Die Hyperbare Sauerstofftherapie

Adjuvant zur Behandlung von

Nekrotisierender Fasciitis

Fournier Gangrän

in den Druckkammerzentren

des VDD e.V.

Verband Deutscher
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Zusammenstellung von Informationen

für Ärzte

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Zusammenfassende Beurteilung

Mit der Verfügbarkeit der hyperbaren Sauerstoffbehandlung sollte das sonst übliche therapeutische Vorgehen bei nekrotisierender Fasciitis dahingehend umgestellt werden, dass möglichst neben Antibiose, Intensivmedizin, chirurgischen Maßnahmen die hyperbare Sauerstoffbehandlung (HBO) eingesetzt wird.

Die nekrotisierende Fasciitis breitet sich als lebensbedrohliche Entzündung von Haut und vor allem der Unterhaut sehr schnell im subkutanen Gewebe und entlang den Faszien aus. Hauptkeim ist der beta-haemolytische Streptokokkus A, sehr häufig finden sich aber Mischinfektionen. Diabetes ist unter anderen Prädispositionsfaktoren (Alkoholismus, Immunsuppression) von besonderer Wichtigkeit. Die Diagnose muss möglichst frühzeitig gestellt werden, damit umgehend richtig interveniert werden kann. MRT kann neben dem einfachen Fingerdruck Gas zuverlässig im entzündlichen Gewebe aufdecken. Mittels Gramfärbung an Aspirat aus dem veränderten Gebiet lässt sich der Leitkeim oft feststellen.

Gezielte IV Antibiose ist neben dem sofortigen großzügigen chirurgischen Débridement Basis der Therapie.

Die Hyperbare Sauerstofftherapie hat eine dreifach wirkende antiinfektiöse Potenz und sollte adjuvant – sofern verfügbar – ebenfalls eingesetzt werden.

Durch seine direkte Wirkung auf Bakterien, Verbesserung der zellulären Abwehrmechanismen des Körpers und synergistische Effekte auf die Wirkung von Antibiotika ist die HBO in Kombination mit Chirurgie und Antibiotika als adjuvante Therapie extrem nützlich bei der Behandlung von Gewebsinfektionen sowohl mit anaeroben als auch aeroben Bakterien in hypoxischen Wunden und Geweben. Ihre Nützlichkeit wurde klar belegt mit einer großen Zahl von in vitro und in vivo experimenteller Forschung und im Weiteren bestätigt durch extensive klinische Serien. Der Vorteil, den die HBO im Bereich infektiöser Erkrankungen bewirkt ist vor allem auf die adäquate Wiederherstellung normaler oder übernormaler Sauerstoffpartialdrücke in hypoxischen infizierten Geweben zurückzuführen (Mathieu 96).

Die besonders in dem dem Infektionsbereich anliegenden Gewebe gemessene Hyperoxygenation verhindert das weitere Vordringen der Mikroorganismen (Korhonen).

Bei der vital gefährdenden Erkrankung sind mögliche Kontraindikationen für die HBO zu relativieren

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Necrotizing soft tissue infections

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Rationale

Hyperbaric oxygen therapy is a recognized accepted adjunct to surgical debridements, antibiotic therapy and maximal goal-directed critical care therapy for infections of soft tissues that result in necrosis. A number of clinical scenarios, specific lesions and syndromes have been described over the years, based on the affected tissues and location of infection, the etiologic organism or combination of organisms involved in the infection, and particular host immunologic and vascular risk factors. In all of these clinical situations, there appears to be the common denominator of the development of hypoxia resulting in necrosis.

Hypoxia is known to impair phagocytosis by polymorphonuclear leukocytes [1]. After an infective process is initiated, metabolic products of aerobic and anaerobic metabolism tend to lower the oxidation-reduction potential (E_h), leading to a drop in pH, which creates a milieu for growth of strict and facultative anaerobic organisms. When the blood supply to the skin is affected by involvement within a phlegmon, with edema and necrosis in the deep fascial layers in which they reside, the decreased perfusion pressure and ischemia predispose to rapid progression and advancement of the infectious process within the skin and subcutaneous tissues, exacerbated by the dysfunctioning polymorphonuclear leukocytes. Local hypoxia occurs, with up-regulation of endothelial adherence molecules, resulting in leukocyte adhesion and endothelial cytotoxicity. Leukocytes may become sequestered in vessels, impairing local immunity, and incomplete substrate oxidation results in hydrogen and methane accumulation in the tissues. Tissue necrosis occurs, with purulent discharge and gas production. Quantities of gas within tissues are frequently seen in gas gangrene, crepitant anaerobic necrotizing cellulitis and necrotizing fasciitis.

Hyperbaric oxygen therapy can reduce the amount of hypoxic leukocyte dysfunction occurring within an area of hypoxia and infection [1, 2, 3] and provide oxygenation to otherwise ischemic areas, thus limiting the spread and progression of infection. The diffusion of oxygen dissolved in plasma in the circulation, where it is initially carried in large vessels, proceeds to areas of poorly perfused tissue, from regions of very high O_2 saturation down a gradient to lower oxygen levels in tissue. Integrin inhibition decreases leukocyte adherence, reducing systemic toxicity [5].

In cases where the antibiotic being used requires oxygen for transport across cell walls, hyperbaric oxygen therapy can act to enhance antibiotic penetration into target bacteria. Enhancement of the post-antibiotic effect by hyperbaric oxygen has been demonstrated for aminoglycosides and *Pseudomonas* [6].

Clinical classification of the necrotizing infections of soft tissues is easiest early in the course of infection, when anatomic levels of involvement of skin, superficial or deep fascia and muscle involvement can be assessed either during exploration, on punch biopsy or by radiologic investigation. However, as infection progresses, distinction between some of the clinical entities may become blurred, as full-thickness necrosis extends into muscle late in the course of progression of the infection from the fascia outwards into fat and skin, and inwards into muscle, involving all layers.

At presentation, it may be difficult to differentiate these necrotizing soft tissue infections one from another, or from clostridial myositis and myonecrosis, until either Gram stain or cultures are available. Considering their historical differences and evolution, it remains useful to examine the separate categories of infection separately in order to anticipate pathways of extension of infection, anticipate complications and identify when adjunct hyperbaric oxygen therapy should be considered.

CLINICAL ENTITIES: *NECROTIZING FASCIITIS*

Introduction

Necrotizing fasciitis is an acute, potentially fatal infection of the superficial and deep fascia of the skin and soft tissues, which progresses to ischemic dermal necrosis after involvement of the dermal blood vessels which traverse the fascial layers. The popular media refer to this entity as infection with "flesh-eating bacteria."

Etiology

Necrotizing fasciitis was initially described and named "hemolytic streptococcal gangrene" by Meleney in 1924 [7]. He described an illness characterized by gangrene of subcutaneous tissues, followed by rapid necrosis of the overlying skin from involvement of the blood ves-sels supplying the skin, which are found in the affected fascial layers. All his patients grew hemolytic strepto-cocci on cultures, and the patients were all seriously ill. Surgical extirpation appeared to be the therapeutic approach. Reference to this entity as necrotizing fasciitis appears around the time of the report by Wilson [8].

The characteristic level of infection is at the deep fascia. Because infection with necrosis is noted to spread along fascial planes deep to the skin, it is not an un-common event for there to be minimal skin signs early on. Pain out of proportion to findings could be an early tip-off to the presence of deep fascial infection. Since blood vessels supplying overlying skin travel through fascia, it is the involvement of these vessels by infec-tion that leads to rapid progression to dermal necrosis.

Microbiologically, groups A, C or G beta-hemolytic streptococci can be isolated from tissue specimens in 50 to 90% of case series, with one or two more organ-isms often also accompanying the streptococci in up to half the cases. The occurrence of *Staphylococcus aureus* plus anaerobic streptococci is also known as Meleney's synergistic gangrene. Commonly isolated organisms include *Enterobacteriaceae*, *Enterococci*, *Bacteroides* species and *Peptococcus* species. *Candida* species have also been reported [9].

Necrotizing fasciitis is also reported to be caused by community-acquired strains of methicillin-resistant *Staphylococcus aureus* (CA-MRSA) alone [10]. In many cases, infection is polymicrobial, with *Entero-bacteriaceae* and anaerobes frequently isolated.

Risk factors

The most common risk factors associated with ne-crotizing fasciitis are traumatic breaks in the skin – most commonly lacerations, insect bites, burns, deep abrasions, puncture wounds or following surgery, particularly those involving bowel perforations. Diabetes appears to be a strong risk factor, as are obesity, alcoholism, smoking and intravenous drug abuse. Reports of necrotizing fasciitis as a result of infection of otherwise typical lesions of chicken pox have been published [11]. An association with the use of non-steroidal anti-inflammatory agents has also been sug-gested [12,13]. NSAIDs are cyclo-oxygenase inhibitors and may have an adverse effect on neutrophil-killing and cell-mediated immunity. NSAIDs are reported to inhibit monocyte superoxide production [14].

Most common sites of occurrence of necrotizing fasci-itis are the lower extremities, while an increased incidence in the upper extremities is seen in the parenteral drug abuse population. However, any location of the body can be affected, including the abdominal wall of neonates, in association with omphalitis [15]. Involvement of the scrotum and perineum in the male is known as Fournier's gangrene, which is essentially necrotizing fasciitis of the superficial perineal fascia, also known as Colles' fascia. From there, infection can spread to the penis and scrotum via Buck's fascia or Dartos' fascia, while extension to the abdominal wall can occur via Scarpa's fascia. Perianal or perirectal infection may also spread into these areas, and undrained or inadequately drained perirectal abscesses are often cited as a source of Fournier's gangrene.

Perineal necrotizing fasciitis can also occur in the female. Diabetes mellitus remains a strong risk factor in this particular form of necrotizing fasciitis as well. Fournier's gangrene is more likely to have multiple mixed organisms cultured, particularly *Enterobacteri-aceae*, Group D streptococci and anaerobic organisms such as *Bacteroides fragilis*.

Clinical presentation

The patient with necrotizing fasciitis will typically present with an acute combination of pain and swelling, which may or may not be accompanied by fever and chills. There may already be a focus of cellulitis appar-ent, but in some instances early on, there may be very few skin changes. In some patients, there may be pain out of proportion to the skin findings, which may not be unexpected considering that the initial level of infection is the fascia, not necessarily the skin. In others, manifestations of a large phlegmon may be quite obvious, although at times the area of infection may have been assumed to be cellulitis and not a more serious form of infection. Pain may proceed to numbness as a result of compression of nerves which also pass through the fascia.

With time, however, the infection will rapidly proceed to cause areas of blistering and bullae formation. Hints of darkening of the skin may appear as perfusion decreases, until obvious areas of dermal ischemia appear, making the skin appear dusky, grayish or frankly black. Upon exploration of the process, a clinical diagnosis can be confirmed at the time of biopsy or debridement, when the

fascia is grossly observed by the surgeon to be necrotic, and will give way easily to a probing finger or surgical clamp, giving the sensation of "thunking" of the skin against the underlying muscle layers, instead of remaining tight and crisply defined. It has been suggested that limbs of patients with necrotizing fasciitis, as opposed to those with cellulitis only, may be observed to have markedly reduced tissue oxygen saturations as measured by near-infrared spectroscopy throughout the involved site, with ox-ygen saturations in the 52% ±18% range, compared to con-trol measurements of 86% ±11% in uninvolved sites [16].

In the neonate, necrotizing fasciitis of the abdominal wall can be seen as a complication of omphalitis in 10 to 16% of cases [17] and appears to carry over a 50% mortality rate even when treated with aggressive debridement of involved skin, subcutaneous tissue and fascia [18].

A number of diagnostic observations have been made to enable confirmation of the diagnosis of necrotizing fasciitis. Frozen section soft-tissue biopsy early in the evolution of a suspect lesion may provide definitive diagnosis [19]. CT scan findings are also revealing. Asymmetrical fascial thickening that was at least twice the contralateral side and associated with fat stranding was seen in 80% of 20 patients with necrotizing fasciitis. Gas tracking along fascial planes was seen in 55%, characteristically did not involve muscle and was not associated with abscess formation [20]. The authors note that the areas of black, gangrenous skin were far smaller than the widespread infection in the underlying fascial planes. Also of note was that seven of the 20 patients had associated deep space abscesses requiring immediate surgical drainage, which demonstrates the need for CT studies to assess extent of disease, particularly in patients who do not appear to be responding to therapy.

Magnetic resonance imaging (MRI) also demonstrates the extent of affected tissue well, is able to differentiate fluid and gas through differential signal intensities and is useful in differentiating cellulitis from necrotizing fasciitis after injection of gadolinium contrast. But in a study of 15 patients, MRI overestimated the extent of deep fascial involvement in one patient who had cellulitis only following intramuscular injections, which showed up on MRI as thickening of both superficial and deep fascia of the deltoid muscle [21].

Cultures of deep tissue at the time of debridement for aerobes, anaerobes and fungi are imperative, as up to 75% of patients in some series have demonstrated polymicrobial etiologies. Fungal cultures are particularly important in the immunocompromised, diabetic and cancer populations and in patients who have not responded to standard antibacterial antibiotics.

Without hyperbaric therapy amputation rates of 26% [22] up to 50% [23] are reported in cases of necrotizing fasciitis of the extremities. Mortality in reported series ranges from 16.9% up to 66% without the use of hyperbaric oxygen. Mortality is often associated with delayed diagnosis, underlying immunocompromise and underlying heart disease, degree of leukocytosis, septic shock and severe underlying metabolic abnormalities.

In the neonate, necrotizing fasciitis is reported as a complication of omphalitis, balanitis, mastitis, post-operative complication and fetal monitoring [24]. In four of six cases found in a literature review neonates who received hyperbaric oxygen therapy survived, while the overall mortality rate was 39/66 (59%). In a group of neonatal omphalitis patients with abdominal wall necrotizing fasciitis reported from Children's Hospital in Los Angeles, seven out of eight cases died, for a mortality rate of 87% [25] without hyperbaric oxygen therapy. In a series of 32 cases of omphalitis from Seattle over a 10-year period, seven developed necrotizing fasciitis, and five of the seven died. Of the four who received hyperbaric oxygen treatments the two patients who did survive were noted to have resolved their systemic sepsis more rapidly, and had healthier granulation tissue on the perimeter of the debridement. Neither survivor treated with hyperbaric oxygen required any further debridements before their wounds were closed [26].

Gozal *et al.* [27] treated necrotizing fasciitis patients with combined antibiotics, radical surgery and hyperbaric oxygen and reduced the historic mortality rate from 38% to 12.5%. Of 29 patients reported retrospectively by Riseman *et al.* [28], 12 were treated by surgical debridement and antibiotics only, and 17 received hyperbaric oxygen treatments in addition. Both groups had similar parameters of age, race, sex, wound bacteriology and antimicrobial therapy. Body surface area was also similar. However, perineal involvement (53% *vs*. 12%) and septic shock (29% *vs.* 8%) were more common in the hyperbaric group, yet the overall mortality was significantly lower at 23%, versus 66% in the non-hyper-baric oxygen-treated group. Additionally, only 1.2 debridements per patient in the hyperbaric treatment group were performed *vs.* 3.3 debridements per patient in the surgery-plus-antibiotics-only group.

Differential diagnosis

Clearly, a goal when making the diagnosis of necrotizing fasciitis is to make it as early as possible so as to be able to start appropriate treatments and avoid rapid spreading and the onset of sepsis. Time is tissue.

The main differential diagnoses include standard cellulitis, which may be a precursor of necrotizing fasciitis in some cases, and erysipelas, with its erythematous well-delineated border. Additional entities which should be considered include clostridial myositis and myonecrosis; non-clostridial myositis and myonecrosis; toxic shock syndrome, which may accompany necrotizing fasciitis; zygomycotic gangrenous cellulitis; mixed aerobic/anaerobic necrotizing cellulitis; toxic epidermal necrolysis (TEN), also known as Lyell's disease, usually due to exposure to particular medications; and staphylococcal scalded skin syndrome, also known as Ritter's disease, due to exfoliative toxins produced by staphylococci, with the latter two entities being most common in neonates and children under 5 years of age.

