intercollegiate Guidelines Network; FG, Fournier's gangrene; HBO, hyperbaric oxygenation.



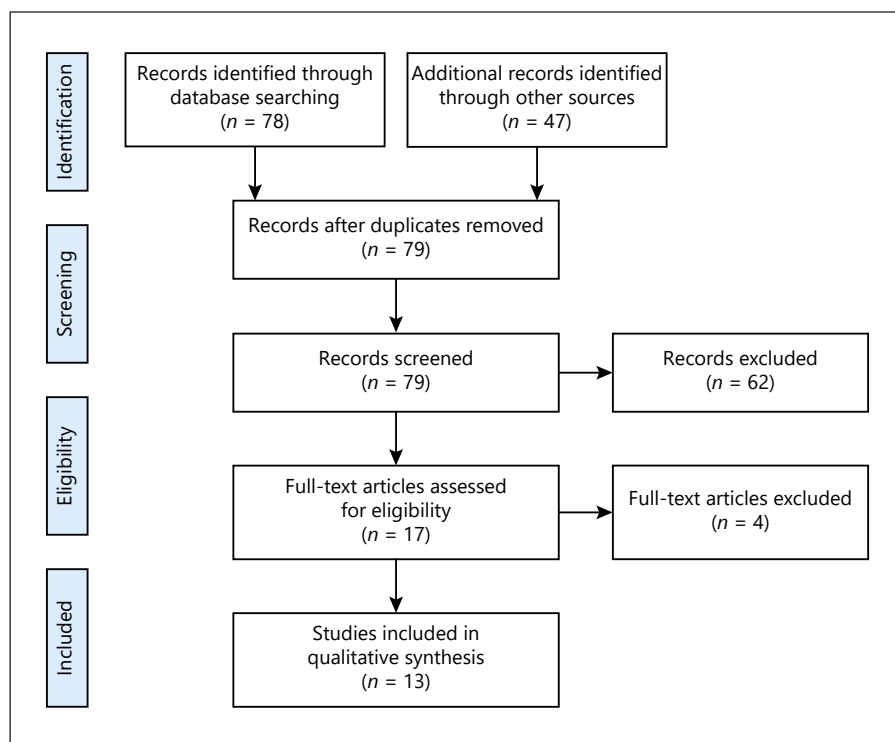


Fig. 2. PRISMA flowchart.

in the HBO group. However, these 5 case-control studies included a total of 319 patients; 145 of these patients were treated with adjunct HBO therapy. Overall, this is leading to a mortality rate of 16.6% in the HBO group and 25.9% in the non-HBO group [20, 21, 28, 31, 33].

Reporting of methodological quality parameters was incomplete in all of the 13 studies. Overall, risk of bias was assessed as moderate to high and the quality of evidence was rated rather low. Table 3 shows the summary of risk of bias assessment using SIGN methodology checklist for each included study.

## Discussion

We conducted a systematic review to compare the treatment of FG with or without the use of HBO as an adjunct therapy. This is a crucial topic since FG is a rare but severe disease with a high mortality rate, and final outcome of FG failed to improve over the last 10 years despite more intensive critical-care therapy [1]. On the whole, we were able to identify 13 retrospective studies for our review. Furthermore, 5 of the included studies had a case control design with a total of 319 patients; 145 of these patients were treated with adjunct HBO [20, 21, 28, 31, 33].

To our knowledge, this is the first systematic review on HBO therapy in FG. Interestingly, a narrative review about this topic was published early in 1986 by Eltorai et al. [39]. The authors concluded that in the exceedingly early stage, HBO may avert gangrene or reduce it. It is important to have a high index of awareness of this disease amongst the medical profession. More work is needed for the more precise definition, classification, and management of the complex syndrome of FG [39]. However, systematic reviews have been published about different entities of necrotizing soft tissue infections, also including FG. The newest 1, published in 2019, by Fauno and Ovesen [40], included 21 studies, of which 19 were case series with a control group. The authors stated that the evidence of HBO therapy in necrotizing soft tissue infection is weak and biased. There is a strong need for RCTs.

Furthermore, we were not able to include 1 study which met our inclusion criteria since there was only an English abstract available, while the full-text article is in Portuguese. Rosa and Guerreiro [41] reported a retrospective case series of 34 patients over the last 25 years in 2015. In the abstract, the following conclusion was stated: Although FG is a rare condition, it is nevertheless a fatal illness, namely, in patients with comorbidities. HBO therapy is recommended as an adjunct to conventional

**Table 2.** Specification of administration of HBO in the included studies ( $n = 13$ )

Reference	Administration of HBO
Creta et al. [28]	No exact specification
Anheuser et al. [20]	No exact specification
Li et al. [21]	After initial debridement, HBO was given twice a day for 5–7 days (2.5 units of absolute atmospheric oxygen, 90–120 min each time, interval for 10 h)
Zagli et al. [29]	HBO therapy (20 min each at 2.4 units of ATA, 100% oxygen, 14 sessions) was started after surgical debridement
Yoshida et al. [30]	No exact specification
Mindrup et al. [23]	No exact specification
Korhonen et al. [32]	After the initial debridement each patient was exposed to pure oxygen at 2.5 ATA for 90–120 min. Two or 3 such treatments were given during the first 24 h after admission. Thereafter, the treatments were continued twice daily. A total of 7–10 treatments was usually sufficient
Hollabaugh et al. [33]	No exact specification
Pizzorno et al. [34]	All patients received HBO (minimum 5 and maximum 24 cycles, consisting of 90 min 2.5 ATA)
Baykal et al. [35]	After initial debridement HBO therapy was given at a pressure of 2.8 ATA for 60 min, a 5-min air break, and then 2.0 ATA for 60 min 3 times a day for the first 3 days. The next 3 days, the patient received HBO at 2.0 ATA for 120 min twice a day, and the last days he received 2.0 ATA for 120 min once a day
Lucca et al. [36]	Immediately after surgical debridement, the patient was treated with 100% oxygen at 2.5 atmospheres of pressure. He was treated twice daily for 2 days, and daily thereafter for a total of 20 treatments
Ziser et al. [37]	After initial surgical debridement, a total of 7 HBO treatments were given, 100% oxygen at a pressure of 2.8 to 3.0 ATA. Total oxygen breathing time was 90 min, corresponding to two 45-min cycles divided by a 5-min air break. Three treatments were given in the first 24 h and 1 every 12 h thereafter
Riegels-Nielsen et al. [38]	No exact specification, but it is said that 3.0 ATA was used

