ANAEROBIC SOFT TISSUE INFECTIONS

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Introduction

Anaerobic soft tissue infections are a group of soft tissue infections in which the primarily infected tissue is either the muscle, fascia or subcutaneous tissue. This type of infection involves necrosis with a swift rate of development, causing major tissue damage and often endangering the patient's life (1,2). Even though at the onset the infection can be distinguished by the tissue involved, the infectious process spreading swiftly to other tissues makes identifying them quite impossible after some days or even hours. That is why they are often referred to under the general term of necrotizing soft tissue infections (NSTI). These infections can also develop in a wide range of anatomical sites with each their specificities (3,4). Clinical presentations depend on the extent of tissue injury, the virulence of the microorganisms responsible and patient risk factors (especially vascular). In all these clinical situations, hypoxia appears to cause the development and extension of necrosis.

Clinical presentation

Gas gangrene (*Clostridium* myonecrosis) is an anaerobic infection starting within muscle tissue, caused by anaerobic spore-forming bacteria from the *Clostridium* species, with *Clostridium perfringens* found in about 90% of cultures. *Clostridium* spores may be found everywhere in the environment and are a major source of contamination in open traumatic wounds. *Clostridium* bacteria produce a large number of exotoxins, the alpha-toxin being the most lethal through its hemolytic and tissue necrotizing effects leading to extensive tissue necrosis and severe shock.

Necrotizing fasciitis is another acute, life-threatening infection starting within the superficial and deep skin fascia. Because infection with necrosis spreads within the deep fascia under the skin, it is not unusual for few or no cutaneous signs to be seen at the onset of the infection. Microbiologically, necrotizing fasciitis has been subdivided into Type 1, polymicrobial and Type 2, caused by beta-hemolytic streptococci groups A, C, or G (Type 3, caused by marine organisms such as *vibrio vulnificus* is unusual in Europe). Tissue hypoxia caused by the infectious process is quite specific to these infections. For instance, it has been shown that the rapid destruction of tissue with group A beta-hemolytic *streptococcus* is the result of toxin-induced ischemia caused by the co-aggregation of platelets and neutrophils initiated by platelet P-selectin. This forms a complex that can impede blood flow and cause vascular occlusion (5).

The culture of deep tissue recovered during the first debridement procedure is essential. In many cases, the infection is polymicrobial, with frequently isolated enterobacteria and anaerobes. The usual organisms isolated include: enterobacteria, *Bacteroides* species and *Peptococcus*. Some *Candida* species have also been reported (6), and fungal cultures are particularly important in diabetics and immunocompromised patients who do not respond to conventional antibiotics. Necrotizing fasciitis may also be caused by strains of community-acquired methicillin-resistant *Staphylococcus aureus* (MRSA) alone or combined with anaerobic *streptococci* (Meleney's synergetic gangrene) (7).

The risk factors for NSTI are traumatic lesions of the skin or mucosa (lacerations, insect bites, burns, deep abrasions, puncture wounds, or after surgery, especially involving perforations of the intestine). Diabetes seems to be a significant risk factor, as are obesity, alcoholism, smoking and the abuse of intravenous drugs. The use of non-steroidal anti-inflammatory drugs has also been suggested as a risk factor (8).

The most common sites of NSTI are the lower limbs, while an increase in the incidence in the upper extremities occurs where drug addiction is involved. However, any part of the body can be affected, including the abdominal wall of newborns, combined with omphalitis. The involvement of submandibular and cervical spaces also known as Ludwig angina is a frequent complication of dental or pharyngeal infections and may spread within 24 to 48 hours to the mediastinum with pericardial, pleural or lung involvement. The involvement of the scrotum and perineum in humans is termed Fournier(’s) gangrene, which is essentially a necrotizing fasciitis of the superficial perineal fascia. This can spread the infection to the penis and scrotum and to the abdominal wall. Perianal or perirectal infection can also spread in these areas and undrained or poorly drained perirectal abscesses are often quoted as a source of Fournier’s gangrene. Perineal necrotizing fasciitis may also occur in women and can be seen after inadequate drainage of Bartholin abscesses. Diabetes mellitus remains an important risk factor in this particular form of necrotizing fasciitis. Thus Fournier’s gangrene is more likely to be polymicrobial, with the frequent involvement of enterobacteria, group D *streptococcus,* and anaerobes such as *Bacteroides fragilis*.