In the neonate with omphalitis, violaceous discoloration of the skin appears to be a strong marker for the emergence of necrotizing fasciitis. *Vibrio vulnificans* infections cause blistering infection quite commonly, and are seen in patients who have either been swim-ming in waters along the Gulf of Mexico or have been eating shellfish from that area. *Aeromonas* infections also occur following open wounds acquired in sea water. Cutaneous anthrax may present with a blackened central area and surrounding edema.

Clinical management

Numerous studies have continued to demonstrate the beneficial effect of hyperbaric oxygen therapy in the management of necrotizing fasciitis. Wilkinson and Doolette [29] reported a five-year retrospective cohort Australian study of 44 patients with necrotizing soft tissue infec-tion, between 1994 and 1999, looking at the primary outcome of survival to hospital discharge, and secondary outcomes of limb salvage and long-term survival after hospital discharge.

Logistic regression analysis determined the strongest association with survival was the intervention of hyperbaric therapy (p=.02). Hyperbaric oxygen therapy increased survival with an odds ratio of 8.9 (95% confidence interval, 1.3-58.0) and a number of three needed to treat to benefit. Hyperbaric oxygen therapy also reduced the incidence of amputation (p=.05) and improved long-term outcome (p=.002).

In the series by Escobar *et al.* there were no further amputations beyond those already done prior to transfer once hyperbaric oxygen therapy was initiated in their series of 42 patients [30]. The negative study by Brown *et al.* [31], which purports to be a multicenter retro-spective review of treatment of 54 patients at three facilities over 12 years, had numerous discrepancies in the demographics of their two groups. Half of the hyperbaric oxygen-treated group of 30 patients, all from one institution, were noted to have clostridial infections, while the non-hyperbaric treated group had only four of 24 patients (17%) with clostridial infection. Six of the 30 in the hyperbaric group are noted to have the diagnosis of clostridial myositis and myonecrosis, whereas only one of the non-hyperbaric oxygen-treated patients was so diagnosed. Hence this clearly shows the same diseases were not being compared in this study.

Additionally, as pointed out in a subsequent letter to the editor [32], 80% of the patients received four or fewer treatments, the remaining 20% received between five and seven treatments, and the timing of these treatments is not specified. If the guidelines were followed – *i.e.*, treating three times in the first 24 hours, and then twice per day until the patient is stable and shows no relapse of toxicity between treatments – the gas gangrene patients in this study were treated for less than a day and a half, which is a shorter period of time than most other studies. The others were treated for around two days.

In the Wilkinson study, patients received a median of eight treatments, which is more than that received by the patient with the greatest number of treatments in Brown *et al*. The authors state that the mortality dif-ference between the two groups (9/30, or 30% of the hyperbaric group, *vs.* 10/24, or 42% in the non-hyper-baric group) was not statistically significant. Thus the Brown *et al.* study should not be used as an argument that the use of hyperbaric oxygen for truncal necrotiz-ing fasciitis is "controversial," because these mortality statistics are not comparable, with a different mix of diagnoses in the two. The problem is compounded by the fact that the numbers themselves are small, resulting in a study that had insufficient power to demonstrate a statistically significant result. Furthermore the study does not add to the literature of necrotizing fasciitis involving the limbs and other non-truncal sites.

Fortunately, cases of Fournier's gangrene in the literature are usually studied and reported as a distinct group. Hollabaugh *et al.* [33] reported a retrospective series of 26 cases from the University of Tennessee's five

hospitals. Of the 15 patients with identifiable sources for their infections, eight had urethral disease or trauma, five had colorectal disease, and two had penile prostheses. All patients were managed with prompt surgical debridement and broad-spectrum antibiotics. Procedures performed included urinary diversion, fecal diversion and multiple debridements. Fourteen of the 26 were additionally treated with hyperbaric oxygen.

The group treated with hyperbaric oxygen had a mortality rate of 7% *vs.* 42% in the group not receiv-ing hyperbaric oxygen (p=.04), with a combined overall mortality rate of 23%. The one patient who died while receiving hyperbaric oxygen therapy had been progressing well without evidence of ongoing infection, but suffered an acute MI not thought to be related to the underlying disease process. In the non-hyperbaric group, deaths were usually attributed to ongoing or fulminant sepsis.

Relative risk for survival was 11 times greater in the group receiving hyperbaric oxygen therapy. This study did not show a decrease in the number of debride-ments by HBO_2 therapy, but was confounded due to the larger number of patients who died and thus were not able to get further debridements. Delay to treatment was not a factor in the different groups.

Additional series include that of the Genoa, Italy, group [34] who treated 11 patients without any deaths, and all delayed corrective procedures healed without infectious complications. Another 33 patients were reported in a series from Turku, Finland [35]. These patients were treated at 2.5 atm abs, in conjunction with antibiotics and surgery. Three patients died, for a mor-tality rate of 9%. Hyperbaric oxygenation was observed to reduce systemic toxicity, prevent extension of the ne-crotizing process, and increased demarcation, improv-ing overall outcomes. Two of the three patients who died were moribund upon arrival to their facility. Management included diverting colostomies for those patients with a perirectal or perineal source, and orchiectomy, although sometimes reported in all series, is not routinely done since the blood supply to the testes is from the spermatic vessels which do not perfuse the scrotum and penis. Suprapubic cystostomy was indicated and performed when the source of the infection was genitourinary.

Due to the difficulty in making direct comparisons of clinical series, a Fournier's gangrene Severity Index Score was developed [36] in order to assess a number of variables rather than the presence of the disease itself. The score uses degrees of deviation from normal of physiologic variables to generate a score that correlates with patient mortality. It is clear that the amount of disease, related by some to body surface area of involvement, may be a significant variable.

The Duke University analysis of 50 consecutive patients seen at their institution over a 15-year period had a 20% overall mortality rate [37]. Three statistically significant predictors of outcome were identified when examined using univariate analysis: extent of infection, depth of the necrotizing infection and treatment with hyperbaric oxygen.

However, the same data using multivariate regres-sion analysis identified only the extent of the infection as the only statistically significant independent predictor of outcome in the presence of other co-variables. Patients with disease involving a body surface area of 3.0% or less all survived. The numbers of patients with disease extent greater than 3%, where hyperbaric oxygen would thus be expected to play a role, became smaller, and with small numbers of patients, the power of the study to demonstrate a significant response was not present. Using multivariate analysis, the p-value for statistical significance for hyperbaric oxygen treatments was equal to .06.

With such strong case series evidence of reductions in morbidity and mortality for necrotizing fasciitis and the subset of Fournier's gangrene, it is difficult to envision ever seeing a controlled, double-blinded study of hyperbaric oxygen therapy.

Patient selection criteria

Patients who are candidates for hyperbaric oxygen treatments will have had the diagnosis of a necrotizing soft tissue infection made. Strongest consideration should be given to patients who are compromised hosts, as they are likely to fare the worst with their infection. Significant organ failure is not a contraindication to treatment, as long as the treating chamber facility is properly staffed to manage the specific complications of the individual patient, particularly those on ventilators and pressors.

Clinical management

The recommended hyperbaric oxygen treatment protocol for necrotizing fasciitis includes initiating therapy at 2.0 to 2.5 atm abs pressure for 90 minutes of oxygen, given twice a day for the first few days, until there appears to be no further extension of necrosis in previously debrided areas and infection is "controlled" [38]. If there is doubt of the diagnosis and clostridial myositis and myonecrosis are still in the differential diagnosis, higher-pressure treatments of 2.8 to 3.0 atm abs should be used, using the gas gangrene protocol of three treatments in

the first 24 hours. Some hyperbaric specialists may switch to once-per-day treatments once the patients appear stabilized to be sure that the process does not relapse, prior to stopping. Hyperbaric oxygen therapy is an adjunct to, and does not substitute for, standard wound care, debridement of necrotic tissue, drainage of fluid collections and abscesses, use of antibiotics directed at the expected range of organisms, use of intra-venous gamma globulin, particularly if the necrotizing soft tissue infection is associated with Group A hemolytic streptococcal infection and toxic shock syn-drome [39] and goal-directed management of sepsis.

OTHER NECROTIZING BACTERIAL INFECTIONS

NON-CLOSTRIDIAL MYONECROSIS

This is a particularly aggressive soft tissue infection, which clinically acts much like the clostridial myositis syndrome, with widespread involvement of muscle and fascia. It has also been called "synergistic necrotizing cellulitis" [40]. It is differentiated from necrotizing fasciitis by the muscle involvement, although infec-tion from necrotizing fasciitis, if left to progress, will ultimately spread into muscle, and may be indistin-guishable from non-clostridial myositis at that point.

Organisms described to be involved include the anaerobic *Peptococcus* species, the *Peptostreptococcus* species and the *Bacteroides* species, and are often mixed with aerobic members of *Enterobacteriaceae* [41]. Clinically, the patient will present with exquisite local tenderness, minimal skin changes and drainage of "dishwater" pus from skin surface ulcerations, which become enveloped in blue-gray gangrene. Most patients are quite ill systemically. Half of the patients are bacter-emic. Gas can also be seen. This is often described as the entity when Fournier's gangrene extends onto the abdominal wall and pelvis, involving muscle and fascia alike. Treatment remains surgical debridement.

Since there is a very frequent component of anaer-obic organisms in this entity, it would seem reasonable to use the same rationale as for treatment of necrotizing fasciitis and a similar treatment protocol.

CREPITANT ANAEROBIC CELLULITIS

This category encompasses both clostridial and non-clostridial skin infection. There is abundant tissue gas, but no fascial or muscle involvement. When clostridial species are present in this situation, the conditions are not conducive to toxin formation, and the patient will lack marked systemic toxicity. It is most commonly reported after local trauma to the lower extremities in patients with vascular insufficiency. Organisms reported include *Clostridium* species, *Peptococcus* species, *Peptostrepto-coccus* species, *Bacteroides* species and *Enterobacter-iaceae*. Gas formation causes the typical "crepitance" palpable within the skin. Antibiotics and surgical therapy in normal hosts is usually adequate therapy. Hyperbaric oxygen therapy should be considered in compromised hosts and in those failing to respond. Mortality rate is given at around 10%.

PROGRESSIVE BACTERIAL GANGRENE

This is a subacute process, characterized by slowly progressive dermal ulceration, usually found on the abdominal wall or thorax. It was first described by Cullen in a patient after drainage of an appendiceal abscess [42]. It does not extend to deep fascia. It usually develops at a surgical site, such as a colostomy or ileostomy site. The area around the wound becomes erythematous, swollen and tender, with progression to induration. A central purple area develops and proceeds to slough off as the lesion enlarges and develops a granulation area centrally, surrounded by a gangrenous margin. The path-ology is said to be related to progressively expanding infection created by the synergism between aerophilic and anaerobic/microaerophilic bacteria. It is thought to be similar to, or be identical to, Meleney's ulcer, which has as its hallmark a progressive, slowly extending rim of necrosis, which may tunnel subcutaneously and spread in an occult fashion. It is also seen following lymph node surgery in the neck, axilla or groin. Hyper-baric oxygen therapy has been shown to lead to improve-ment when other standard therapies have failed [43].

ZYGOMYCOTIC GANGRENOUS CELLULITIS

Rationale

Introduction: In the immunocompromised population, infection with opportunistic organisms is a not uncom-mon occurrence. Opportunistic organisms typically do not cause disease in normal host patients, but due to particular deficits in the immune response of various categories, these otherwise unusual organisms become common findings in the abnormal host population. Until now, the discussion has centered on bacterial and bacte-rial toxin-induced diseases, but fungal organisms may also become significant pathogens in that population of patients. A significant virulence factor of these organisms is their characteristic invasion of blood vessels, causing ischemia, hypoxia and progressive necrosis of tissue, thus creating a niche which would physiologically appear

to be amenable to alteration through the use of hyperbaric oxygen therapy. This form of infection is certainly considered one of the necrotizing soft tissue infections.

Etiology

Zygomycosis is the name given to the group of fungal infections caused by pathogenic molds belonging to the class *Zygomyces*, in the phylum *Zygomycota*. The term "phycomycosis" has also been used, but is less commonly used today. *Zygomyces* is further divided into two orders, *Mucorales* and *Entomophthorales*. The *Mucorales* usually cause infections that are acute in onset, aggressive, rapidly progressive and angioinvasive. These infections are commonly called mucormycoses. In the family *Mucoraceae* within the order *Mucorales* are organisms of the genera *Absidia*, *Apophysomyces*, *Mucor*, *Rhizomucor* and *Rhizopus*.

Additional less common families include *Cunninghamellaceae* with organisms of the single genus *Cunningha-mella*, and *Saksenaceae*, with the single genus *Saksenaea*, and others [44]. Organisms in the order *Entomoph-thorales* are *Conidiobolus coronatus* and *Basidiobolus ranarum*. These produce a group of infections that tend to be more indolent, but clearly pathologic and chronically progressive. They typically do not invade blood vessels, although some recent reports do suggest that this may occur at times.

Risk factors

Recognized risk factors for *zygomycoses* are numerous. The leading risk factor appears to be diabetes mellitus, particularly in the setting of ketoacidosis or uncon-trolled hyperglycemia. It is reported that 70% of cases of rhinocerebral zygomycosis occur in the setting of ketoacidosis [45]. The acidotic environment is said to be ideal for fungal growth, while white blood cell activity is inhibited in the hyperglycemic environment [46, 47, 48]. It has been shown that acidosis disrupts the inhibitory activity of sera against fungal growth by interrupting the capacity of transferrin to bind iron, which would normally keep it from being available to the fungal species [49].

Another group of patients at risk are those with iron overload syndromes. These patients are at risk for more significant infections due to the presence of higher levels of iron, a growth factor for most bacteria and fungi capable of synthesizing endogenous metal chelators, or siderophores. Also at risk are patients on metal chelators, such as dialysis patients receiving deferoxamine [50, 51] for removal of aluminum. Since deferoxamine is normally cleared by the kidney, levels of the drug remain high in the dialysis population, prolonging the time that iron bound to it can be utilized by the fungi. Other susceptible patients are those with underlying malignancies, especially leukemias; patients with neutropenia; solid organ and bone marrow transplant patients, and patients who are actively or passively immunosuppressed. Patients who have been on broad-spectrum antibiotics may have fungal overgrowth, which is also a risk factor. The organisms are ubiquitous fungi, and commonly inhabit decaying matter such as common garden soil. Introduction of infection is often related to antecedent trauma [52]. A history of exposure to organisms through farm accidents or trauma in the garden would not be unusual. Gastrointestinal involvement is associated with extreme malnutrition, and is though to be related to oral ingestion of spores of the organisms. Around 5% of patients appear to have no risk factors whatsoever.

Clinical presentations

The most common manifestations of zygomycosis are sinusitis, rhinocerebral infection, soft tissue infection, pneumonia, gastrointestinal involvement and disseminated infection. In the sinusitis and rhinocerebral forms of the infection, initial symptoms would be similar to routine sinusitis, with sinus pain, congestion, and drainage. The infection then accelerates, extending into adjacent structures and tissues, with development of erythema, progressing to violaceous or dusky to frankly black tissue in the nares, turbinates, palate or orbit.

The organisms appear to have a predilection for invasion of arteries, lymphatics and nerves. Invasion of vascular structures leads to a fibrin reaction and development of a mucor thrombus within vessels, which leads to infarction. The infarcted tissue becomes acidotic and permissive for even further fungal ingrowth and proliferation. Lack of perfusion prevents antibiotic penetration into affected tissues.

Extension into adjacent periorbital and orbital structures is often found even early on. Clinical manifestations can include periorbital edema, tearing and proptosis. Involvement of the optic nerve will be marked by blurring, followed by loss, of vision. Abnormalities of eye movement may occur as markers of cranial nerve involvement.

Extension can also move inferiorly into the hard palate via the maxillary sinuses; black, necrotic ulcers may be found on the palate, and the nasal turbinates may appear black and necrotic. Infection may extend into the cranial vault, either via the ethmoid sinus and through the cribriform plate, or through the orbital apex into

the area of the cavernous sinus, producing the orbital apex syndrome, consisting of ophthalmoplegia and fifth cranial nerve involvement, progressing to cavernous sinus thrombosis, and thrombosis of the internal carotid artery. This can result in major hemispheric stroke and altered consciousness. Due to the propensity for angio-invasion, fungemia can occur, disseminating the infection systemically. Rhinocerebral mucormycosis has a very high mortality rate. Standard treatment consists of the antifungal antibiotic Amphotericin B lipid complex or liposomal Amphotericin B, in a dose of 5 mg/kg daily and surgical debridement when indicated. Survivors have usually had earlier diagnosis and surgical debridements.

