

**THE ROLE OF HYPERBARIC OXYGEN THERAPY IN FOURNIER'S GANGRENE:  
LITERATURE REVIEW**

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## ABSTRACT

**Introduction:** Fournier's Gangrene is a severe necrotising infection that can be fatal if not recognised and treated immediately. Treatment consists of a combination of conventional therapy with a multidisciplinary approach (early diagnosis, surgical debridement, antibiotic therapy, intensive care and reconstructive surgery) and adjuvant therapy with hyperbaric oxygen therapy sessions.

**Objective:** To identify the role and evaluate the efficacy of hyperbaric oxygen therapy in Fournier's gangrene.

**Method:** To conduct the following narrative review a research question was outlined using the PIO methodology. Subsequently, a literature review was conducted using the *PubMed, Scopus and CINAHL Complete databases* from December 2020 to February 2021.

**Results:** Eight studies emerged from the literature review showing that the use of **adjuvant Hyperbaric oxygen therapy (HBOT)** in combination with classical treatment has beneficial effects and enhances the efficacy of hyperbaric oxygen therapy, resulting in lower mortality rates, in contrast to the average number of hospital days spent in intensive care, which do not undergo any significant change. But in contrast to mortality, the average number of days spent in intensive care differed significantly in favour of the standard treatment group.

**Conclusion:** The combined effect of hyperbaric oxygen therapy with conventional therapy offers a significant advantage in the management of FG; furthermore, HBOT is associated with a significant survival advantage.

**Keywords:** *Fournier's gangrene, Fournier's disease, Hyperbaric oxygen therapy and HBOT*

## INTRODUCTION

Necrotising fasciitis, better known as "Fournier's Gangrene" (FG), is a polymicrobial infection caused by aerobic and anaerobic microorganisms acting synergistically to cause severe soft tissue infection (NSTI), targeting the genital, perineal and perianal region [1,2]. The term, coined by the scholar Wilson, first appeared in the scientific world in 1952 [3]. FG is now considered a rare disease [4-6], predominantly affecting males (10 to 1 ratio) with a mean age of 50 years [4,7], with an incidence rate ranging from 0.3 to 15.5 cases per 100000 inhabitants [8,9]. It is associated with high morbidity and mortality between 3% and 67% [4]. FG has a subtle and rapid pathogenesis, so much so that some authors have divided the disease into 4 phases[5]: (i) the initial phase occurs within 24-48 hours and is associated with non-specific symptoms, such as itching, oedema, erythema and partial hardening of the affected tissues; (ii) the second phase is brief and invasive with the presence of local inflammatory manifestations; (iii) the third phase is the necrotic phase in which there is a rapid deterioration, which may evolve into septic shock, with the risk of spreading necrosis to the anterior abdominal wall and thighs; (iv) the fourth phase is one of spontaneous repair which occurs after a few months, during which epithelial regeneration and healing take place [5]. From an aetiological point of view, the bacteria responsible for this infection include group A Streptococcus as the most common monomicrobial culprit [10,11], while Escherichia coli, Bacteroides, Staphylococcus, Proteus, Streptococcus, Pseudomonas and Enterococcus are among the polymicrobial culprits [12,13]. Microorganisms have been found in the urogenital tract and in the digestive tract: the causes of bacterial presence in the urogenital tract are urethral stenosis, scrotal abscesses, orchitis, epididymitis, renal abscess, ureteral trauma, renal calculosis, bladder and penile cancer, prostate biopsy and catheterization [14,15], while the presence of bacteria in the digestive tract is found in outbreaks originating from perianal abscesses, colorectal tumours, appendicitis, acute diverticulitis, Crohn's disease, incarcerated hernias and perforation of the rectum, particularly caused by a foreign body [16,17]. Without treatment, the process may not only