HBO, hyperbaric oxygenation; ATA, absolute atmospheric pressure.

treatment and should be considered whenever available. To further assess the role of HBO therapy in the treatment of this condition, additional studies should be carried out [41]. Still, we identified another interesting study, with a full text only available in Spanish, which included FG patients receiving HBO therapy, but the study focused on the benefit as well as use of FG severity index (FGSI). The author concluded that FGSI score did not predict disease severity and the patient's survival. Metabolic aberrations and extent of disease seemed to be significant risk factors for predicting FG severity and patient's survival [42].

The data of the included studies for this systematic review were very heterogeneous; thus, we were not able to perform a meta-analysis. Most notable are the differences in administering HBO therapy. Several of the included studies did not describe how HBO was administered.

This makes the results difficult to compare, even in a descriptive manner, and raises questions, as follows: When is the right time point to start HBO therapy? Which absolute atmospheric pressure should be used? At the moment, there is no established therapy protocol for HBO in FG patients available. Therefore, further studies are urgently warranted to address these questions. Furthermore, the study populations are very heterogeneous in terms of mortality rate. Interestingly, only 2 studies give a detailed information of how severe the disease has presented prior to inclusion and treatment with HBO including FGSI [21, 28]. Furthermore, there is a moderate to high risk of bias in all included studies, mostly due to the retrospective study design.

The most important result of this systematic review arises from the 5 case-control studies. Overall, this is leading to a mortality rate of 16.6% in the HBO group

**Table 3.** Risk of bias summary of all included studies (SIGN)

Reference	SIGN overall quality	Main reasons for decision
Creta et al. [28]	Acceptable	Selection bias Reporting bias
Anheuser et al. [20]	Acceptable	Selection bias Reporting bias
Li et al. [21]	Acceptable	Selection bias Detection bias
Zagli et al. [29]	Unacceptable	Selection bias Detection bias Reporting bias
Yoshida et al. [30]	Unacceptable	Selection bias Detection bias Reporting bias
Mindrup et al. [23]	Acceptable	Selection bias Reporting bias
Korhonen et al. [32]	Acceptable	Selection bias Reporting bias
Hollabaugh et al. [33]	Acceptable	Selection bias Reporting bias
Pizzorno et al. [34]	Unacceptable	Selection bias Detection bias Reporting bias
Baykal et al. [35]	Unacceptable	Selection bias Detection bias Reporting bias
Lucca et al. [36]	Unacceptable	Selection bias Detection bias Reporting bias
Ziser et al. [37]	Unacceptable	Selection bias Detection bias
Riegels-Nielsen et al. [38]	Unacceptable	Selection bias Detection bias Reporting bias

SIGN, Scottish Intercollegiate Guidelines Network.

and 25.9% in the non-HBO group [20, 21, 28, 31, 33]. All authors of these studies reported a significant lower mortality rate in the HBO group except Mindrup et al. [31]. They discussed their results critically and stated that there was a trend toward higher baseline morbidity in the HBO group, suggesting that treatment may have been given to patients who were more severely ill [31]. Interestingly, Anheuser et al. [20] described that despite

the fact that the HBO treated group was better in terms of mortality, the wound debridement frequency and length of hospitalization were significantly higher in the HBO group. On the whole, these facts suggest that some patients might benefit from adjunct HBO therapy especially in terms of mortality rate, but FG is still a very complex disease, which is sometimes difficult to predict [42]. So, a defined patient group who will benefit from HBO in FG must be identified in further investigations. It is also noteworthy that the results for HBO therapy in FG in this systematic review are slightly better than the results from the review of HBO in other necrotizing soft tissue infections [40]. This might be due to multiple underlying conditions, such as pathogen spectrum and pathogenicity or different wound healing conditions in the various body areas. This might be a hint that necrotizing soft tissue infections are actually a group of diseases and each group should precisely be defined. This will also be problematic with the unpublished registered prospective trial on HBO from Copenhagen University Hospital since all entities of necrotizing soft tissue infections are included.

Even if HBO has potential in FG therapy, not every hospital has fast access to an HBO chamber. Furthermore, there is no established therapy protocol for HBO. Finally, we must assume that this systematic review has limitations, we only included English and German publications, which is a selection bias.

## Conclusions

We conclude that, despite the risk of bias, HBO has the potential as an adjunct in FG treatment, but it is challenging to carry out further studies or even RCTs due to the rareness of this disease, restricted availability of HBO and the complex character of FG. We, therefore, suggest a prospective register trial first to answer some of the primary open questions and then plan a proper RCT to precisely define the role of HBO in FG treatment.

## Statement of Ethics

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. For this type of study, a formal consent was not required.



## Conflict of Interest Statement

All authors declare that they have no conflict of interest regarding this manuscript.

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## Authors Contributions

L.S., P.A., S.S., F.M.E.W., and J.K. participated in the design of the review and critical revision of the article. L.S., P.A., and J.K. participated in data acquisition, data analysis, and drafting of the article.

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