Pulmonary involvement is the second most common type of zygomycosis overall, seen particularly in patients with leukemia and lymphoma [53]. Isolated solitary nodular lesions, lobar involvement, cavitary lesions and disseminated lesions have all been reported [54]. Erosion of the fungus into mediastinal structures, par-ticularly the pulmonary artery, with massive hemoptysis, is a fatal occurrence. Wedged infarctions of the lung may be seen, as a manifestation of thrombosed pulmonary vessels, from angio-invasion [55].

One of the manifestations of cutaneous infection includes a rapidly progressive, ascending, necrotizing infection consistent with necrotizing fasciitis, which can involve an extremity or the torso. Aerial hyphae can sometimes be grossly visualized in wounds infected with zygomycosis organisms, as a loose, whitish, cottony exudate covering the surface of open wounds. Risk factors for the development of cutaneous and subcutan-eous involvement include various types of breakdown of the skin barrier, including puncture wounds, other trauma and burn wounds. Mortality rates of 30% to 70% are reported in necrotizing fasciitis with these organisms, depending on the underlying condition associated with the infection. Since diabetic ketoacidosis is a treatable condition, reversal of the acidosis affords an opportunity for the host response to reconstitute, and thus may have a decreased mortality compared to the patients with non-reversible conditions.

The GI syndrome is characterized by abdominal pain and distention, associated with nausea and vomiting. Fever and hematochezia may occur. Stomach, ileum and colon are most commonly affected. Most such diagnoses are made post-mortem, but, if suspected, may require lapa-rotomy to manage the bowel infarctions that may occur [56].

Differential diagnosis

Upon initial presentation, rhinocerebral mucormycosis may be misidentified as the more common routine bacterial sinusitis due to usual Gram-positive or anaer-obic organisms, although there should not be any necrotic lesions in those cases. However, once evidence of necrosis is apparent, or in the proper clinical set-tings, there should be no hesitation in ordering a biopsy, looking for the various fungal forms, which are quite characteristic wide, non-septate hyphae branching off at right angles; and signs of angioinvasive processes should be sought.

Affected tissue usually has neutrophilic infiltrates, and inflammatory vasculitis is seen, involving both arteries and veins. Cultures for routine aerobic, anaerobic and fungal organisms should always be sent. Cavernous sinus thrombosis can occur as an extension of suppura-tive, usually staphylococcal, facial cellulitis or abscess, but there would not be the typical lesions in the nose or sinuses. Radiological studies, such as plain films or CT scans, may show more extensive bone necrosis than was anticipated. Orbital cellulitis and bacterial osteo-myelitis of the frontal bone or orbit are other entities which may clinically resemble this form of zygomycosis.

Lung involvement may be non-specific, and can look like other cases of atelectasis, pneumonia, granulomatous disease or, particularly in patients with cancer, infection due to *Aspergillus* species. Use of radiologic studies may hasten the diagnosis. In a retrospective analysis of CT findings in 16 cases of pulmonary zygomycosis *vs*. 29 cases of invasive pulmonary aspergillosis at the University of Texas M.D. Anderson Cancer Center [57], logistic regression analysis of clinical characteristics demonstrated that:

a. concomitant sinusitis and
b. voriconazole prophylaxis were significantly associated with pulmonary zygomycosis.

CT scan findings of multiple ($\geq$10) nodules and pleural effusion were both independent predictors of pulmonary zygomycosis, suggesting potential clues in differenti-ating the two types of infections.

Pulmonary mucormycosis can also be confused with standard pulmonary embolism. Gastrointestinal disease must be differentiated from other bowel infections, perforation and staphylococcal necrotizing entero-colitis, seen in infants.

Rationale for use of hyperbaric oxygen therapy

From a physiological viewpoint, mechanistic steps are only now being discovered to explain the virulence and invasiveness of the filamentous fungi in causing disease. Each of these mechanisms, as discovered, would well be worth testing in the presence of hyperbaric oxygen to assess potential roles for hyperbaric oxygen therapy. Filamentous fungi are aerobic and thus it is not expected that there would be a direct effect on fungi under clinical hyperbaric conditions.

Hyperbaric oxygen therapy in the setting of zygomycosis could be beneficial in a number of ways. The angioinvasive character of these infections creates areas of hypoxia, ischemia and subsequent necrosis, which will directly affect neutrophilic killing of organisms, as phagocytosis becomes inefficient. Areas of tissue that are ischemic due to partial loss of perfusion can be made normoxic during hyperbaric therapy, and restore immune mechanisms that have become dysfunctional due to hypoxia.

The neutrophil has a significant role in defending against filamentous fungi, despite the larger size of the hyphae. Engulfment by neutrophils and damage to hyphae is correlated with response to infection. Both mononuclear and polymorphonuclear white cells of normal hosts kill *Rhizopus* by generation of oxidative metabolites and cationic peptide defensins [58, 59, 60]. Comparison of antifungal function of human polymorphonuclear leukocytes against hyphae of *Rhizopus oryzae* and *Rhizopus microsporus*, the most frequently isolated zygomycetes, with that of *Absidia corymbifera* have shown that oxidative burst responses by PMNs, and PML-induced hyphal damage, were significantly lower in response to the *Rhizopus* species than to the *Absidia* species, and that hyphal damage increased when PMLs were incubated with interferon-gamma and granulocyte-macrophage colony-stimulating factor (GM-CSF) [61].

Mouse bronchoalveolar macrophages prevent germination of spores *in vitro* and *in vivo* in a murine model, and this ability is blocked by corticosteroid therapy. Correction of hypoxia for such critical cells should enhance oxidative killing of fungi. The significant hallmark of zygomycoses is their ability to invade blood vessels, causing blood vessel inflammation, thrombosis and tissue necrosis in many different tissues, and subsequent hematogenous dissemination to other organs. Penetration of endothelial cells lining blood vessels must be a key step in the pathophysiology of zygo-mycosis. Studies examining these steps are crucial in defining additional steps to treat infection, by blocking fungal dissemination. It has been demonstrated that *Rhizopus oryzae* spores adhere to subendothelial ma-trix proteins better than hyphae, but spores and hyphae adhere equivalently to human umbilical vein endothe-lial cells [62]. Phagocytosis of *Rhizopus oryzae* by endo-thelial cells was also shown to damage the endothelial cells, raising the question of whether such steps could be related to subsequent thromboses. Hyperbaric oxygen research has not begun to delve into these neutrophil and fungal/endothelial interactions, but is sorely needed.

Much of the surgery required to manage the necrotizing aspects of infection involving sinuses, orbit and skull is quite deforming, and the addition of hyperbaric oxygen to wound management would facilitate generation of granulation tissue, epithelialization and bone healing. Additionally, there are other non-specific mechanisms that are still being worked out for several forms of sepsis, which appear to be positively affected by hyperbaric oxygen [63, 64].

Standard therapy involves the use of antifungal antibiotics and definitive debridement of necrotic tissue. Hyperbaric oxygen clinical studies to date have gen-erally been either isolated case reports or retrospec-tive case series and literature reviews. John *et al*. [65] reported such a literature review of 28 published cases that had received hyperbaric oxygen treatments. Among the *Mucorales* isolates, there were 11 cases of *Rhizopus* species, followed by three cases of *Apophysomyces* species, and two cases each of *Mucor* and *Absidia*. Three isolates from *Entomophthoramycoses* were *Con-idiobolus* species. Risk factors in these patients were a spectrum of the typically seen range, with 17/28 (61%) being diabetics, 10 of whom had ketoacidosis; five patients (18%) developed their infections after trauma; one patient was on systemic steroids; three (11%) had hematological malignancies or bone marrow transplants; and three (11%) had no known risk factors for zygo-mycosis. Overall survival rate was 86%, which encompassed a 94% survival rate in diabetic patients, but only a 33% survival rate in patients with hematological malignancies or bone marrow transplants. All patients except for two had also received Amphotericin B. Despite the range of cases, all groups were small, and there were no case controls to which to compare the case responses.

In a large series of all cases of zygomycosis found in the literature since 1885, 929 cases of zygomycosis were reported and analyzed by Roden *et al.* [66]. Survival rates were reported by type of treatment received. 44 patients were identified as having received hyper-baric oxygen therapy, and in that group, 64% of patients

survived. Other treatments identified and survival rates were:

- amphotericin B deoxycholate recipients: 324 survivors of 532 patients (61%);
- amphotericin B lipid formulation: 80 survivors of 116 patients (69%);
- itraconazole, ketoconazole or posaconazole: 10 survivors of 15 patients (67%);
- no antifungal therapy at all: 59 survivors of 333 patients (18%);
- surgery alone: 51 survivors out of 90 patients (57%);
- surgery plus antifungal therapy: 328 survivors out of 470 cases (70%);
- granulocyte colony-stimulating factor: 15/18 (83%);
- granulocyte transfusion: two survivors out of seven cases (29%);
- patients who received no therapy at all: eight survivors out of 241 cases (3%).

Major difficulties arise with these data, particularly since these studies usually do not differentiate between intent to treat studies or salvage therapy when standard treat-ment appears to be failing, and whether the cases are related to use of antibiotics, surgery or hyperbaric oxygen therapy. This is an observed difficulty in interpreting large numbers of individual case reports and series [67].

The case reported by Bentur *et al.* of mucormy-cosis of the fourth finger of the hand in a diabetic pa-tient with ketoacidosis is such a case [68]. Hyperbaric oxygen therapy was begun only after other modalities, including Amphotericin B, amputation of the affected finger, followed by wide debridement of the hand and fasciotomy of the forearm had been tried and the disease continued to progress. After receiving 29 hyperbaric treatments, the infection appeared improved, and the patient went on to see her wounds healed.

Similarly, the case of an *Entomophthorales* infection in the medial orbit of an 18-month-old is another example of hyperbaric oxygen therapy used as salvage therapy [69] in conjunction with radical surgery when the organism was found to be resistant to all available antifungal antibiotics.

Thus, any future database of cases of zygomycoses treated with hyperbaric oxygen therapy should document classification of cases by whether hyperbaric oxygen was used as an early adjunct, at the time of initial institution of therapy, or as "rescue," or "salvage" therapy. In addition, hyperbaric oxygen would normally be considered an adjunct to use of antibiotics and indicated surgery, and such subgroup analysis was not done in the Roden report. It is unfair to compare the results if hyperbaric oxygen therapy were started late in the treatment course, as salvage therapy, when an initial course of antibiotics and surgical debridement have been determined to have failed, and infection is progressing and considered to be refractory, as opposed to surgery and antibiotics, started early on, without hyperbaric oxygen.

Appropriate comparisons can be made when hyper-baric therapy is added as an adjunct to the initial man-agement of surgery and antibiotics. A strong argument for controlling for such variables in different studies is well-advised, and is comparable to the discussions in the medical literature related to other salvage interventions, such as a new antibiotic, where the answers to the questions of how much of the treatment effect is attributable to the commencement of therapy, and how much is attributable to the natural history of partially treated disease, can rarely be separated out [70]. In the setting of a rare, relatively unusual infection, it is a given that randomized studies would be unrealistic, and those authors recommend that carefully selected, matched, contemporaneous control subjects are likely to be the most useful alternative. Although these comments were made in reference to use of newer antifungal antibiotics, the same observations would apply to the analysis of hyperbaric oxygen therapy.

Treatment

Antibiotic treatment should be commenced with an Amphotericin B preparation. The fungus is relatively refractory to standard medical therapy; thus maximally tolerated doses of Amphotericin B deoxycholate should be used, usually 1.0 to 1.5 mg/kg/day. Lipid complex forms of Amphotericin B doses are better tolerated, and doses are higher. The dose of Amphotericin B lipid complex (Abelcet) and liposomal Amphotericin B (AmBisome) is 5 mg/kg/day.

It has been observed that the use of voriconazole as fungal prophylaxis in the hematopoietic stem cell transplant population is a risk factor for developing zygomycosis [71] and should be avoided. Other current-ly available azoles, such as ketoconazole, itraconazole, fluconazole or miconazole are not efficacious, either. Posaconazole, a newer extended-spectrum oral azole, has demonstrated *in vitro* and *in vivo* activity against zygomycetes, and has been used as salvage therapy for 24 patients with zygomycetes infections who were intolerant of, or whose infections were resistant to, standard antifungal therapy [72]. Surgical debridement should be

considered, based on area of involvement, and sequential debridements may be necessary to control spread. Frozen-section guided debridement has been advocated to assure adequate margins [73]. Reconstructive surgery may also be necessary once the infection has been cleared. Intense management of the underlying predisposing cause of infection is also a marker for successful therapy. In diabetics with reversible acidosis, recovery rates are higher than in those patients with underlying malignancy and immunosuppression. Immunosuppressive drugs should be reduced in dosage or discontinued if possible during attempts to control the infection.

Hyperbaric oxygen therapy should be considered as adjunctive therapy, and does not replace adequate antifungal therapy. There are no clinical data that might suggest a specific treatment pressure to use in the setting of zygomycosis infection. It would be appropriate to commence hyperbaric oxygen treatments early in the course, rather than as salvage therapy, in the 2.4 to 3.0 atm abs range of pressures, twice a day during the acute phase of the illness, to enhance the immune response to the fungal hyphae and protect borderline ischemic areas from progression of ischemia to necrosis. Many of the successful cases have been treated with up to 30 treatments, although there are no controlled studies that would suggest a specific treatment course or pressure. Due to the rarity of the infection, it is unlikely that a prospective controlled trial could ever be done at a single institution, and thus adequate data would likely require multicenter studies, controlling for intent-to-treat *vs.* salvage therapy, timing of hyperbaric therapy, depth and duration of treatments, as well as extent of infection at time of diagnosis, number of debridements necessary, and category of predis-posing factor, along with other standard parameters.

Evidence-based review

From a physiological viewpoint, all necrotizing soft tissue infections should benefit from hyperbaric oxygen treatments, considering all the physiologic steps that enhance host response to infection.

Although some authors claim that hyperbaric oxy-gen therapy remains controversial in treating necrotizing fasciitis, due to lack of prospective, randomized, blinded or double-blinded controlled studies comparing hyperbaric oxygen treatments *vs.* no hyperbaric treatments, other authors have concluded that the improvements in morbidity and mortality compared to historical morbidity and mortality data, would make it unethical to perform such randomized clinical trials on patients, as it would deny a well-substantiated adjunctive treatment for a disease with a high rate of morbidity and mortality with generally few risks of complications from the treatments. There are in fact no prospective randomized, controlled trials either, using just surgery, or surgery and antibiotics, for necrotizing fasciitis, either; yet these interventions are widely used without question, based on retrospective studies and clinical series as well. Thus the argument against using hyperbaric oxygen therapy because of a lack of randomized controlled trials [74] cannot be seriously entertained.

There are numerous clinical series that do show reduced morbidity and mortality when hyperbaric oxygen has been used for numerous forms of necrotizing fasciitis, including Fournier's gangrene. This would make it a highly recommended adjunct to antibiotics and surgical debridements.

For necrotizing fasciitis related to the zygomycoses, the very high incidence of morbidity, disfigurement and mortality in a population that is overall usually quite compromised, leads to the conclusion that early institution of hyperbaric oxygen therapy is indicated – *i.e.*, when the diagnosis is made, rather than waiting until signs of failure to respond to what is seemingly standard therapy, and then attempting to use hyperbaric oxygen treatments in a salvage mode, when the chances of success would seem less likely.

Numerous case reports of success, even when hyperbaric oxygen treatments have been used in a salvage mode, support this recommendation. The disease pro-cess, which involves angioinvasive infection leading to ischemia, infarction and extension of infection, appears to be one that hyperbaric oxygen treatments interfere with.

Utilization review

Twice-a-day hyperbaric oxygen treatments during the acute phase of necrotizing soft tissue infections are advised, until extension of necrosis has been halted. Due to the natural history of often relentless progres-sion and undetected foci of necrosis, these treatments would then be followed by once-daily treatments, over an extended period, until the infection is well-controlled, which may take up to 30 treatments. Utilization review should be requested after 30 treatments.

Cost impact

Under a diagnosis-related group (DRG) system, where reimbursement is made on a daily basis, no matter what treatments are given, the cost of the treatments would be borne by the hospital while the patient is an inpatient.