rapidly spread to the abdominal wall, dorsal region, upper limbs and retroperitoneum, but also lead to sepsis, multi-organ failure and death [1,18,19]. Systemic diseases listed as risk factors for the development of FG include: diabetes mellitus, alcoholism, hypertension, obesity, smoking, immune suppressive conditions such as HIV infection, radiotherapy and chemotherapy [4,7,20-23]. In terms of semeiotics, the most frequent manifestations include pain, erythema, oedema and necrosis of the scrotum or the perianal and perineal region, often associated with fever and chills [24-26]. Other symptoms are mostly localised and include the presence of blisters, crackles, cyanosis and malodorous discharge; however, it should be emphasised that the skin manifestations are the 'tip of the iceberg', while the infection spreads rapidly and aggressively along deep fascial planes [27,28]. The FGSI (*Fournier's Gangrene Severity Index*) scale is used to estimate the severity of Fournier's gangrene. It uses 9 parameters: temperature, pulse, respiratory rate, sodium, potassium and creatinine levels, haematocrit, leukocytosis and bicarbonate levels. Each parameter is assigned a score from 0 to 4. A high FGSI score denotes a worse prognosis [29]. Treatment of FG includes management of sepsis according to guidelines (early diagnosis, surgical debridement, antibiotic therapy, intensive care and reconstructive surgery) [30] and hyperbaric oxygen therapy (HBOT) is highly recommended whenever possible [31].

Hyperbaric oxygen therapy is a therapeutic approach that involves the use of 100% pressurised oxygen, which is delivered in an airtight chamber. HBOT has a bactericidal action on anaerobes and reduces the activity of endotoxins in the presence of high oxygen levels. This treatment has provided benefits such as improved neutrophil phagocytic action, fibroblast proliferation and angiogenesis, reduced oedema, absence of free radicals and increased intracellular transport of antibiotics [32,33]. Adverse effects associated with this treatment approach are relatively rare, but there are not enough studies that have investigated the role of HBOT in FG [34,35]. Among the few studies presented in literature, adverse events include barotrauma of the tympanic membrane and paranasal sinuses, the possibility of sudden onset of epileptic seizures and pulmonary and central

nervous system toxicity caused by oxygen[36]. However, the use of hyperbaric oxygen therapy in the management of FG is widely discussed, sometimes even controversially, because clinical evidence regarding HBOT in these infections is scarce and of generally low quality and, moreover, the use of hyperbaric oxygen therapy is not standard of care in many centres, so much so that some authors recommend HBOT as an adjuvant treatment [37], while others do not recommend it as routine use in the management of FG [38]. This literature review aims to investigate the role that HBOT plays in Fournier's gangrene, its effectiveness and influence on some variables. Some studies show that HBOT reduces the extent of necrosis, mortality, morbidity rates [39,40] and the need for further surgery [41]. The strength of this review is to highlight that, although oxygen therapy is a second-line treatment, in all the studies reported in this review, it still plays a decisive role in the treatment of Fournier's gangrene, as it allows *restitutio ad integrum*.

### Objective of the study

Identify the role and evaluate the effectiveness of hyperbaric oxygen therapy in Fournier's gangrene.

## MATERIALS AND METHODS

### Study design

A narrative review of the literature was conducted using an evidence method. To conduct the review, a research question was outlined using the Population, Intervention, Outcome (PIO) methodology. The PIO specifies the population to be studied, the intervention to be implemented and the outcomes (Table 1).

<b>Population (P)</b>	Adult patients with FG
<b>Intervention (I)</b>	Hyperbaric oxygen therapy
<b>Outcome (O)</b>	Management/resolution of FG

**Table 1.** Question according to the PIO method. *FG= Fournier's gangrene*

## Research strategy

The research of the articles was carried out through the following databases *PubMed*, *Scopus* and *CINAHL Complete* in the time period from December 2020 to February 2021.

The following keywords were used:

*"Fournier's Gangrene"*, *"Fournier's Disease"*, *"Gangrena de Fournier"*, *"Hyperbaric Oxygen Therapy"*, *"hbot"*, *"hyperbaric oxygen"* and *"oxygen therapy"*.

For each MeSH *term*, the respective synonyms have been identified in each database. Next, advanced search terms were set up, using the Boolean operators 'OR' and 'AND' to cross terms in different combinations and make the search more specific. The only limit included is the date of publication: only articles published within the last 10 years were taken into account.