Patients with NSTI undergo pain, swelling, which may or may not be accompanied by fever. They may already show local signs of cellulitis or very few skin changes. Over time, however, the infection will spread quickly, causing the development of bullae, with areas of necrosis.

The clinical classification of NSTI is easy at the beginning of the infection, when the anatomical depth levels (skin, superficial or deep fascia, or muscles) can still easily be assessed by exploration, biopsy or radiological examination. However, as the infection develops, it becomes increasingly difficult to determine which clinical entity is at stake, especially when necrosis extends from muscle through skin, fat and fascia or vice versa.

Soft tissue biopsy at an early stage of infection can establish a definite diagnosis (9). Computed tomography (CT) or MRI may help to make a diagnosis and assess the extent of lesions. Gas along the fascia planes is observed in 55% of cases without reaching the muscles nor being combined with the development of abscesses (10). However, in a study of 15 patients, MRI overestimated the fascia involvement (11).

Differential diagnosis includes other disorders of soft tissues such as Lyell syndrome or staphylococcal skin syndrome (also known as Ritter's disease, caused by exfoliative toxins produced by *staphylococci*, more usual for under-five-year-olds).

Tissue necrosis is generally combined with fulminating generalized toxicity, which can lead to shock with multi-organ failure. Where the condition is not swiftly diagnosed and handled with immediate aggressive management, it often proves quickly fatal (2). When treated, fatality rates between 10% and 70% are shown, with little evidence of any great improvement over the last forty years.

Standard management and outcome (HBOT excluded)

The key element of therapy is immediate surgical debridement of all dead tissue. It has been shown that delay to the first surgical debridement is linked with higher mortality (12–14). The initial debridement procedure is often followed by several others, since it is difficult for physicians to make a proper assessment of the delimitation between infected and normal tissues during surgery. Surgery should be combined with swift antibiotic and intensive care.

Even with early and aggressive surgery, mortality rates range from 30% to 40%. Amputation rates range from 26% to 50% in lower limb NSTI without HBOT. Mortality is often linked with late diagnosis, and / or underlying immunosuppression.

Rationale for the use of HBOT

Pathophysiology

The initial event in the onset of NSTI is bacteria inoculation in the tissue which may appear "spontaneous" or a result of trauma or surgery. Swift bacterial growth is followed by massive tissue infiltration by neutrophils. Secondarily, toxin activated coagulation and tissue oedema lead to thrombosis of all the supply microcirculation and induce tissue ischemia and gangrene. Once the infectious process has begun, the metabolic products of aerobic and anaerobic metabolisms tend to lower the redox potential (Eh) leading to a drop in pH creating a favorable environment for the development of anaerobic organisms. In addition, the hypoxia induced by the microcirculation thrombosis impairs phagocytosis by polymorphonuclear leukocytes (15). Local hypoxia leads to an activation of endothelial adhesion molecules, resulting in the adhesion of leukocytes and endothelial cytotoxicity. Leukocytes can be trapped in the vessels with consequent damage to the local immunity and incomplete oxidizing of the substrates, leading to an accumulation of methane and hydrogen in tissues. Tissue necrosis occurs with purulent discharge and gas production. Quantities of gas in tissues frequently occur with conditions such as gas gangrene, necrotizing cellulitis and necrotizing fasciitis.