Due to the life-, limb- and tissue-threatening aspects of these infections, the cost impact of hyperbaric treatments is justified. Adjunctive use of hyperbaric oxygen therapy may reduce the length of hospital stay and the number of procedures needed to attain infection control.

REFERENCES

1. Mandell G. Bactericidal activity of aerobic and anaerobic polymorphonuclear neutrophils. Infect Immun 1974; 9:337-341.
2. Mader JT, Adams KR, Sutton TE. Infectious diseases: Pathophysiology and mechanisms of hyperbaric oxygen. J Hyperbaric Med 1987; 2:133-140.
3. Hunt TK, Lensey M, Grislis G, Sonne M, Jawez E. The effect of differing ambient oxygen tensions on wound infection. Ann Surg 1975; 181:35-39.
4. Knighton DR, Fiegel VD, Halverson T, Schneider S, Brown T, Wells CL. Oxygen as an antibiotic: the effect of inspired oxygen on bacterial clearance. Arch Surg 1990; 125: 97-100.
5. Thom SR, Mendiguren I, Hardy K, Bolotin T, Fisher D, Nebolon M, et al. Inhibition of human neutrophil beta-2 integrin-dependent adherence by hyperbaric O2. Am J Physiol 1997; 272:C770–777.
6. Park MK, Muhvich KH, Myers RA, Marsella L. Hyperoxia prolongs the aminoglycoside-induced postantibiotic effect in Pseudomonas aeruginosa. Antimicrob Agents Chemother 1991; 35(4):691-695.
7. Meleney FL. Hemolytic streptococcus gangrene. Arch Surg 1924; 9:317-364.
8. Wilson B. Necrotizing fasciitis. Am Surgeon 1952; 18:426-431.
9. Anaya DA, Pachen Dellinger E. Necrotizing soft-tissue infection: diagnosis and management. Clin Infect Dis 2007; 44:705-710.
10. Miller LG, Perdreau-Remington F, Rieg G, Mehdi S, Perl-roth J, Bayer AS, Tang AW, Phung TO, Spellberg B. Necrotizing fasciitis caused by community-associated methicillin-resistant Staphylococcus aureus in Los Angeles. N Engl J Med 2005; 352:1445-1453.
11. Brogan TV, Nizet V, Waldhausen JHT, Rubens CE, Clarke W. Group A streptococcal necrotizing fasciitis complicating primary varicella: a series of fourteen patients. Pediatr Infect Dis J 1995; 14:588-594.
12. Rimailho A, Riou B, Richard C, Auzepy P. Fulminant necrotizing fasciitis and nonsteroidal anti-inflammatory drugs. J Infect Dis 1987; 155:143-146.
13. Zerr DM, Alexander ER, Duchin JS, Koutsky LA, Rubens CE. A case-control study of necrotizing fasciitis during primary varicella. Pediatrics 1999; 103:783-790.
14. Bell AL, Adamson H, Kirk F, McCaigue MD, Rotman H. Diclofenac inhibits monocyte superoxide production ex vivo in rheumatoid arthritis. Rheumatol Int 1991; 11:27-30.
15. Sawin RS, Schaller RT, Tapper D, Morgan A, Cahill J. Early recognition of neonatal abdominal wall necrotizing fasciitis. Am J Surg 1994; 167:481-484.
16. Wang T-L, Hung C-R. Role of tissue oxygen saturation monitoring in diagnosing necrotizing fasciitis of the lower limbs. Ann Emerg Med 2004; 44:222-228.
17. Lally KP, Atkinson JB, Wooley MM, Mahour GH. Necrotizing fasciitis: a serious sequela of omphalitis in the newborn. Ann Surg 1984; 199:101-103.
18. Sawin RS, Schaller RT, Tapper D, Morgan A, Cahill J. Early recognition of neonatal abdominal wall necrotizing fasciitis. Am J Surg 1994; 167:481-484.
19. Stamenkovic I, Lew PD. Early recognition of potentially fatal necrotizing fasciitis: the use of frozen-section biopsy. N Engl J Med 1984; 310:1689-1693.
20. Wysoki MG, Santora TA, Shah RM, Friedman AC. Necrotizing fasciitis: CT Characteristics. Radiology 1997; 203:859-863.
21. Schmid MR, Kossman T, Duewell S. Differentiation of necrotizing fasciitis and cellulitis using MR imaging. Am J Roentgenol 1998; 170:615-620.
22. Anaya DA, McMahon K, Nathens AB, Sullivan SR, Foy H, Bulger E. Predictors of mortality and limb loss in necrotizing soft tissue infections. Arch Surg 2005; 140:151-157.
23. McHenry CR, Piotrowski JJ, Petrinic D, Malangoni MA. Determinants of mortality for necrotizing soft-tissue infections. Ann Surg 1995; 221:558-563.
24. Hsieh W-H, Yang, P-H, Chao H-C, Lai J-Y. Neonatal necrotizing fasciitis: report of 3 cases and review of the literature. Pediatrics 103 (4):e53. Online at http://pediatrics.aappublications.org/cgi/content/full/103/4/e53
25. Lally KP, Atkinson JB, Woolley MM, Mahour GH. Necrotizing fasciitis: a serious sequela of omphalitis in the newborn. Ann Surg 1984; 199:101-103.
26. Sawin RS, Schaller RT, Tapper D. Early recognition of neonatal abdominal wall necrotizing fasciitis. Am Jour Surg 1994; 167:481-484.
27. Gozal D, Ziser A, Shupak A, Ariel A, Melamed Y. Necrotizing fasciitis. Arch Surg 1986; 121:233-235.

28. Riseman JA, Zamboni WA, Curtis A, Graham DR, Konrad HR, and Ross DS. Hyperbaric oxygen therapy for necrotizing fasciitis reduces mortality and the need for debridements. Surgery 1990; 108:847-850.

29. Wilkinson D, Doolette D. Hyperbaric oxygen treatment and survival from necrotizing soft tissue infection. Arch Surg 2004; 139:1339-1345.

30. Escobar SJ, Slade JB, Hunt TK, Cianci P. Adjuvant hyperbaric oxygen therapy (HBO2) for treatment of necrotizing fasciitis reduces mortality and amputation rate. Undersea Hyperb Med 2006; 32(6):437-443.

31. Brown DR, Davis NL, Lepawsky M, Cunningham J, Kortbeek J. A multicenter review of the treatment of major truncal necrotizing infections with and without hyperbaric oxygen therapy. Am J Surg 1994; 167:485-489.

32. Monestersky JH, Myers RAM. Letter to the editor: Hyperbaric oxygen treatment of necrotizing fasciitis. Am J Surg 1995; 169:187-188.

33. Hollabaugh RS, Dmochowski RR, Hickerson WL. Fournier's gangrene: Therapeutic impact of hyperbaric oxygen. Plast Reconstr Surg 1998; 101:94-100.

34. Pizzorno R, Bonini F, Donelli A, Stubinski R, Medica M, Carmignani G. Hyperbaric oxygen therapy in the treatment of Fournier's Disease in 11 male patients. J Urol 1997; 158:837840.

35. Korhonen K, Him M, Niinikoski J. Hyperbaric oxygen in the treatment of Fournier's Gangrene. Eur J Surg 1998; 164:251-255.

36. Laor E, Palmer LS, Tolia BM. Outcome prediction in patients with Fournier's Gangrene. J Urol 1995; 154:89-92.

37. Dahm P, Roland FH, Vaslef SN, Moon RE, Price DT, Georgiade GS, Viewig J. Outcome analysis in patients with primary necrotizing fasciitis of the male genitalia. Urol 2000; 56:31-36.

38. Lepawsky M. Necrotizing soft tissue infections. In: Feldmeier JJ (Chair and Ed.). Hyperbaric oxygen 2003: Indications and results-The hyperbaric oxygen therapy committee report. Kensington, MD: Undersea and Hyperbaric Medical Society, 2003; pp. 69-78.

39. Kaul R, McGeer A, Low DE, Green K, Schwartz B. Population-based surveillance for group-A streptococcal necrotizing fasciitis: clinical features, prognostic indicators, and microbiologic analysis of seventy-seven cases: Ontario Group A Streptococcal study. Am J Med 1997; 103:18-24.

40. Stone HH, Martin JD. Synergistic necrotizing cellulitis. Ann Surg 1972; 175:702-711.

41. Bessman AN, Wagner W. Nonclostridial gas gangrene. JAMA 1975; 233:958.

42. Cullen TS. A progressively enlarging ulcer of abdominal wall involving the skin and fat, following drainage of an abdominal abscess, apparently of appendiceal origin. Surg Gynecol Obstetr 1924; 38:579-582.

43. Ledingham IM, Tehrani MA. Diagnosis, clinical course and treatment of acute dermal gangrene. Br J Surg 1975; 62:364-372.

44. Chayakulkeeree M, Ghannoum MA, Perfect JR. Zygomycosis: the re-emerging fungal infection. Eur J Clin Microbiol Infect Dis 2006; 25:215-229.

45. McNulty JS. Rhinocerebral mucormycosis: predisposing factors. Laryngoscope 1982; 92:1140-1143.

46. Bagdade JD, Root RK, Bulger RJ. Impaired leukocyte function in patients with poorly controlled diabetes. Diabetes 1974; 23:9-15.

47. Nielson CP, Hindson DA. Inhibition of polymorpho-nuclear leukocyte respiratory burst by elevated glucose concentration. Diabetes 1989; 38(8):1031-1035.

48. Alexiewicz JM, Kumar D, Smogorzewski M, Klin M., Massry SG. Polymorphonuclear leukocytes in non-insulin dependent diabetes mellitus: abnormalities in metabolism and function. Ann Int Med 1995; 123 (12): 919-924.

49. Artis WM, Fountain JA, Delcher HK, Jones HE. A mechanism of susceptibility to mucormycosis in diabetic ketoacidosis: transferrin and iron availability. Diabetes 1982; 31:1109-1114.

50. Windus DW, Stokes TJ, Julian BA, Fenves AZ. Fatal rhizopus infections in hemodialysis patients receiving deferoxamine. Ann Int Med 1987; 107:678-680.

51. Boelaert JR, Van Roost GF, Vergauwe PL, Verbanck C, De Vroey C, Segaert MF. The role of deferoxamine in dialysis-associate mucormycosis: report of three cases and review of the literature. Clin Nephrol 1988; 29:261-266.

52. Cocanour CS, Miller-Crouchett P, Reed RL, Johnson PC, Fischer RP. Mucormycosis in trauma patients. J Trauma 1992; 32:12-15.

53. Tedder MJ, Spratt JA, Anstadt MP, Hegde SS, Tedder SD, Lowe JE. Pulmonary mucormycosis: results of medical and surgical therapy. Ann Thorac Surg 1994; 57:1044-1050.

54. Ribes JA, Vanover-Sams CL, Baker DJ. Zygomycetes in human disease. Clin Microbiol Revs 2000; 13:236-301.

55. Murray HW. Pulmonary mucormycosis with massive fatal hemoptysis. Chest 1975; 68:65-68.

56. Michalak DM, Cooney DR, Rhodes KH, Telander RL, Kleinberg F. Gastrointestinal mucormycosis in infants and children: a cause of gangrenous intestinal cellulitis and perforation. J Pediatr Surg 1980; 15:320-324.

57. Chamilos G, Marom EM, Lewis RE, Lionakis MS, Kontoyiannis DP. Predictors of pulmonary zygomycosis versus invasive pulmonary aspergillosis in patients with cancer. Clin Infect Dis 2005; 41:60-66.

58. Diamond RD, Haudenschild CC, Erickson III NF. Monocyte-mediated damage to Rhizopus oryzae hyphae in vitro. Infect Immun 1982; 38:292-297.

59. Waldorf AR. Pulmonary defense mechanisms against opportunistic fungal pathogens. 1989; Immunol Ser 47:243-271.

60. Waldorf AR, Ruderman N, Diamond RD. Specific susceptibility to mucormycosis in murine diabetes and bronchoalveolar macrophage defense against Rhizopus. J Clin Invest 1984; 74:150-160.

61. Gil-Lamaignere C, Simitsopoulou M, Rollides E, Maloukou A, Winn RM. Interferon-γ and granulocyte-macrophage colony-stimulating factor augment the activity of polymorphonuclear leukocytes against medically important zygomycetes. J Inf Dis 2005; 191:1180-1187.

62. Ibrahim AS, Spellberg B, Avanessian V, Fu Y, Edwards, Jr. E. rhizopus oryzae adheres to, is phagocytosed by, and damages endothelial cells in vitro. Infect Immun 2005; 73:778783.

63. Imperatore F, Cuzzocrea S, De Lucia D, Sessa M, Rinaldi B, Capuano A, Liguori G, Filippelli A, Rossi F. Hyperbaric oxygen therapy prevents coagulation disorders in an experimental model of multiple organ failure syndrome. Intensive Care Med 2006; 32:1881-1888.

64. Buras JA, Holt D, Orlow D, Belikoff B, Pavlides S, Reenstra WR. Hyperbaric oxygen protects from sepsis mortality via an interleukin-10-dependent mechanism. Crit Care Med 2006; 34 (10): 2624-2629.

65. John BV, Camilos G, Kontoyiannis DP. Hyperbaric oxygen as an adjunctive treatment for Zygomycosis. Clin Microbiol Infect 2005; 11:515-517.

66. Roden MM, Zaoutis TE, Buchanan WL, Knudsen TA, Sarkisova TA, Schaufele RL, Sein M, Sein T, Chiou CC, Chu JH, Kontoyiannis DP. Epidemiology and outcome of Zygomycosis: a review of 929 reported cases. Clin Inf Dis 2005; 41:634-653.

67. Almyroudis NG, Konoyiannis DP, Sepkowitz KA, De Pauw BE, Walsh TJ, Segal BH. Issues related to the design and interpretation of clinical trials of salvage therapy for invasive mold infection. Clin Inf Dis 2006; 43:1449-1455.

68. Bentur Y, Shupak A, Ramon Y, Abramovich A, Wolfin G, Stein H, Krivoi N. Hyperbaric oxygen therapy for cutaneous/ soft-tissue Zygomycosis complicating diabetes mellitus. Plastic and Reconstr Surg 1998; 102:822-824.

69. Temple ME, Brady MT, Koranyi KI, Nahata MC. Periorbital cellulitis secondary to Conidiobolus incongruous. Pharmacotherapy 2001; 21 (3):351-354.

70. Powers JH. Salvage therapy trials in fungal disease: challenges and opportunities. Clin Inf Dis 2006; 43:1456-1459.

71. Trifilio SM, Bennett CL, Yarnold PR, McKoy JM, Parada J, Mehta J, Chamilos G, Palella F, Kennedy L, Mullane K, Tallman MS, Evens A. Scheetz MH, Blum W, Kontoyiannis DP. Breakthrough Zygomycosis after voriconazole administration among patients with hematologic malignancies who receive hematopoietic stem-cell transplants or intensive chemotherapy. Bone Marrow Transplantation 2007; 39:425429.

72. Greenberg RN, Mullane K, van Burick J-AH, Raad I, Abzug MJ, Herbrecht R, Langston A, Marr KA, Schiller G, Schuster M, Wingard JR, Gonzalez CE, Revankar SG, Corcoran G, Kryscio RJ, Hare R. Posaconazole as salvage therapy for Zygomycosis. Antimicrob Agents and Chemother 2006; 50 (1): 126-133.

73. Langford JD, McCartney DL, Wang RC. Frozen section-guided surgical debridement for management of rhino-orbital mucormycosis. Am J Ophthalmol 1997; 124:265-267.

74. Jallali N, Withey S, Butler PE. Hyperbaric oxygen as ad-juvant therapy in the management of necrotizing fasciitis. Am J Surg 2005; 189(4):462-466.

Die Anwendung der HBO befürworten u.A.:

Mao JC, Carron MA, Fountain KR, Stachler RJ, Yoo GH, Mathog RH, Coticchia JM.: **Craniocervical necrotizing fasciitis** with and without thoracic extension: management strategies and outcome Am J Otolaryngol. 2009 HBO integriertJan-Feb;30(1):17-23. Epub 2008 Jul 10

OBJECTIVE: First objective was to review cases of craniocervical necrotizing fasciitis (CCNF) at Wayne State University/Detroit Medical Center (Detroit, MI) for the last 18 years. Second was to analyze patients with and without thoracic extension for contributing factors.