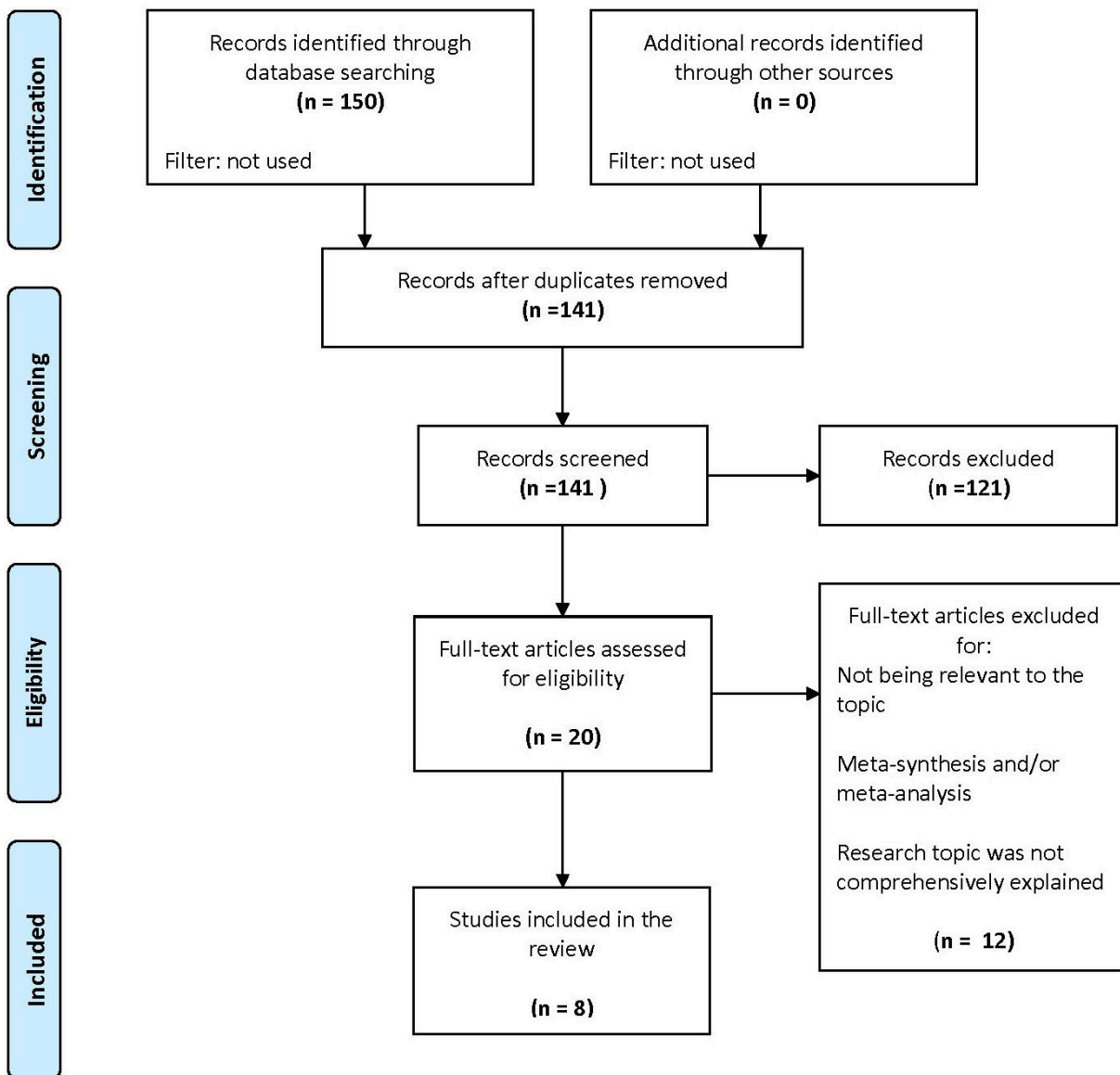
The formulation of the *keywords* and *MeSH* terms was carried out jointly by the two authors in order to comply with validity criteria and reduce search *bias* . Similarly, the authors also collaborated in the retrieval of articles and *full-texts* and their respective evaluations, to identify *reports* relevant to the research topic. The search terms are shown in Table 2.