Providing oxygen at high partial pressures has been advocated as additional treatment for handling NSTI. HBO increases PtO2 in NSTI in order to save critical ischemic areas (16). In infections caused by anaerobic and facultative organisms, a sufficiently high level of PtO2 provides a bacteriostatic or bactericidal effect, increasing the bacteria's vulnerability. For instance, oxygen at 3 ATA proves bactericidal against *Clostridium perfringens*. Of perhaps even greater relevance is that spore germination and toxin development are inhibited by exposure to HBO at 2 ATA for short periods.

There are a number of key situations in which oxygen plays an important role in limiting tissue destruction. Leukocytes are involved in the removal of wound remains (including bacteria). Most of these functions are highly sensitive to oxygen. Phagocytosis involves the consumption of oxygen (15). The improvement in the physiological range of oxygenation significantly improves the effectiveness of phagocytosis (16). In the healing process, low PtO2 levels inhibit fibroblast migration and collagen production. HBO has also been shown to stimulate neo-angiogenesis.

Preventing leukocyte activation ultimately reduces the damage associated with ischemia-reperfusion and the subsequent peroxidation of lipids. Indeed, the basic mechanisms of HBOT seem to involve a complex balance between the generation of reactive oxygen species and the upregulation of antioxidant defences (17). Despite reduced leukocyte adhesion, there is experimental evidence that HBOT does cause immune deficiency. HBOT does not reduce the viability of neutrophil functions such as degranulation or phagocytosis (17), and some sepsis models suggest that HBOT provides positive effects (18, 19).

In addition, hyperoxia potentiates the efficiency of antibiotics, improves that of the white blood cells, and reduces inflammation (15,20–22). In cases where the antibiotic used requires oxygen for transport through the bacteria walls, HBO enhances the antibiotic's penetration in the bacteria targetted. This has been shown for aminoglycosides and *Pseudomonas* (23).

Evidence – based review of the use of HBO

Animal study

In 1973, an experimental model of *Clostridium* myonecrosis was established by inoculation in the hind legs of traumatized dogs. Dogs were treated with various combinations of surgery, antibiotics and HBOT. Combination therapy using all three modalities clearly proved to be the most effective strategy (25). Other animal models have suggested similar success of combination therapies including HBOT (26,27) and whereas others did not (28).

Clinical studies

Many studies have demonstrated the beneficial effects of HBOT in the management of necrotizing fasciitis.

Gozal et al. treated necrotizing fasciitis with antibiotics, surgical excision and HBOT and reduced their historical mortality rate from 38% to 12.5% (29). Of the 29 patients retrospectively reported in two historical cohorts by Riseman et al., 12 were treated by debridement surgery and antibiotics before this center were able to provide HBOT, and 17 later by debridement surgery, antibiotics and HBOT. Both groups were similar. However, perineal localization (53% vs 12%) and septic shock (29% against 8%) were more frequently involved for patients in the group treated with HBO, combined with a lower mortality rate (23% vs. 66%) and less repeat surgery (30). Some retrospective cohort studies have shown a significant decrease in mortality rates where HBOT is combined with other forms of therapy (30–33), a significant decrease in amputations (34), while others report no change in mortality (35) as in the study of Massey et al. (36). But in this last study, groups of patients showed widely differing NSTI etiologies. The 32 subjects provided with HBOT were patients with infections of the perineum (19 patients i.e. 59%), no cases involving the upper extremities were included. On the other hand, for patients not provided with HBOT (48), 7 (15%) involved the upper extremities and only 11 (23%) involved the perineum (36). A much larger retrospective analysis from 1988 to 2009 was reported by Soh et al., this study included about 45,913 patients with NSTI (37). 405 patients were given HBOT. Patients with NSTI who were provided with HBOT showed significantly lower mortality rates (4.45% vs 9.4%, $p = 0.001$) than those who were not (37). A recent and large cohort study in 1,583 patients with NSTI shows a life-saving effect of HBOT for the patients whose conditions were the worst (38).