METHODS: Retrospective review of 660 patients with necrotizing fasciitis treated at WSU/DMC from January 1989 to January 2007 was conducted. Data regarding source/extent of infection, presenting signs/symptoms, computed tomography, microbiology, antibiotics, comorbidities, number/type of operations, hyperbaric oxygen (HBO) therapy, hospital duration, complications, and overall outcome were compared/analyzed between patients with and without thoracic extension.

RESULTS: **Twenty patients** with CCNF for the past 18 years met the inclusion criteria. Ten patients had thoracic extension, and 10 patients did not have. Individuals in the thoracic extension group were likely to be older, had increased comorbidity, required more surgical debridement, experienced increased postoperative complications, and had lower overall survival. Three patients with thoracic extension underwent HBO therapy and 66% survived.

CONCLUSION: This is the largest single institutional review of CCNF comparing patients with and without thoracic extension. Patients with thoracic extension have a poorer outcome as follows: 60% (6/10) survival vs 100% (10/10) for those without thoracic extension ($P < .05$). The CCNF patients without thoracic extension treated at our institution all survived after prompt medical and surgical intervention. Overall survival of CCNF patients without thoracic extension may be attributed to rigorous wound care, broad-spectrum intravenous antibiotics, aggressive surgical debridement, and vigilant care in surgical intensive care unit. **The HBO therapy should be included if the patient can tolerate it.**

Richard F **Edlich**; Kathryne L Winters; Charles R Woodard; L D Britt; William B Long: Massive soft tissue infections: necrotizing fasciitis and purpura fulminans. J Long Term Eff Med Implants. 2005; 15(1):57-65

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Necrotizing fasciitis and purpura fulminans are two destructive infections that involve both skin and soft tissue.

Necrotizing fasciitis is characterized by widespread necrosis of subcutaneous tissue and the fascia. Historically, group A beta-haemolytic streptococcus has been identified as a major cause of this infection. However, this monomicrobial infection is usually associated with some underlying cause, such as diabetes mellitus. During the last two decades, scientists have found that the pathogenesis of necrotizing fasciitis is polymicrobial. The diagnosis of necrotizing fasciitis must be made as soon as possible by examining the skin inflammatory changes. **Magnetic resonance imaging** is strongly recommended to detect the presence of air within the tissues. Percutaneous aspiration of the soft tissue infection followed by prompt **Gram staining** should be conducted with the "finger-test" and rapid-frozen section biopsy examination. Intravenous **antibiotic** therapy is one of the cornerstones of managing this life-threatening skin infection. **Surgery** is the primary treatment for necrotizing fasciitis, with early surgical **fasciotomy** and debridement. Following **debridement**, skin coverage by either Integra Dermal Regeneration Template or AlloDerm should be undertaken. **Hyperbaric oxygen** therapy complemented by intravenous polyspecific **immunoglobulin** are useful adjunctive therapies.

Purpura fulminans is a rare syndrome of intravascular thrombosis and hemorrhagic infarction of the skin; it is rapidly progressive and accompanied by vascular collapse.

There are three types of **purpura fulminans**: neonatal purpura fulminans, idiopathic or chronic purpura fulminans, and acute infectious purpura fulminans. Clinical presentation of purpura fulminans involves a premonitory illness followed by the rapid development of a septic syndrome with fever, shock, and disseminated intravascular coagulation. The diagnosis and treatment of these conditions is best accomplished in a regional burn centre in which management of multiple organ failure can be conducted with aggressive debridement and fasciotomy of the necrotic skin. The newest revolutionary advancement in the treatment of neonatal purpura fulminans is the use of activated protein C.

Sugihara A[1], Watanabe H, Oohashi M, Kato N, Murakami H, Tsukazaki S, Fujikawa K.: The effect of hyperbaric oxygen therapy on the bout of treatment for soft tissue infections. J Infect. 2004 May;48(4):330-3.

OBJECTIVES:

Hyperbaric oxygen (HBO) therapy is often combined with antibiotic therapy for infections such as gas gangrene and osteomyelitis. Although numerous investigations have been undertaken to assess the effect of adjunctive HBO therapy on the treatment of infections, the bout of treatment has not been referred in the previous investigations. The purpose of this retrospective study was to evaluate the efficacy of HBO therapy on the bout of treatment for soft tissue infections.

PATIENTS AND METHODS:

In the period between 1994 and 2001, we treated **23 patients** with soft tissue infections. Nine patients were treated with antibiotic chemotherapy alone, and 14 patients were treated with a combination of antibiotic chemotherapy and HBO therapy. The mean bout of treatment was compared between these two groups.

RESULTS:

The mean bout treated with a combination of antibiotic and HBO was significantly shorter than that with antibiotic alone.

CONCLUSION:

Our result indicates that **HBO therapy combined** with antibiotic therapy is able to **shorten the bout of treatment** for soft tissue infections. Therefore, we recommend HBO therapy combined with antibiotic therapy for soft tissue infections.

PMID: 15066334 [PubMed - indexed for MEDLINE]

Hollabaugh RS Jr[1], Dmochowski RR, Hickerson WL, Cox CE. :Fournier's gangrene: therapeutic impact of hyperbaric oxygen. Plast Reconstr Surg. 1998 Jan;101(1):94-100.

Abstract

Many controversial issues exist surrounding the disease pathogenesis and optimal management of Fournier's gangrene. In Fournier's original descriptions, the disease arose in healthy subjects without an obvious cause. Most contemporary studies, however, are able to identify definite urologic or colorectal etiologies in a majority of cases.

To investigate disease presentation, treatment modalities, and overall mortality, a **retrospective** analysis of Fournier's gangrene from a single institution is presented. Since 1990, **26 cases** of Fournier's gangrene have been diagnosed at the University of Tennessee. An evaluation of intercurrent disease revealed that 38 percent of the patients had diabetes mellitus, 35 percent manifested ethanol abuse, and 12 percent were systemically immunosuppressed. Fifteen patients (58 percent) presented with identifiable etiologies for their disease: 31 percent (8) urethral disease or trauma, 19 percent (5) colorectal disease, and 8 percent (2) penile prostheses.

Management in all cases involved prompt surgical debridement with initiation of broad-spectrum antibiotics. Multiple debridements, orchiectomy, urinary diversion, and fecal diversion were performed as clinically indicated. **Fourteen patients received hyperbaric** oxygen as adjuvant therapy.

Statistically significant results were noted with mortality rates of 7 percent in the group receiving hyperbaric oxygen (n = 14) versus 42 percent in the group not receiving hyperbaric oxygen (n = 12). Overall mortality was 23 percent. Controversy still surrounds disease pathogenesis in Fournier's gangrene, particularly in regard to etiology. Our study corroborates current trends in that a clear focus or origin was identified in a majority of the cases.

Although a grim prognosis usually accompanies the diagnosis, this study shows **significant improvement combining traditional surgical and antibiotic regimens with hyperbaric oxygen therapy**.

PMID: 9427921 [PubMed - indexed for MEDLINE]

Korhonen K.: Hyperbaric oxygen therapy in acute necrotizing infections with a special reference to the effects on tissue gas tensions. Ann Chir Gynaecol Suppl. 2000;(214):7-36.

Abstract

Clostridial gas gangrene and perineal necrotizing fasciitis or Fournier's gangrene are rare but serious infections with an acute onset, rapid progression, systemic toxemia and a high mortality rate.

The aim of this study was to investigate the efficacy of surgery, antibiotic treatment, surgical intensive care and in particular the role of hyperbaric oxygen (HBO) in the management of these infections. An **experimental rat model** was used to investigate the possibilities for measuring tissue oxygen and carbon dioxide tensions during hyperbaric oxygen treatment. In addition to this preliminary experimental study, Silastic tube tonometer and capillary sampling techniques were tested to measure the effect of hyperbaric oxygen treatment on subcutaneous oxygen and carbon dioxide tensions in patients with necrotizing fasciitis and healthy controls.

Between January 1971 and April 1997, **53 patients** with Clostridial **gas gangrene** were treated in the Department of Surgery, University of Turku. The patients underwent surgical debridement, broad spectrum antibiotic therapy and a series of hyperbaric oxygen treatments at 2.5 atmospheres absolute pressure (ATA). Twelve patients died (22.6%). Hyperbaric oxygen therapy in gas gangrene **seems to be life-, limb- and tissue saving**. Early diagnosis remains essential. Patient survival can be improved if the disease is recognized early and appropriate therapy instituted promptly.

Between February 1971 and September 1996, **33 patients** with perineal **necrotizing fasciitis** were treated in the Department of Surgery, University of Turku. The management included surgical debridement of the necrotic tissue with incisions and drainage of the involved areas, antibiotic therapy, hyperbaric oxygen treatment at 2.5 ATA pressure and surgical intensive care. Three patients died giving a mortality rate of 9.1%. The survivors received hyperbaric oxygen therapy for 2-12 times. Our results indicate that hyperbaric oxygenation is an **important therapeutic adjunct** in the treatment of Fournier's gangrene.

Electrical equipment should not be used unsheltered in a hyperbaric chamber due to the increased risk of fire. The subcutaneous tissue gas tensions of rats were therefore measured using a subcutaneously implanted Silastic tube tonometer and a capillary sampling technique. The method was successfully adapted to hyperbaric conditions. The subcutaneous oxygen tension levels increased five fold and the carbon dioxide tension levels two fold compared to initial levels. The PO2 and PCO2 of subcutaneous tissue and arterial blood were measured directly in six patients with necrotizing fasciitis and three healthy volunteers in normobaric conditions and during hyperbaric oxygen exposure at 2.5 ATA pressure. The measurements were carried out in healthy tissue and at the same time in the vicinity of the infected area of the patients. During HBO at 2.5 ATA subcutaneous oxygen tensions increased several fold from baseline values and carbon dioxide tensions also increased, but to a lesser degree in both healthy and infected tissues. When examining the subcutaneous PO2 levels measured from patients with necrotizing fasciitis, the **PO2 was regularly higher in the vicinity of the infected area than in healthy tissue.** In general, HBO

treatment resulted in a marked increase in tissue oxygenation in both healthy tissue and in the vicinity of infected tissue. **The hyper-oxygenated tissue zone surrounding the infected area may be of significance in preventing the extension of invading microorganisms.**

PMID: 11199291 [PubMed - indexed for MEDLINE]

Hassan Z[1], Mullins RF, Friedman BC, Shaver JR, Brandigi C, Alam B, Mian MA.: Treating necrotizing fasciitis with or without hyperbaric oxygen therapy. Undersea Hyperb Med. 2010 Mar-Apr;37(2):115-23.

Abstract

There is not enough clinical data to support the benefit of adjuvant HBO2 therapy for necrotizing fasciitis (NF).

We **retrospectively** reviewed our **67 NF cases** to compare the outcomes of adjuvant HBO2 therapy versus non-HBO2 therapy. The overall outcome and morbidity criteria were compared between a group of **29 NF patients** who received the adjuvant **HBO2** and a group of the remaining **38 NF patients** treated by only surgery and other standards of care.

This study did not find any difference between the groups in average length of hospital stay, and their mortality. However, six (25%) of the non-HBO2 group patients required **amputation** of extremities compared to one of the HBO2 group (**Fisher exact p = 0.09**).

Although the benefit of adjuvant HBO2 therapy remains controversial for NF, and the outcomes of this study are not statistically significant, there is a trend in clinical outcomes which shows that the **therapy has the potential to reduce the number of amputation and salvage extremities.**

These findings necessitate multicenter, prospective, case control study to assess the possible benefit of adjuvant HBO2 therapy for NF.

PMID: 20462144 [PubMed - indexed for MEDLINE]

Wilkinson David, David Doolette: Hyperbaric oxygen treatment and survival from necrotizing soft tissue infection. Arch Surg. 2004 Dec; 139(12):1339-45

Hyperbaric Medicine Unit, Department of Anaesthesia and Intensive Care, Royal Adelaide Hospital and The University of Adelaide, Adelaide, Australia. dwilkins@mail.rah.sa.gov.au

HYPOTHESIS: Necrotizing soft tissue infection (NSTI) refers to a spectrum of infective diseases characterized by necrosis of the deep soft tissues. Features of manifestation and medical management have been analyzed for association with outcome. The use of hyperbaric oxygen (HBO(2)) therapy has been recommended as an adjunctive treatment but remains controversial.

DESIGN: Retrospective cohort study.

SETTING: A major tertiary hospital.

PATIENTS: All patients admitted with a diagnosis of NSTI across a 5-year period.

INTERVENTION: Features of manifestation and medical management were analyzed for their association with survival to hospital discharge. Long-term survival was analyzed for the intervention of HBO(2) therapy.

MAIN OUTCOME MEASURES: Primary outcome was survival to hospital discharge. Secondary outcomes were limb salvage and long-term survival after hospital discharge.

RESULTS: **Forty-four patients** were reviewed, with 6 deaths (14%). Survival was less likely in those with increased age, renal dysfunction, and idiopathic etiology of infection and in those not receiving HBO(2) therapy. Logistic regression determined the strongest association with survival was the intervention of HBO(2) therapy (P = .02). Hyperbaric oxygen therapy increased survival with an odds ratio of 8.9 (95% confidence interval, 1.3-58.0) and a number needed to treat of 3. For NSTI involving an extremity, **HBO(2) therapy significantly reduced the incidence of amputation (P = .05). Survival analysis revealed an improved long-term outcome for the HBO(2) group (P = .002).**

CONCLUSION: Hyperbaric oxygen therapy was associated with improved survival and limb salvage and should be considered in the setting of NSTI.

Escobar SJ, Slade JB Jr, Hunt TK, Cianci P.: Adjuvant hyperbaric oxygen therapy (HBO2)for treatment of necrotizing fasciitis reduces mortality and amputation rate. Undersea Hyperb Med. 2005 Nov-Dec;32(6):437-43

Department of Hyperbaric Medicine, Doctors Medical Center, San Pablo, CA, USA.

OBJECTIVE: A retrospective analysis of **42 patients** with necrotizing soft tissue infections treated with adjunctive HBO2 to ascertain efficacy and safety. Overall mortality was 11.9% and morbidity 5%.´

SUMMARY BACKGROUND DATA: Necrotizing soft tissue infections have historically high rates of mortality and morbidity, including amputation. Common misconceptions that prevent widespread use of adjunctive HBO2 for this diagnosis include delays to surgery, increased morbidity, and significant complications.

METHODS: Forty-two consecutive patients (average age 56.1) with necrotizing fasciitis presenting to a major referral centre were treated with adjunctive HBO2 as part of an aggressive program of surgery, antibiotics, and critical care. Involved areas included the lower abdomen (15 patients), thigh and perineum (9 patients), flank (4 patients), lower leg (3 patients), and arm, shoulder, and axilla (2 patients). Co-morbidities included diabetes mellitus, chronic renal failure, intravenous drug abuse, peripheral vascular disease, and malignancy.

RESULTS: Mortality was 11.9% (5 patients). Both amputations (a finger and a penis), occurred prior to transport to our facility. The average number of surgical debridements was 2.8 per patient; 1.25 performed prior to the start of HBO. The infectious process was controlled after an average of 7 HBO2 treatments were administered to ensure successful wound closure. Complications consisted of only mild ear barotrauma in 3 patients (7%), and confinement anxiety in 17 (41%) but did not prevent treatment.

CONCLUSION: Compared to national reports of outcomes with "standard" regimens for necrotizing fasciitis, our experience with HBO2, adjunctive to comprehensive and aggressive management, demonstrates **reduced mortality (34% v. 11.9%),** and **morbidity (amputations 50% v. 0%).** The treatments were safe and no delays to surgery or interference with standard therapy could be attributed to HBO2.

PMID: 16509286 [PubMed - indexed for MEDLINE]

Barclay, Laurie: Hyperbaric Oxygen May Improve Outcome in Necrotizing Soft Tissue Infection *Archives of Surgery*. 2004; 139:1339-1345

Hyperbaric oxygen improves survival and limb salvage in necrotizing soft tissue infection (NSTI), according to the results of a retrospective cohort study published in the December issue of the *Archives of Surgery*.

"Necrotizing soft tissue infection (NSTI) refers to a spectrum of infective diseases characterized by necrosis of the deep soft tissues," write David Wilkinson, FANZCA, from the Royal Adelaide Hospital and The University of Adelaide in Australia, and colleagues. "Features of manifestation and medical management have been analyzed for association with outcome. The use of hyperbaric oxygen (HBO_2) therapy has been recommended as an adjunctive treatment but remains controversial."