Database	Term	Limits	Results
<b>PUBMED</b>	(( <i>"Fournier's Gangrene"</i> [All Fields] OR <i>"Fournier's Disease"</i> [All Fields]) AND <i>"Hyperbaric Oxygen Therapy"</i> [All Fields]) AND (y_10 [Filter])	Publication date: Last 10 years	27
<b>SCOPUS</b>	<i>"Fournier's Gangrene"</i> OR <i>"Fournier's Disease"</i> AND <i>"Hyperbaric Oxygen Therapy"</i> )	Publication date: 2012-2021	107
<b>CINAHL Complete</b>	gangrena de fournier OR fournier's gangrene AND (hbot or hyperbaric oxygen) AND oxygen therapy	Publication date: 2011-2021	16

**Table 2.** Search terms

**Inclusion and exclusion criteria**

The following criteria were set for the search. We included (a) primary studies; (b) studies carried out on the adult population of both sexes; (c) studies published in the past 10 years. We excluded: (A) secondary studies; (b) editor's reviews and / or letters to the editor; (c) studies with subjects under the age of 18; (d) studies in which the role of hyperbaric oxygen therapy was not fully exposed. The detailed procedure used in the selection of articles is presented below in the form of a flow chart shown in Figure 1.



**Figure 1.** PRISMA Flow Diagram of the literature review

Our search strategy yielded a total of 150 preliminary stage articles (27 on Pubmed ,107 on Scopus and 16 on CINAHL *Complete*). 9 duplicate articles were excluded. The remaining 141 were assessed by title and *abstract*, 121 were discarded because they were not relevant to the objective or inconsistent with the inclusion criteria. Of the 20 remaining articles, after reading the *full-text*, 12 records were discarded as they were secondary studies or not relevant to the research question. 8 articles were included in the review after a full evaluation of the text. The two authors independently conducted the literature review and no discrepancies emerged between the evaluators.

## RESULTS

Eight studies relevant to our question emerged and Table 3 summarises their characteristics and results. Fournier's Gangrene is a severe necrotising infection that can be fatal if not detected and treated immediately. Treatment consists of a combination of conventional therapy with a multidisciplinary approach (early diagnosis, *surgical* debridement, antibiotic therapy, intensive care and reconstructive surgery) and adjuvant therapy with hyperbaric oxygen therapy sessions. This is confirmed in the articles that follow. A retrospective study [42] has shown that the use of adjuvant HBOT, in combination with classic treatment is associated with reduced mortality: this percentage was lower in the group treated with HBOT than in the control group treated with the standard approach ( 3.7% vs 28.8%). This finding is further confirmed in other studies [43,44]: in the retrospective, multicentre observational study by Anheusera et al. [44], mortality in patients treated with HBOT was 0% vs. 4.4% mortality for patients not receiving adjuvant treatment. In the latter study, as opposed to mortality, a variable on which it is important to pay attention was the average days spent in intensive care, which differed significantly in favour of the standard treatment group. In fact, the *frequency* of wound debridement and hospital stay were significantly higher in the hyperbaric oxygen therapy group (13 vs 5 debridements and 40 vs 22 days). However, the latter