In the literature, Fournier's gangrene cases are usually studied and presented as a separate group. Hollabaugh et al. reported a retrospective study of 26 cases (31). All patients were treated with surgical debridement and antibiotics. 14 of the 26 were also given HBOT. The group treated with HBOT showed a mortality rate of 7% against 42% within the group where HBOT was not provided ($p = 0.04$) (31). In Dahm et al.'s study involving around 50 consecutive patients (1984-1998), the three items which showed a statistical link with outcome were : the extent of the infection (< or > 3%), depth of necrotizing infection and HBOT (39).

Current protocol

HBOT is always used combined with surgery and antibiotics. Precise details of dosages for HBOT vary between studies, but most involve HBOT sessions of 60 to 90 minutes of exposure to oxygen at 2.5 or 3 ATA, repeated 2-3 times a day on the first day, then twice a day over the next days. The various centers keep providing HBOT for a period of 5 to 7 days or until wounds are healed.

Cost impact

The adjunctive use of HBOT is thought to reduce the number of surgical procedures and amputations required to control infection. However, as patients undergoing amputation may be discharged earlier than patients undergoing limb salvage with flaps after the infection has been controlled, this could actually generate additional costs and procedures in the rehabilitation phase of recovery. Further studies analyzing indirect costs such as those generated by amputation are required.

Conclusion

We strongly recommend the use of HBO for the treatment of NSTI, particularly perineal gangrene. (Type 1 recommendation; Level C evidence)

HBOT must be integrated into a treatment protocol combining immediate and adequate surgery and antibiotics targeting the anaerobic and aerobic bacteria most likely to be involved.

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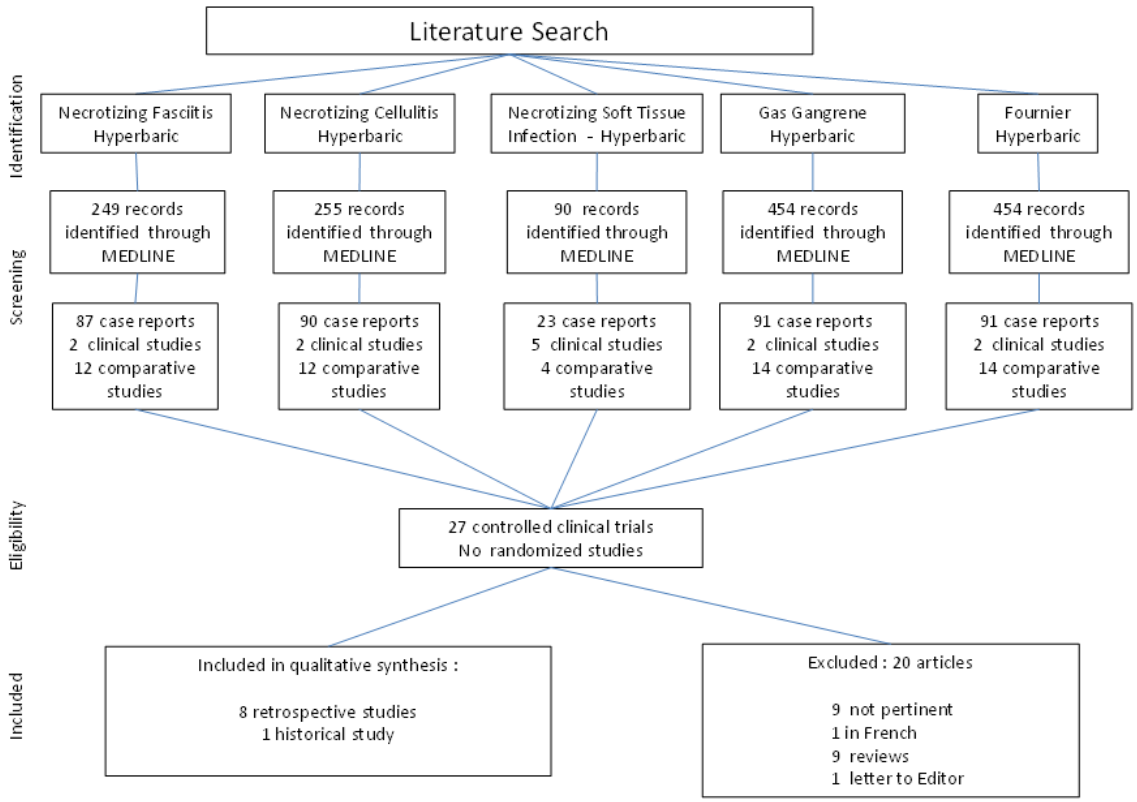
Literature Search
Identification
Necrotizing Fasciitis Hyperbaric
Necrotizing Cellulitis Hyperbaric
Necrotizing Soft Tissue Infection - Hyperbaric
Gas Gangrene Hyperbaric
Fournier Hyperbaric
Screening
249 records identified through MEDLINE
255 records identified through MEDLINE
90 records identified through MEDLINE
454 records identified through MEDLINE
454 records identified through MEDLINE
87 case reports
2 clinical studies
12 comparative studies
90 case reports
2 clinical studies
12 comparative studies
23 case reports
5 clinical studies
4 comparative studies
91 case reports
2 clinical studies
14 comparative studies
91 case reports
2 clinical studies
14 comparative studies
Eligibility
27 controlled clinical trials
No randomized studies
Included
Included in qualitative synthesis :
8 retrospective studies
1 historical study
Excluded : 20 articles
9 not pertinent
1 in French
9 reviews
1 letter to Editor