Records of all patients admitted with a diagnosis of NSTI to a major tertiary hospital during a five-year period were analysed for the association of various clinical features with survival to hospital discharge, and for the association of HBO_2 therapy with long-term survival. The primary outcome measure was survival to hospital discharge, and secondary outcome measures were limb salvage and long-term survival after hospital discharge.

Of **44 patients** whose records were reviewed, six (14%) died. Factors associated with mortality were increased age, renal dysfunction, unknown etiology of infection, and lack of HBO_2 therapy. Based on logistic regression, the best predictor of survival was the use of HBO_2 therapy (P = .02), which increased survival nearly nine-fold (odds ratio, 8.9; 95% confidence interval, 1.3-58.0; number needed to treat, 3).

When NSTI involved an extremity, HBO_2 treatment reduced the incidence of amputation (P = .05). Survival analysis revealed that the HBO_2 group had an improved long-term outcome (P = .002).

"Hyperbaric oxygen therapy was associated with improved survival and limb salvage and should be considered in the setting of NSTI," the authors write. "Hyperbaric oxygen therapy can be provided safely to patients who are intubated and require intensive care. The incidence of ear barotrauma in this study (eight of 29 patients) suggests prophylactic myringotomy should be routinely considered prior to initiating HBO_2 therapy."

Medscape

Reviewed by Gary D. Vogin, MD

Dahm P, Roland FH, Vaslef SN, Moon RE, Price DT, Georgiade GS, Vieweg J. Outcome analysis in patients with primary necrotizing fasciitis of the male genitalia. Urology 2000; 56 (1): 31-35

OBJECTIVES: To characterize patients with primary necrotizing fasciitis of the male genitalia (Fournier's gangrene) and to identify risk factors and prognostic variables of survival.

METHODS: **Fifty consecutive patients** with primary necrotizing fasciitis of the male genitalia treated at our institution during a 15-year period between 1984 and 1998 were retrospectively analyzed. Of these patients, 44 (88.0%) were found to be eligible for analysis of the outcome parameters. Univariate survival analysis was performed using the Kaplan-Meier algorithm followed by multivariate analysis of statistically significant variables. Six patients (12.0%) who were severely immunocompromised were studied separately.

RESULTS: Medical comorbidities were prevalent, with diabetes being the most common condition (50%). The overall mortality rate was 20% (10 of 50). Three statistically significant predictors of outcome were identified among the variables analyzed. These were the extent of the infection (P = 0.0262), the depth of the necrotizing infection (P = 0.0107), and treatment with hyperbaric oxygen (P = 0.0115). Multivariate regression analysis of these variables identified the extent of the infection (P = 0.0234) as the only statistically significant, independent predictor of outcome in the presence of other covariables.

CONCLUSIONS: The involved body surface area appears to be the most important prognostic variable, with a significant impact on outcome. Given the high mortality of the disease entity and a **trend toward the improved survival of patients receiving hyperbaric oxygen, this treatment form appears indicated in more severe cases.** Immunocompromised patients, who frequently have an atypical and fulminant clinical course, appear to constitute a separate group with a dismal prognosis

de Vaumas C, Bronchard R, Montravers P. [Non pharmacological treatment of severe cutaneous infections: hyperbaric oxygen therapy, dressings and local treatments]. Ann Fr Anesth Reanim. 2006 Sep;25(9):986-9. Epub 2006 May 3. French. PubMed PMID: 16675193.

Beside conventional therapy, the management of necrotizing cellulitis and fasciitis is based on non-pharmacological treatments.

Hyperbaric oxygen therapy and dressings are the most29 frequently used techniques. The usefulness of hyperbaric oxygen therapy is clearly demonstrated in experimental studies while the efficacy of this technique is poorly assessed in clinical practice.

The French consensus conference has concluded to an adjuvant role of hyperbaric oxygen therapy combined to intensive care management, surgery and antibiotic therapy.

Occlusive conventional dressings using humid or vaseline gauze dressings are largely used. Calcium alginate or silver coated dressings might be useful. In addition, vacuum-assisted closure therapy could be proposed in replacement of conventional dressings.

Eltorai IM, Hart GB, Strauss MB, Montroy R, Juler GL. The role of hyperbaric oxygen in the management of Fournier's gangrene. Int Surg 1986; 71 (1): 53-58.

Fournier's gangrene of the external genitals is a complex entity characterized by acute onset, rapid progress to gangrene, toxemia and high mortality rate. The disease may be primary as described by Fournier or secondary with a detectable cause in the colo-rectal area, the lower urogenital tract or in the perineum. The disease may affect healthy young males (originally described by Fournier) or elderly subjects especially with general ill health, cancer, diabetes, liver or renal failure, immunosuppression, etc.

The microbiology is as complex as the etiology. The nosiology is likewise complex. Because the mortality is high, it is important to be aggressive in therapy.

Triple attack is necessary, viz.: antibiotic coverage for aerobes and anaerobes, general supportive measures and adequate surgical debridement**. We, recommend Hyperbaric Oxygen Therapy (HBO) treatment in specialized centers as an adjunctive measure since we had no mortality in the cases we treated.** In expert centers, HBO has very few complications, which are outweighed by the benefit the patient gets. The one-man chamber is the commonest in use, but for a compromised patient the multiplace may be more appropriate. **In the very 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 Fournier

Flanagan CE, Daramola OO, Maisel RH, Adkinson C, Odland RM. Surgical debridement and adjunctive hyperbaric oxygen in cervical necrotizing fasciitis. Otolaryngol Head Neck Surg. 2009 May;140(5):730-4. PubMed PMID: 19393420.

OBJECTIVE: To review our management of cervical necrotizing fasciitis (CNF) with the use of adjunctive hyperbaric oxygen therapy (HBO).

STUDY DESIGN: Case series with chart review.

SUBJECTS AND METHODS: Evaluation of **ten patients** with CNF between 2001 to 2006.

RESULTS: There were five male and six female patients. Mean age was 43 +/- 11 years. Eight cases resulted from an odontogenic source. Comorbidities included diabetes mellitus, hypertension, and substance abuse. All patients had computed tomography scans performed, received intravenous antibiotics, and underwent surgical debridement. Eight patients underwent surgery within 24 hours. The average number of debridements was 2.2 +/- 0.8. Hospitalization was twice as long for diabetic patients (15.5 +/- 8.16 days) compared with nondiabetic patients (7.5 +/- 1.6 days, P = 0.029).

Nine patients had HBO therapy. **Combined data revealed a possible decrease in length of hospitalization with HBO therapy (P < 0.001).** No mortality was documented.

CONCLUSION: **In addition to early and aggressive medical management and surgical debridement, this study suggests that HBO therapy is a beneficial adjunct by potentially decreasing length of hospitalization.** Randomized trials are still needed to demonstrate its efficacy.

Krasova Z, Matusek A, Chmelar D. Prinos hyperbaroxie v lecbe nekrotizujici fasciitidy. [Hyperbaric oxygenation in the treatment of necrotizing fasciitis]. Vnitr Lek 1992; 38 (7): 640-644.
The authors present the results of treatment provided to 11 patients with necrotizing fasciitis who were after a surgical operation and after administration of antibiotics treated in a hyperbaric chamber. A total of 8 patients (82%) recovered completely. The authors discuss the theory of action of hyperbaric oxygen on microorganisms and draw attention to the possible reduction of mortality of this serious disease when using **hyperbaric oxygenation. The latter is considered an important auxiliary method which supplements surgical treatment, rational antibiotic therapy and in particular careful intensive care**

A standard treatment procedure for necrotizing fasciitis in the head and neck region was introduced in 1999 at Rigshospitalet (National Hospital of Denmark) Copenhagen. The new procedure introduced more drastic surgical debridement than before, combined with a set antibiotic regime and intravenous gamma globulin and **adjunctive hyperbaric oxygen treatment** (HBO). To evaluate the effect of this, a **retrospective** study was undertaken, involving **19 patients** treated for NF at the ENT department from 1996-2004. Between 1996 and 1999 eight patients were treated **(non-HBO**) from 1999-2004 eleven patients were treated (**HBO group**). Length of antibiotic treatment was very similar in the two groups (mean 22.5 days) as was bacteriology. Aetiological focus differed marginally with the HBO group showing a clear tendency towards odontogen focus. The HBO group was found to undergo significantly more debridement procedures (3.36). The most drastic difference in the two groups however, was the reduction in mortality. The non-HBO group had a mortality of 75% and in the HBO group they all survived. This obviously resulted in

a prolonged hospital stay for the HBO group (mean 30.8 days). The study concluded that the reduction in mortality was due to the combined effects of the different entities in the new treatment guidelines. It was not possible to isolate a specific factor responsible for the change.

Mathieu D. Place de l'oxygenotherapie hyperbare dans le traitement des fasciites necrosantes. [Hyperbaric oxygen for the treatment of necrotizing fasciitis]. Ann Dermatol Venereol 2001; 128 (3 Pt 2): 411-418.

Necrotizing fasciitis (NF) is a severe often life threatening bacterial infection. There are 2 main reasons to use hyperbaric oxygen (HBO2): the polymorphism of the bacterial flora with a predominance of anaerobes, either strict or aerotolerant; and the tissular necrosis due to an extensive disseminated microvascular obstruction within the infected area. **Association of HBO2 to antibiotics and surgery is based on strong pathophysiological findings as well as on evidences from animal studies. Clinical evidence in human is still lacking even if published data supports its use in severe cases. Controversy on its use as a treatment for NF is caused more by the difficulty to dispose of a hyperbaric equipment allowing for the management of a patient in critical state, than by doubt on its real efficiency**

31Pizzorno R, Bonini F, Donelli A, Stubinski R, Medica M, Carmignani G. Hyperbaric oxygen therapy in the treatment of Fournier's disease in 11 male patients. J Urol 1997; 158 (3 Pt 1): 837-840.

PURPOSE: Optimal tissue oxygenation, as obtained by hyperbaric oxygen therapy, potentiates or restores the host's bactericidal mechanisms and wound healing activity in patients afflicted by serious synergeic aerobic and anaerobic infections of the cutaneous and subcutaneous tissues. Furthermore, hyperbaric oxygen therapy has a direct toxic effect on anaerobic bacteria. We describe our experience with hyperbaric oxygen therapy in the treatment of **11 patients** with Fournier's syndrome.

MATERIALS AND METHODS: The average age of our patients was 59.5 years; the most common predisposing condition was diabetes. **All patients were treated with antibiotic therapy and hyperbaric oxygen therapy (minimum 5 and maximum 24 cycles, consisting of 90 minutes 2.5 atmosphere absolute pressure). Furthermore, 6 of these patients underwent surgical debridement of the wounds and 3 patients underwent delayed reconstructive surgery**.

RESULTS: The results we obtained with hyperbaric oxygen therapy as an adjunctive measure for the treatment of these infections were excellent; our mortality rate for Fournier's disease was 0. Moreover, no complications whatsoever were observed. Furthermore, the 3 patients who underwent delayed corrective surgery presented with well healed tissues and their operations were not complicated by infections or other pathological conditions.

CONCLUSIONS: We believe that our findings, although limited in number, **underline the excellent results that can be obtained with hyperbaric oxygen therapy as an adjunct treatment in Fournier's disease**

Riseman JA, Zamboni WA, Curtis A, Graham DR, Konrad HR, Ross DS : Hyperbaric oxygen therapy for necrotizing fasciitis reduces mortality and the need for debridements. Surgery. 1990 Nov;108(5):847-50
Memorial Medical Center, Southern Illinois University, Springfield.

Twenty-nine patients with necrotizing fasciitis were treated from 1980 to 1988. This study evaluates how the addition of hyperbaric oxygen (HBO) therapy to surgical treatment has affected mortality and the number of debridements required to achieve wound control in these patients.
Two groups of patients were viewed: **group 1** (n = 12) received surgical debridement and antibiotics only; **group 2** (n = 17) received HBO (90 minutes at 2.5 atm, average 7.4 treatments) in addition to surgery and antibiotics. Both groups were similar in age, race, sex, wound bacteriology, and antimicrobial therapy. Body surface area affected was similar, however, perineal involvement was more common in group 2 (53%) than in group 1 (12%). The admitting conditions of patients in group 1 (non-HBO) were diabetic, 33%; white blood cell count more than 12,000, 50%; and shock, 8%. The admitting conditions of patients in group 2 (HBO) were diabetic, 47%; white blood cell count more than 12,000, 59%; and shock, 29%.
Although group 2 patients receiving HBO were more seriously ill on admission, **mortality was significantly lower (23%) compared to group 1 (66%) (p less than 0.02).** In addition, only 1.2 debridements per group 2 patient were required to achieve wound control versus 3.3 debridements per group 1 patient (p less than 0.03).
The addition of HBO therapy to the surgical and antimicrobial treatment of necrotizing fasciitis significantly reduced mortality and wound morbidity (number of debridements) in this study, especially among nonclostridial infections. **We conclude that HBO should be used routinely in the treatment of necrotizing fasciitis**.

PMID: 2237764 [PubMed - indexed for MEDLINE]

Heyboer M. Logue CJ :NECROTIZING FASCIITIS, ADJUNCTIVE HYPERBARIC OXYGEN THERAPY, AND ITS IMPACT ON PATIENT OUTCOME INCLUDING MORBIDITY AND MORTALITY RATE *UHM 2008, Vol. 35, 278 No. 4 — Abs tracts from UHMS ASM 2008.* D131 (was T131)

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INTRODUCTION: Necrotizing fasciitis is a rare but severe illness. It is associated historically with high morbidity and mortality rates. The mainstay of treatment includes aggressive surgical debridement, broad-spectrum antibiotics, and critical care management. Recent meta-analysis suggests that the mortality rate in the absence of adjunctive hyperbaric oxygen therapy remains 34%, and amputation rates have been reported as high as 50%. Controversy remains regarding the adjunctive use of hyperbaric oxygen in the treatment of necrotizing fasciitis.

METHODS: Retrospective analysis of **sixty-four consecutive patients** presenting to a major referral center from May 2000 — December 2007 for **hyperbaric oxygen therapy** with a diagnosis of necrotizing fasciitis in the context of aggressive surgical debridement, broad spectrum antibiotics, and critical care management. Multiple end-points reviewed including age, gender, co-morbidities, location of infection, severity of illness, mortality rate, amputation rate, and level of function.

RESULTS: Frequent co-morbidities included diabetes and obesity. The location of the necrotizing fasciitis included the trunk/perineum/buttock (69%), face/neck (3%), and extremity (28%). Critical care management included initial ICU admission (77%), intubation (61%), and pressor support (41%). Results show a mortality rate of 3.1% and an amputation rate of 1.6%. Patients underwent a mean of 5.4 debridements and 3.7 hyperbaric oxygen treatments.

CONCLUSION: Our findings suggest that the addition of adjunctive hyperbaric oxygen therapy to the overall management of necrotizing fasciitis results in a **significant reduction in mortality and amputation rates** when compared to study results of patients not treated with hyperbaric oxygen therapy. This is in the context of a patient population with severe disease as evidenced by the high rate of torso infection, ICU management, intubation, and pressor support. Patients had low complication rates with all but one due to middle ear barotrauma.

Logue C, **Heyboer** M, Lambert D, Hardy K, Thom S: NECROTIZING FASCIITIS: A RETROSPECTIVE CASE SERIES OF PATIENTS TREATED WITH SURGERY, ANTIBIOTICS AND ADJUVANT HYPERBARIC OXYGEN THERAPY. UHM 2010; 37: 333 C33

The Institute for Environmental Medicine at the University of Pennsylvania, Pa., USA

Introduction: Necrotizing fasciitis (NF) is a severe disease entity associated with high mortality rates even when treated appropriately with prompt surgical debridement and IV antibiotics. Adjunctive hyperbaric oxygen therapy (HBO2) may improve outcomes based upon previous basic science research and published case series. We performed a retrospective analysis of adult patients referred to our facility to receive adjunctive HBO2 for NE
Methods: We identified **62 consecutive adult patients** who were referred to our facility to receive **adjunctive HBO2** for NF from 2002-2008. We also identified **58 adult patients** from hospital records who were appro-priately diagnosed with NF and were not consulted or referred for HBO2 over the same time period. We performed comparative analysis of data from the two groups. Vital signs and laboratory data were collected and APACHE II scores were calculated at the time of first presentation of the patient to a medical facility.
Results: Mortality rate in the HBO2 group (3/62) was significantly lower than the control group (15/58). However, patients in the control group were older (56.9 vs. 50.8 years), had longer delay to surgery (51.9 vs. 30.2 hours), and had fewer debridements (4.0 vs. 5.3). Patients in the HBO2 group had higher APACHE II scores than the control group (11.9 vs 9.9).
Conclusions: In this retrospective analysis of cohorts, mortality rate of patients with NF who received adjunc-tive HBO2 was significantly lower than those who did not (4.8% vs 24.1%). Based on APACHE II scores, these patients were sicker at the time of presentation as Well. Since the control group was older and had longer delays to surgery, it is difficult to attribute the mortality benefit to HBO2 alone. This study illustrates that it reasonable to consider HBO2 as adjunctive treatment for NF, along with prompt surgical debridement and IV antibiotics.