contrasts with a retrospective, multicentre study present in the literature [45], in which the variables of length of hospital stay, direct costs of hospital stay, complications and mortality in the three FG classes (minor, moderate and major), regardless of treatment, were not significantly different. In contrast, subjects receiving adjuvant therapy with HBOT had a lower rate of complications (45% vs. 66%) and deaths (4% vs. 23). In a retrospective analysis of 60 patients, first treated with broad-spectrum antibiotics and then undergoing surgery within 24 hours of admission, it was observed that fasciotomy alone was an insufficient treatment and that in many patients debridement was necessary (average of 3.1 *debridements*), combined with early diagnosis, intensive care and in some cases colostomy, with the addition of hyperbaric oxygen therapy sessions, which demonstrated an increase in survival [46]. In this study, 12 patients were treated with HBOT, with a survival rate of 100% (12/12 patients), compared to 66.7% (32/48) of patients who did not undergo HBOT. In addition, hyperbaric oxygen therapy, as shown in Chao et al's case-control study [29] of 28 subjects, reduces infection rates and improves prognosis, although the most effective method for FG remains surgical treatment. However, due to the depth of the retroperitoneal space, the presence of large cavities and soft tissue, the lesions are diffuse and it is often difficult to completely debride the *necrotic* tissue during surgery. Therefore in such conditions, hyperbaric oxygen therapy used as an adjunct to standard therapy can reduce debridement sessions and times, shorten the length of drainage tube use, reduce healing time and improve the prognosis process of FG. In this study, as in previous studies, the experimental group had a lower mortality rate than the non-HBOT control group (12.5% vs. 33.3%). These findings are supported by two studies: a retrospective and descriptive study conducted by accessing the medical records of 34 FG patients who underwent HBOT from 1989 to 2014 [47] and a single-center, case-control study involving 341 subjects, which described the potential benefits of HBOT in FG from a pathophysiological perspective (inflammation, modulation of reperfusion injury and facilitation of wound healing), with respective reduction in mortality [48].

AUTHORS	TITLE	YEAR	REVIEW	TYPE OF STUDY	SAMPLE	METHOD	RESULTS	CONCLUSIONS
Feres O, Feitosa MR, from Rocha J, Miranda J., Santos L., Feres Ac et al.	Hyperbaric oxygen therapy decreases mortality due to Fournier's gangrene: a retrospective comparative study	2021	Medical Gas Research	Retrospective Study	n=197 (control group: n = 118; experimental group: n = 79)	Variables were extracted from a database containing medical records.  (sociodemographic characteristics and clinical data such as: number of HBOT, comorbidities, anatomical classification of FG, photographic documentation of gangrene and 30-day mortality). The patients, all operated on by the same surgical team, were divided into the experimental group (undergoing HBOT) and the control group.	In the control group, 34 out of 118 patients (28.8%) died, whereas in the experimental group, 3 out of 77 patients (3.7%) died ( $P < 0.001$ ).	The use of adjuvant HBOT in combination with traditional treatment is associated with reduced mortality.
Anheusera P, Mühlstädt S, Kranz J, Schneidewind L,	Significance of Hyperbaric Oxygenation in the	2018	Urology International	Observational-retrospective-multicent	n = 62 (control group (A): n = 45;	Sociodemographic and clinical variables	ICU treatment was reported in 69% of	HBOT has a positive influence on the treatment of Fournier's Gangrene: in fact

Steffens J, Fornarab P.	Treatment of Fournier's Gangrene: A Comparative Study			er study	experimental group (B): n = 17)	<p>were taken and analysed using medical records. experimental.</p> <p>The patients, all operated on by the same surgical team, were divided into the experimental group (undergoing HBOT) and the control group.</p>	<p>patients in group A and 100% of patients in group B, with a mean ICU stay of 9 and 32 days for patients in groups A and B, respectively. The frequency of wound debridement and hospital stay were significantly higher in group B (13 vs 5 debridement and 40 vs 22 days). Mortality was 0% in group B and 4.4% in group A.</p>	it reduces mortality to 0%.
Chao L, Xu Z, Long-Fei L, Fan Q, Jin-Bo C, Xiong-Bing Z.	Hyperbaric Oxygen Therapy as an Adjuvant Therapy for Comprehensive Treatment of Fournier's Gangrene	2015	Urology International	Retrospective Studies	n=28 (control group: n = 12; experimental group: n = 16)	<p>The records of 28 FG patients were reviewed and the following variables were analysed: age, Fournier's Gangrene Severity Index number (FGSI), number of surgical debridements, drainage</p>	<p>The mortality rate was lower in the HBOT group at 12.5% (2/16) than in the non-HBOT group, which was 33.3% (4/12). The difference in the number of surgical debridements, drainage stay and cure time</p>	The combined effect of hyperbaric oxygen therapy with conventional therapy offers significant advantages in the management of Fournier's gangrene.