Study (authors, year)	Type	Nb of patients	Aim(s) / Evaluation criteria	HBOT protocol (pressure, duration, nb of sessions)	Results	Conclusion / Ccomment
Wilkinson, 1960	Retrospective cohort study	44	Mortality	2.8 ATA 60 mn	HBOT improved ICU outcome (*P* = .02), long-term outcome (*P* = .002) and reduced the incidence of amputation (*P* = .05)	In favour of HBOT
Brown, 1994	Retrospective analysis	54	Length of hospital stay, ICU stay, or duration of antibiotic therapy, Mortality	2.5 to 3.0 ATA 90 mn	No differences in length of hospital stay, in ICU stay, nor in duration of antibiotic therapy. Mortality rates were 9/30 (30%) in the HBOT group versus 10/24 (42%) (NS) in the non-HBOT group	NS : Few HBOT sessions
Shupak, 1995	Retrospective analysis	37	Length of hospital stay, Number of surgical debridement procedures, Mortality	?	No differences in mortality (36% in HBO group versus 25%) nor in length of hospitalization for survivors. A difference was shown regarding the number of surgical debridement procedures required per patient (3.3 in HBOT group versus 1.5)	NS
Hollabaugh, 1998	Retrospective study	26	Mortality		The group treated with HBOT showed a mortality rate of 7% against 42% for the group without HBOT (p = 0.04)	In favour of HBOT
Dahm, 2000	Retrospective study	50	Mortality	2.5 to 3 ATA 90 mn	One of three predictors of outcome identified was HBOT (P= 0.0115)	In favour of HBOT
Escobar, 2005	Retrospective analysis	42	Amputation		HBOT reduced mortality (34% v. 11.9%) and morbidity (amputations : 50% v. 0%)	In favour of HBOT
Massey, 2012	Retrospective analysis	80	Mortality, Amputation	2.8 ATA 45 mn	No decrease in mortality nor amputation rates with HBOT	NS : Groups not similar
Soh, 2012	Retrospective analysis	45 913	Mortality	?	Patients given HBOT showed a lower mortality rate (4.5 vs. 9.4 %, p = 0.001)	In favour of HBOT
Shaw, 2014	Cohort study	1 583	Hospital length of stay, Complications, Mortality	?	For severe NSTI the HBOT group showed fewer complications (45% vs. 66%; p < 0.01) and fewer deaths (4% vs. 23%; p < 0.01)	In favour of HBOT for severe NSTI