Tamura T, Iida K, Saito M, Shiota S, Nakayama H, Yoshida S.: Effect of hyperbaric oxygen on **Vibrio vulnificus** and murine infection caused by it. Microbiol Immunol. 2012 Oct;56(10):673-9. doi: 10.1111/j.1348-0421.2012.00491.x

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Vibrio vulnificus is a bacterium known to cause fatal necrotizing soft tissue infection in humans. Here, a **remarkable therapeutic effect of hyperbaric oxygen** (HBO) on V. vulnificus infection provoked by its injection into mouse footpads is described. HBO was shown to be bactericidal to this bacterium in vitro as well as in the infected tissue. The bactericidal activity of HBO was shown to be due to reactive oxygen species (ROS), the efficacy of HBO against V. vulnificus infection being accounted for by the high sensitivity of this bacterium to ROS. Besides being somewhat weak in ROS-inactivating enzyme activities, this bacterium is also unusually sensitive to ultraviolet light and other DNA-damaging agents. It seems likely that the sensitivity of V. vulnificus to HBO is mainly due to its poor ability to repair oxidative damage to DNA. These findings encourage clinical application of HBO against potentially fatal V. vulnificus infection in humans.

 PMID: 22775062 [PubMed - in process]

Gegen die HBO sprechen:

George ME1, Rueth NM, Skarda DE, Chipman JG, Quickel RR, Beilman GJ.: Hyperbaric oxygen does not improve outcome in patients with necrotizing soft tissue infection. Surg Infect (Larchmt). 2009 Feb;10(1):21-8. doi: 10.1089/sur.2007.085.

Abstract

BACKGROUND:

Patients with necrotizing soft tissue infections (NSTIs) require prompt surgical debridement, appropriate intravenous antibiotics, and intensive support. Despite aggressive treatment, their mortality and morbidity rates remain high. The benefit of hyperbaric oxygen (HBO) as an adjunctive treatment is controversial. We investigated the effect of HBO in treating NSTIs.

METHODS:

We analyzed clinical data retrospectively for **78 patients** with NSTIs**: 30 patients** at one center were treated with surgery, antibiotics, and supportive care; **48 patients** at a different center received adjunctive HBO treatment. We compared the two groups in terms of demographic characteristics, risk factors, NSTI microbiology, and patient outcomes. To identify variables associated with higher mortality rates, we used logistic regression analysis.

RESULTS:

Demographic characteristics and risk factors were similar in the HBO and non-HBO groups. The mean patient age was 49.5 years; 37% of the patients were female, and 49% had diabetes mellitus. Patients underwent a mean of 3.0 excisional debridements. The median hospital length of stay was 16.5 days; the median duration of antibiotic use was 15.0 days. In 36% of patients, cultures were polymicrobial; group A Streptococcus was the organism most commonly isolated (28%). We identified **no statistically significant differences** in outcomes between the two groups. The mortality rate for the HBO group (8.3%) was lower, although not significantly different ($p = 0.48$), than that observed for the non-HBO group (13.3%). The number of debridements was greater in the HBO group (3.0; $p = 0.03$). The hospital length of stay and duration of antibiotic use were similar for the two groups. Multivariable analysis showed that hypotension on admission and immunosuppression were significant independent risk factors for death.

CONCLUSIONS:

Adjunctive **use of HBO to treat NSTIs did not reduce the mortality rate, number of debridements, hospital length of stay, or duration of antibiotic use**. Immunosupression and early hypotension were important risk factors associated with higher mortality rates in patients with NSTIs.

PMID: 18991520 [PubMed - indexed for MEDLINE]

Mindrup SR[1], Kealey GP, Fallon B.: Hyperbaric oxygen for the treatment of fournier's gangrene. J Urol. 2005 Jun;173(6):1975-7.

Abstract

PURPOSE:

Fournier's gangrene is a necrotizing fasciitis of the genitalia that is associated with high morbidity and mortality. Groups at many institutions have initiated routine adjuvant hyperbaric oxygen (HBO) therapy. We examined whether HBO has made a difference in the morbidity, mortality and costs associated with treating this disease. We also analyzed predictors of extended hospital stay and mortality.

MATERIALS AND METHODS:

The records of patients with the hospital discharge diagnoses of Fournier's gangrene, necrotizing fasciitis, gangrene of the genitalia and scrotal gangrene from 1993 to 2002 were reviewed. Data concerning clinical presentation characteristics, hospital stay, complications, hospital charges and outcomes, including graft failure and death, were analyzed.

RESULTS:

A total of **42 patients** were identified and followed a median 4.2 years. Of the patients 16 underwent surgical debridement and antibiotic therapy alone, and 26 were treated with HBO plus surgery and antibiotics. Overall disease specific mortality was 21.4%, that is 12.5% in the nonHBO group and 26.9% in the HBO group. Three or more complications occurred in 13% of nonHBO and in 19% of HBO cases, of which the most common was myocardial infarction. The skin graft failure rate was 6% (nonHBO) and 8% (HBO). Physical disability was a statistically significant predictor of extended hospital stay ($p < 0.01$). There was a trend toward a correlation between known coronary artery disease and death ($p = 0.2$). A statistically significant difference was noted in average daily hospital charges in nonHBO vs HBO cases ($2,552 vs $3,384 daily, $p < 0.01$).

CONCLUSIONS:

These data do not support routine HBO in the treatment of Fournier's gangrene. There was a **trend toward higher morbidity and mortality in the HBO group**, suggesting that treatment may have been given to patients who were more ill.

PMID: 15879795 [PubMed - indexed for MEDLINE]

Massey PR[1], Sakran JV, Mills AM, Sarani B, Aufhauser DD Jr, Sims CA, Pascual JL, Kelz RR, Holena DN. : J Surg Res. 2012 Sep;177(1):146-51. doi: 10.1016/j.j Hyperbaric oxygen therapy in necrotizing soft tissue infections ss.2012.03.016. Epub 2012 Mar 28.

Abstract

BACKGROUND:

Surgical debridement and antibiotics are the mainstays of therapy for patients with necrotizing soft tissue infections (NSTIs), but hyperbaric oxygen therapy (HBO) is often used as an adjunctive measure. Despite this, the efficacy of HBO remains unclear. We hypothesized that HBO would have no effect on mortality or amputation rates.

METHODS:

We performed a retrospective analysis of our institutional experience from 2005 to 2009. Inclusion criteria were age > 18 y and discharge diagnosis of NSTI. We abstracted baseline demographics, physiology, laboratory values, and operative course from the medical record. The primary endpoint was in-hospital mortality; the secondary endpoint was extremity amputation rate. We compared baseline variables using Mann-Whitney, chi-square, and Fisher's exact test, as appropriate. Significance was set at $P < 0.05$.

RESULTS:

We identified 80 cases over the study period. The cohort was 54% male (n = 43) and 53% white (n = 43), and had a mean age of 55 ± 16 y. There were no significant differences in demographics, physiology, or comorbidities between groups. In-hospital mortality was not different between groups (16% in the HBO group versus 19% in the non-HBO group; $P = 0.77$). In patients with extremity NSTI, the amputation rate did not differ significantly between patients who did not receive HBO and those who did (17% versus 25%; $P = 0.46$).

CONCLUSIONS:

Hyperbaric oxygen therapy does not appear to decrease in-hospital mortality or amputation rate after in patients with NSTI. There may be a role for HBO in treatment of NSTI; nevertheless, consideration of HBO should never delay operative therapy. Further evidence of efficacy is necessary before HBO can be considered the standard of care in NSTI.

PMID: 22487383 [PubMed - indexed for MEDLINE

Brissiaud JC, Azam P, Paret B, Lopy J, Louis C, Collet F . Gangrene cutanee des organes genitaux externes. A propos de 44 cas. [Skin gangrene of the external genitalia. Report of 44 cases]. Chirurgie 1998; 123 (4): 387-393.

Abstract:
STUDY AIM: The aim of this study is to report **44 cases** of male external genitalia cutaneous gangrene, which have been observed at the Principal Hospital of Dakar (Senegal) during a 4-year period.

PATIENTS AND METHODS: The patients all belonged to a black and poor population (mean age: 60 years). Diabetes was present in 11% of the patients. In ten patients, no aetiology was found. The other 34 cases were secondary mainly to urogenital pathology (50%). In 50% of the cases, the lesions were localised on the external genitalia, in the other 50%, the lesions had spread to the hypogastrium and/or the perineum.
Medical treatment included intensive care and triple antibiotic therapy, penicillin, gentamycin and metronidazole. **A hyperbaric oxygen therapy** was associated in 25% of the cases. The surgical treatment in the acute period included incising, debridement, paring, draining, urinary derivation (n = 36), and colostomy (n = 5). Thirteen patients had the benefit of sequential and prospective bacteriological tests

RESULTS: Spontaneous healing was obtained in 48% of the patients within 2 to 3 months. Secondary reconstructive surgery consisted mainly in cutaneous grafts. Global mortality rate was 34%, mortality rate was 30% in the secondary gangrenes, 40% in the primitive gangrenes. Mean hospitalisation duration was 6 weeks. Main sequelae were cheiloid scars.

CONCLUSIONS: The authors try to clarify the nosological imprecisions of this pathology by distinguishing between the secondary types and the primitive types corresponding to Fournier's gangrene, which still inspires many questions concerning its etio-pathogenesis. The surgical treatment must eradicate all necrosis by suited iterative procedures, associated with local care. **Hyperbaric oxygen therapy was not efficient in this series.** This pathology, although rare, needs to be better known, because only an early and efficient surgical and medical treatment will be able to decrease the exceptional gravity of the prognosis

Shupak A, Shoshani O, Goldenberg I, Barzilai A, Moskuna R, Bursztein S.:
Necrotizing fasciitis: an indication for hyperbaric oxygenation therapy? Surgery. 1995 Nov;118(5):873-8
Israel Naval Medical Institute, IDF, Haifa, Israel.
BACKGROUND: The accepted treatment protocol for necrotizing fasciitis (NF) consists of extensive surgery and wide spectrum antibiotics. Hyperbaric oxygenation (HBO) has been recommended as adjuvant therapy for NF, improving patient mortality and outcome. However, the beneficial effect of HBO for NF remains controversial.
METHODS: A retrospective evaluation of treatment outcome in **37 patients** treated for NF between 1984 and 1993 was carried out. The mortality rate, morbidity criteria, and risk factors for grave prognosis were compared between a group of **25 patients** who received **HBO** as part of their treatment protocol and a group of the remaining 12 patients treated by surgical excision and antibiotics alone.
RESULTS: The two groups were found to be similar with regard to age, gender, the incidence of individual risk factors for ominous prognosis, and the Acute Physiology and Chronic Health Evaluation (APACHE) II score for disease's severity on presentation. The mortality rate among the HBO-treated patients was 36%, as opposed to 25% in the non-HBO group. The mean number of surgical débridements required per patient was significantly higher in the HBO group: 3.3 compared with 1.5 in the non-HBO-treated patients. Although the average length of hospitalization for survivors was shorter for the HBO group, the difference between the groups did not reach statistical significance.
CONCLUSIONS: **The results of this study cast doubt on the suggested advantage of HBO in reducing patient mortality and morbidity when used as adjuvant therapy for NF**.

PMID: 7482275 [PubMed - indexed for MEDLINE]

Tabellarische Übersicht über vorhandene Literatur

Erstautor	Jahr	N =	Empfehlung	integriert	Misserfolg	Gruppen	
Mao	2008	20	ja			nein	
Enlich	2005			ja		nein	
Sugihara	2004	23	ja			ja	
Hollabaugh	1998	26	7/40 Fälle	40		ja	
Korhonen	2000	33	9,1% +			nein	
Wilkinson	2004	44	5% +			ja	
Massey	2012	80	nein		16% / 19%	ja	
Escobar	2005	42	11,9%/34%			historisch	
Hassan	2010	67	<Amputation			ja	
Jalali	2005	Meta	ja				
Barclay	2004	44	< 9 x			ja	
Alkallal	2002	1		ja		nein	
Alexander	1998	1		ja		nein	
Angelici	2004	5		Ja		nein	
Bisset	2002			ja			
Blessey	1996			ja			
Bock	1996			ja			
Anwar	2008			ja			
Aydinoz	2007			ja			
Bakker	1985	50	ja				
Bakker	1988		ja				
Ayan	2005	49	ja			nein	
Benrizi	1992	24		ja			
Brown	1994	30	Ja			nein	
Brunet	2000	81		ja			
Cadot	2003			ja			
Catena	2004	12		ja			
Chaplain	1996	20		ja			
Chevallier	1987	13	ja				
Cimsit	2009						
Clark	1999		ja				
Guccia	2009	6		ja			
Dahm	2000	44	ja			nein	
De Backer	1996			ja			
De Decker	2006	1		ja			
De Jong	1992	8		ja			
De Vaumas	2006		ja				
Di Marco	2002	1		ja			
Dominici	1995	1		ja			
Durani	2003	1		ja			
Edwards	2004	1	ja				
Eltorai	1986		ja				
Ersan	1995			ja			
Flam	2008	1	ja	ja			
Flanagan	2009	10	ja			nein	
Gozal	1986		12,5%/72,7%				

Green	1996		ja				
Greinwald	1995	1	ja				
Erstautor	**Jahr**	**N =**	**Empfehlung**	**Etabliert**	**Misserfolg**	**Gruppen**	
Hirn	1993	11					
Hollabaugh	1998	26	7%/42%			ja	
Holmstrom	2000	1		ja			
Hubert	1995			ja			
Hung	2008	1	ja				
Jensen	2009	2		ja			
Jiang	2000	1		ja			
Kaide	2008	Meta	ja				
Kauffman	2000	1		ja			
Kindwall	1992	Meta	ja				
Kingdom	1998	Übers	ja				
Korhonen	1998	33	Ja 9%	ja			
Korhonen	2000	33					
Kostov	1995	3(48)		ja			
Kranz	1986	1		ja			
Krasova	1992	11	Ja 0%/75%			ja	
Langford	1995	6		ja			
Lucca	1990	1		ja			
Marmo	1998	9	ja				
Marszal	1998		ja				
Heyboer	2010	120	Ja 4,8%/24%			ja	
Mastroeni	1999	2	ja				
Meltzer	1997			ja			
Mathieu	2001		ja				
Milovic	2008	6		ja			
Myslinski	2002	1		ja			
Mindrup	2005	42			26,9%/21,4%	ja	
Myers	2009	131		ja			
Paty	1992			ja			
Peled	1994	2		ja			
Pizzorno	1997	11	Ja (0%)				
Plodr	2002			ja			
Radaelli	1987	4		ja			
Riseman	1990	29	Ja 23%/66%			ja	
Ries	2001		ja				
Rath	1998			ja			
Riegels	1984	5		ja			
Heyboer	2008	64	Ja (3,1%)				
Rohmer	1996			ja			
Roquette	2001	1		ja			
Rudack	2003	4		ja			
Schlesinger	2007	1		ja			
Schmidt	2001	52		ja			
Sekeres	2000			ja			
Stenberg	2004	13	ja				
Suner	1999	1		ja			
Shupak	1995	37			36%/25%	ja	
Ukboko	2001			ja			

Verna	2004	2		ja			
Whitesides	2000	12		ja			
Wikerson	1987	1		ja			
Wolf	2008	12	0% +	ja			
Wagner	2011	41		ja			
Yagi	2003	1		ja			
Yuen	2002	1		ja			
Ziser	1985	1		ja			
George	2009	78			8,3%/13,3%		
Massey	2012	80			16%/19%		
Brissiaud	1998	44		Ja	ja		

Meta = Metaanalyse
Empfehlung auch Mortalitätssenkung HBO/ohne HBO

Literaturverzeichnis Fasciitis

Akallal N, Achir A, Regragui W, Farik M, Zidouh S, Benchekroun BA. [Descending necrotizing mediastinitis: a diagnosis not to miss]. Rev Pneumol Clin. 2002 Dec;58(6 Pt 1):355-8. French. PubMed PMID: 12545135

Alexander J, Takeda D, Sanders G, Goldberg H. Fatal necrotizing fasciitis following suction-assisted lipectomy. Ann Plast Surg 1988; 20 (6): 562-565

Angelici AM, Nasti AG, Montesano G, Simonelli I, Palumbo P. [Necrotizing fasciitis: our experience]. G Chir. 2004 May;25(5):167-70. Italian. PubMed PMID: 15382474

Anwar MU, Haque AK, Rahman J, Morris R, McDermott J. Early radical surgery and antimicrobial therapy with hyperbaric oxygen in necrotizing fasciitis. Plast Reconstr Surg. 2008 Jan;121(1):360-1. PubMed PMID: 18176272

Ayan F, Sunamak O, Paksoy SM, Polat SS, As A, Sakoglu N, Cetinkale O, Sirin F. Fournier's gangrene: a retrospective clinical study on forty-one patients. ANZ J Surg. 2005 Dec;75(12):1055-8. PubMed PMID: 16398810.