						tube permanenc e, length of stay with actual time and curative time.	were significantl y lower in the HBOT group than in the non-HBOT group.	
Rosa I, Guerriero F.	Hyperbaric Oxygen Therapy for the Treatment of Fournier's Gangrene: A Review of 34 Cases	2015	Scientific Review by Ordem dos Médicos	Retrospe ctive and descripti ve study	34 cases of patients with FG treated with HBOT	Medical records of patients with FG and treated with HBOT were analysed, taking into account social and clinical variables (aetiology, comorbidity, aggressive surgical debridement, microbiology, antibiotic therapy, number of HBOT sessions and <i>outcomes</i> ).	The mortality rate was 20.8%.	Oxygen therapy is recommended as an adjuvant to standard treatment. It reduces mortality.
Devaney B, Frawley G, Frawley L, Pilcher D.V.	Necrotising soft tissue infections: the effect of hyperbaric oxygen on mortality	2015	Anaesthesia Intensive Care	Single-center, retrospec tive and case-controlle d study	n = 341 (experimental group = 275; non-experimental group = 66)	The research was carried out by extracting data from a database, from 2002 to 2014, establishing the variables to be included in the study and dividing the sample into experiment	Mortality was 14.4% overall, 12% in those treated with HBOT and 24.3% in those not treated with HBOT. ICU support was required in 248 (72.7%) patients.	Mortality is related to disease severity and onset. However, when the FG severity score decreased and the need for ICU was predominant, HBOT was associated with significantly reduced mortality.

						al (subjected to HBOT) and control group.		
Shaw JJ, Psoinos C, Emhoff TA, Shah SA, Santry HP.	Not Just Full of Hot Air: Hyperbaric Oxygen Therapy Increases Survival in Cases of Necrotisin g Soft Tissue Infections	2014	Surgical Infections	Retrospe ctive and multicent er study	n = 14	The University Health Consortiu m (UHC) database containing data collected from 2008 to 2010 of patients with FG who underwent HBOT in specific centres equipped with the HBOT device was used.	The HBOT group had fewer complicati ons (45% versus 66%; p < 0.01) and fewer deaths (4% versus 23%; p < 0.01) than the standard treatment group. In addition, patients who did not receive HBOT were less likely to survive.	Patients undergoing HBOT showed a significant benefit in terms of both reduced complications and survival.
Hung MC, Chou CL, Cheng LC, Ho H, Niu KC, Chen HL et al.	The role of hyperbaric oxygen therapy in treating extensive Fournier's gangrene	2016	Urological Science	Retrospe ctive Study	n=60	From January 2007 to December 2012, data was collected from patients suffering from FG and being treated at Chi Mei Medical. Their medical records were reviewed and analysed.	Patients with septic shock who received HBOT had higher survival rates than patients who did not undergo HBOT [7/7 (100%) versus 4/18 (22.22%).	Adjuvant HBO therapy led to higher survival rates.
Mehl AA, Filho DC, Mantovani LM, Grippa MM, Berger	Managem ent of Fournier's gangrene: experience	2010	Journal of the Brazi lian Colle	Retrospe ctive Study	n = 40 (experimenta l group: 26; control group: 14)	The medical records of patients treated at	The overall mortality found in our study was 20%,	Early recognition of infection combined with invasive and aggressive

R, Krauss D, Ribas D	of a university hospital of Curitiba		ge of Surge ons		Cajuru University Hospital - PUC/PR with a diagnosis of FG were analysed and studied between 1998 and 2006. The diagnosis was established on the basis of the physical examination and clinical history (predisposing factors, aetiology, location of the lesion, laboratory and imaging tests, surgical procedures , antibiotics, use (or not) of a hyperbaric therapy protocol and length of hospital stay). Two groups were then extrapolated: patients receiving standard treatment and patients receiving oxygen therapy treatment.	which corresponds to the rates found in the literature. Patients who combined hyperbaric therapy with clinical and surgical treatment had a mortality rate of 11.5% and for those who underwent only medical and surgical treatment the rate was 37.5%.	treatment is essential to attempt to reduce these prognostic indicators. Broad- spectrum antibiotic regimens have been shown to be most appropriate in conjunction with extensive <i>debridement</i> . Patients undergoing HBOT had a proportionately lower mortality rate than those who did not.
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**Table 3.** Analysis of the studies included within the review.

## DISCUSSION

The aim of the review was to identify the role and assess the effectiveness of hyperbaric oxygen therapy in Fournier's Gangrene. From the studies analysed, it is clear that the primary treatment of Fournier's Gangrene uses a multidisciplinary approach based on conventional therapy (early diagnosis, surgical *debridement*, antibiotic therapy, intensive care and reconstructive surgery). In recent years, hyperbaric oxygen therapy has shown to have an adjuvant role in the treatment of FG, but at the same time a decisive one, as it has allowed a return *ad integrum* with or without surgery. In fact, due to the depth of the retroperitoneal space, the large cavities and non-linear tissue, and the diffuse lesions, it is often difficult to define and carry out a complete *debridement* of the necrotic tissue during surgery, so that tissue hypoxia and infection factors interact and in the post-operative period, poor drainage or the onset of other factors favour the spread of the disease. Therefore it becomes necessary in such conditions, to find an adjuvant therapy that can reduce the infection rates and improve the prognosis. HBOT acts as a bactericide and/or bacteriostatic against anaerobic bacteria by increasing the formation of oxygen free radicals and restores the bactericidal capacity of leukocytes in hypoxic wounds by increasing tissue oxygen tension; in addition, HBOT interacts synergistically with several antibiotics to enhance their effect and thus reduce complications that may occur. Oxygen therapy is commonly started as soon as patients are stabilised (after initial *debridement*) and continued until the wound is completely healed. HBOT as an adjunctive therapy may reduce *debridement* sessions and drainage tube time *in situ*; but the efficacy of hyperbaric oxygen therapy is demonstrated by the exponential decrease in mortality rates reported in all studies, even in those patients where FG is associated with critical situations such as septic shock. It is not possible, however, to conclude that HBOT has a real positive influence on the reduction of average days of hospitalisation and treatment in intensive care units and consequently on health care expenditure, as the studies in the literature are conflicting. In fact, although HBOT has potential in FG therapy, not all hospitals have or can allow the patient rapid access to hyperbaric chambers and

the degree of critical illness accompanying gangrene often precludes access to oxygen therapy. Moreover, there is no established treatment protocol for HBOT and given the rarity of FG cases, it is often very difficult to carry out studies, which is why the role of hyperbaric oxygen therapy is much discussed and, at the same time, a matter of controversy. It must be said that there has not been enough studies carried out in the literature to introduce this type of therapy as a first-line treatment in the clinical routine, but only as a second-line treatment, supporting standard therapy (early diagnosis, surgical debridement, antibiotic therapy, intensive care and reconstructive surgery).

## **CONCLUSION**

The results in the literature review suggest that the combined effect of hyperbaric oxygen therapy with conventional therapy offers a significant advantage in the management of FG and that HBOT is associated with a significant survival benefit. Multicentre studies with a larger sample size are needed to confirm these observations, but are difficult to conduct due to the rarity of FG and the limited availability of HBOT in some centres. With a better understanding of the disease and treatment experience, the management of FG could see significant developments in the future.

## **ABBREVIATIONS**

FG (*Fournier's gangrene*)

FGSI (*Fournier's Gangrene Severity Index*)

HBOT (*Hyperbaric oxygen therapy*)

ICU (*Intensive Care Unit*)

PIO (*Population, Intervention, Outcome*)

## **Conflicts of interest**



The authors state that they have no conflicts of interest associated with this literature review.

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