Aydinoz S, Yildiz S. A different approach to the management of necrotizing fasciitis in neonates: hyperbaric oxygen. Int Wound J. 2007 Mar;4(1):94-5. PubMed PMID: 17425553

Bakker DJ, Kox C. Classification of and therapy for necrotizing soft tissue infections. The role of surgery, antibiotics, and hyperbaric oxygen. Probl Gen Surg 1988; 5 (4): 489-500.

Bakker DJ: Pure and mixed aerobic and anaerobic soft tissue infections. Hyperbaric Oxygen Review 1985;6(2):65-96.

Barclay, Laurie: Hyperbaric Oxygen May Improve Outcome in Necrotizing Soft Tissue Infection Archives of Surgery. 2004; 139:1339-1345

Benizri E, Fabiani P, Migliori G, Quintens H, Chevallier D, Amiel J, Toubol J. Les gangrenes du perinee. Analyse de 24 observations. [Perineal gangrene. Analysis of 24 cases]. Prog Urol 1992; 2 (5): 882-891

Bisset AF, Bazian Ltd, Wessex Institute for Health Research and Development (WIHRD). Hyperbaric oxygen therapy in people wih necrotising fasciitis or Fournier's gangrene. STEER 2002; 2 (14): 1-8

Blessey A, Eubanks A. Hyperbaric oxygen is an important adjunct therapy. Crit Care Nurse 1996; 16 (3): 14-15

Bock KH. Diagnose und Therapie der nekrotisierenden Fasziitis. Hyperbare Oxygenation als erganzende Therapieform. [Diagnosis and therapy of necrotizing fasciitis. Hyperbaric oxygenation as a supplemental therapy form]. Dtsch Med Wochenschr 26-1-1996; 121 (4): 116-117.

Brissiaud JC, Azam P, Paret B, Lopy J, Louis C, Collet F . Gangrene cutanee des organes genitaux externes. A propos de 44 cas. [Skin gangrene of the external genitalia. Report of 44 cases]. Chirurgie 1998; 123 (4): 387-393.

Brogan TV, Nizet V, Waldhausen JH, Rubens CE, Clarke WR. Group A streptococcal necrotizing fasciitis complicating primary varicella: a series of fourteen patients. Pediatr Infect Dis J 1995; 14 (7): 588-594

Brown DR, Davis NL, Lepawsky M, Cunningham J, Kortbeek J . A multicenter review of the treatment of major truncal necrotizing infections with and without hyperbaric oxygen therapy. Am J Surg 1994; 167 (5): 485-489

Brunet C, Consentino B, Barthelemy A, Huart L, Pirro N, Cesari B, Sielezneff Y, Sastre B, Farisse J. Gangrenes perineales: nouvelle approche bacteriologique. Resultats du traitement medicochirurgical (81 cas). [A new bacteriologic approach to perineal gangrene. Results of medico- surgical management. Report of 81 cases]. Ann Chir 2000; 125 (5): 420-427

Cadot P, Rouquette I, Szym P, André JL. [Life-threatening cellulitis, or Fournier's gangrene of the perineum]. J Chir (Paris). 2003 Feb;140(1):22-32. Review. French. PubMed PMID: 12709649

Catena F, La Donna M, Ansaloni L, Agrusti S, Taffurelli M. Necrotizing fasciitis: a dramatic surgical emergency. Eur J Emerg Med. 2004 Feb;11(1):44-8. PubMed PMID: 15167193

Chaplain A, Gouello JP, Dubin J. Cellulites cervicales necrosantes aigues a porte d'entree pharyngee: role possible des anti-inflammatoires steroidiens et non steroidiens. A propos de 5 observations. [Acute cervical necrotizing fasciitis of pharyngeal origin: possible role of steroidal and non-steroidal anti-inflammatory agents. Apropos of 5 cases]. Rev Laryngol Otol Rhinol (Bord) 1996; 117 (5): 377-380.

Chevallier D, Amiel J, Michetti C, Birtwisle Y, Richelme H, Toubol J. Les etats gangreneux du perinee et de la sphere genitale. [Gangrenous states of the perineum and genital region]. J Urol (Paris) 1987; 93 (3): 145-150.

Cimşit M, Uzun G, Yildiz S. Hyperbaric oxygen therapy as an anti-infective agent. Expert Rev Anti Infect Ther. 2009 Oct;7(8):1015-26. PubMed PMID: 19803709

Clark LA, Moon RE. Hyperbaric oxygen in the treatment of life-threatening soft-tissue infections. Respir Care Clin N Am 1999; 5 (2): 203-219.

Cuccia G, Mucciardi G, Morgia G, Stagno d'Alcontres F, Galì A, Cotrufo S, Romeo M, Magno C. Vacuum-assisted closure for the treatment of Fournier's gangrene. Urol Int. 2009;82(4):426-31. Epub 2009 Jun 8. PubMed PMID: 19506410

Dahm P, Roland FH, Vaslef SN, Moon RE, Price DT, Georgiade GS, Vieweg J. Outcome analysis in patients with primary necrotizing fasciitis of the male genitalia. Urology 2000; 56 (1): 31-35

De Backer T, Bossuyt M, Schoenaers J. Management of necrotizing fasciitis in the neck. J Craniomaxillofac Surg 1996; 24 (6): 366-371

De Decker K, Van Poucke S, Wojciechowski M, Ieven M, Colpaert C, Vogelaers D, Jorens PG. Successful use of posaconazole in a pediatric case of fungal necrotizing fasciitis. Pediatr Crit Care Med. 2006 Sep;7(5):482-5. PubMed PMID: 16878050

De Jong Z, Anaya Y, Pontonnier F, Ducasse JL, Izard P, Bloom E, Rouge D. Evolution et traitement de huit malades atteints d'une gangrene perineo-scrotale de Fournier. [Evolution and treatment of 8 patients with Fournier's perineal-scrotal gangrene]. Ann Urol (Paris) 1992; 26 (6-7): 364-367.

de Vaumas C, Bronchard R, Montravers P. [Non pharmacological treatment of severe cutaneous infections: hyperbaric oxygen therapy, dressings and local treatments]. Ann Fr Anesth Reanim. 2006 Sep;25(9):986-9. Epub 2006 May 3. French. PubMed PMID: 16675193

Derancourt C. Quelle prise en charge pour les cellulites et fasciites necrosantes?. [Management of necrotizing cellulitis and fasciitis]. Ann Dermatol Venereol 2001; 128 (3 Pt 2): 452-457

Di Marco L, Berghenti M, Cocuzza C, Manfredini A, Felloni M. Gangrena di Fournier: descrizione di un caso e revisione della letteratura. [Fournier's gangrene. Case report and review]. Chirurgia 2002; 15 (4-5): 157-159

Dominici C, Pacifici A, Trapassi S, Rubino S, Dominici MM. La chirurgia plastica e ricostruttiva nella sindrome di Fournier. [Plastic and reconstructive surgery in Fournier syndrome]. Riv Ital Chir Plast 1995; 27 (1): 101-107

Durrani MA, Mansfield JF. Anesthetic implications of cervicofacial necrotizing fasciitis. J Clin Anesth 2003; 15 (5): 378-381.

Edlich RF, Cross CL, Dahlstrom JJ, Long WB 3rd. Modern Concepts of the Diagnosis and Treatment of Necrotizing Fasciitis. J Emerg Med. 2008 Dec 10. [Epub ahead of print] PubMed PMID: 19081698

Edwards JD, Sadeghi N, Najam F, Margolis M. Craniocervical necrotizing fasciitis of odontogenic origin with mediastinal extension. Ear Nose Throat J. 2004 Aug;83(8):579-82. PubMed PMID: 15487640

Ellis M. Hyperbaric oxygen can be effective in treating postpartum necrotizing fasciitis type I. J Infect 2000; 40 (3): 292-294

Eltorai IM, Hart GB, Strauss MB, Montroy R, Juler GL. The role of hyperbaric oxygen in the management of Fournier's gangrene. Int Surg 1986; 71 (1): 53-58

Ersan Y, Ozgultekin R, Cetinkale O, Celik V, Ayan F, Cercel A. Fournier-Gangraen. [Fournier gangrene]. Langenbecks Arch Chir 1995; 380 (3): 139-143.

Escobar SJ, Slade JB Jr, Hunt TK, Cianci P.: Adjuvant hyperbaric oxygen therapy (HBO2)for treatment of necrotizing fasciitis reduces mortality and amputation rate. Undersea Hyperb Med. 2005 Nov-Dec;32(6):437-43

Flam F, Boijsen M, Lind F. Necrotizing fasciitis following transobturator tape treated by extensive surgery and hyperbaric oxygen. Int Urogynecol J Pelvic Floor Dysfunct. 2009 Jan;20(1):113-5. Epub 2008 May 29. PubMed PMID: 18509584

Flanagan CE, Daramola OO, Maisel RH, Adkinson C, Odland RM. Surgical debridement and adjunctive hyperbaric oxygen in cervical necrotizing fasciitis. Otolaryngol Head Neck Surg. 2009 May;140(5):730-4. PubMed PMID: 19393420

George ME1, Rueth NM, Skarda DE, Chipman JG, Quickel RR, Beilman GJ.: Hyperbaric oxygen does not improve outcome in patients with necrotizing soft tissue infection. Surg Infect (Larchmt). 2009 Feb;10(1):21-8. doi: 10.1089/sur.2007.085.

Geraci G, Pisello F, Lupo F, Cajozzo M, Sciumè C, Modica G. [Fournier's gangrene: case report and review of recent literature]. Ann Ital Chir. 2004 Jan-Feb;75(1):97-106; discussion 106. Review. Italian. PubMed PMID: 15283397.

Gozal D, Ziser A, Shupak A, et al: Necrotizing fasciitis. Arch Surg 1986;121:233-235.

Green RJ, Dafoe DC, Raffin TA: Necrotizing fasciitis. Chest 1996;110(1)219-229.

Greinwald JH, Jr., Wilson JF, Haggerty PG. Peritonsillar abscess: an unlikely cause of necrotizing fasciitis. Ann Otol Rhinol Laryngol 1995; 104 (2): 133-137.

Hassan Z1, Mullins RF, Friedman BC, Shaver JR, Brandigi C, Alam B, Mian MA.: Treating necrotizing fasciitis with or without hyperbaric oxygen therapy. Undersea Hyperb Med. 2010 Mar-Apr;37(2):115-23.

Heyboer M. Logue CJ :NECROTIZING FASCIITIS, ADJUNCTIVE HYPERBARIC OXYGEN THERAPY, AND ITS IMPACT ON PATIENT OUTCOME INCLUDING MORBIDITY AND MORTALITY RATE UHM 2008, Vol. 35, 278 No. 4 — Abs tracts from UHMS ASM 2008. D131 (was T131)

Heyboer Logue C, M, Lambert D, Hardy K, Thom S: NECROTIZING FASCIITIS: A RETROSPECTIVE CASE SERIES OF PATIENTS TREATED WITH SURGERY, ANTIBIOTICS AND ADJUVANT HYPERBARIC OXYGEN THERAPY. UHM 2010; 37: 333 C33

Hirn M. Hyperbaric oxygen in the treatment of gas gangrene and perineal necrotizing fasciitis. A clinical and experimental study. Eur J Surg Suppl 1993; (570): 1-36

Hollabaugh RS Jr1, Dmochowski RR, Hickerson WL, Cox CE. :Fournier's gangrene: therapeutic impact of hyperbaric oxygen. Plast Reconstr Surg. 1998 Jan;101(1):94-100.

Holmstrom B, Grimsley EW. Necrotizing fasciitis and toxic shock-like syndrome caused by group B streptococcus. South Med J 2000; 93 (11): 1096-1098

Hubert J, Fournier G, Mangin P, Punga-Maole M. Gangrene des organes genitaux externes. [Gangrene of the external genitalia]. Prog Urol 1995; 5 (6): 911-924.

Hung JH, Wang JH, Chen CY, Chao KC, Yang MJ, Hung J. Hyperbaric oxygen therapy for cesarean section wound in diabetes mellitus gravida. J Chin Med Assoc. 2008 Jul;71(7):373-6. PubMed PMID: 18653403

Jacoby IJ: Necrotizing soft tissue infections. UHM 2012; 39: 739-752

Jallali N1, Withey S, Butler PE.: Hyperbaric oxygen as adjuvant therapy in the management of necrotizing fasciitis. Am J Surg. 2005 Apr;189(4):462-6.

Jensen KG, Kristensen K. [Necroticing fasciitis in children]. Ugeskr Laeger. 2009 Jan 12;171(3):147. Danish. PubMed PMID: 19174028.

Jiang T, Covington JA, Haile CA, Murphy JB, Rotolo FS, Lake AM. Fournier gangrene associated with Crohn disease. Mayo Clin Proc 2000; 75 (6): 647-649

Kaide CG, Khandelwal S. Hyperbaric oxygen: applications in infectious disease. Emerg Med Clin North Am. 2008 May;26(2):571-95, xi. Review. PubMed PMID: 18406988.

Kauffman CP, Bono CM, Vessa PP, Swan KG. Postoperative synergistic gangrene after spinal fusion. Spine 2000; 25 (13): 1729-1732

Kindwall EP. Uses of hyperbaric oxygen therapy in the 1990s. Cleve Clin J Med 1992; 59 (5): 517-528

Kingdom TT. Cervical necrotizing fasciitis. Curr Opin Otolaryngol Head Neck Surg 1998; 6 (3): 194-198

Korhonen K, Hirn M, Niinikoski J. Hyperbaric oxygen in the treatment of Fournier's gangrene. Eur J Surg 1998; 164 (4): 251-255.

Korhonen K.: Hyperbaric oxygen therapy in acute necrotizing infections with a special reference to the effects on tissue gas tensions. Ann Chir Gynaecol Suppl. 2000;(214):7-36.

Kostov V, Atanasov A, Stoianov K, Kalinova K. Anaerobna neklostridialna infektsiia na melkite tukani. [Anaerobic nonclostridial soft-tissue infection]. Khirurgiia (Sofiia) 1995; 48 (5): 11-14.

Kranz KR, Reed OM, Grimwood RE. Necrotizing fasciitis associated with porphyria cutanea tarda. J Am Acad Dermatol 1986; 14 (2 Pt 2): 361-367.

Krasova Z, Matusek A, Chmelar D. Prinos hyperbaroxie v lecbe nekrotizujici fasciitidy. [Hyperbaric oxygenation in the treatment of necrotizing fasciitis]. Vnitr Lek 1992; 38 (7): 640-644

Langford FP, Moon RE, Stolp BW, Scher RL. Treatment of cervical necrotizing fasciitis with hyperbaric oxygen therapy. Otolaryngol Head Neck Surg 1995; 112 (2): 274-278

Larose-Pierre M, Scrivens Jr JJ, Norwood D, Rappa L. Necrotizing fasciitis caused by group A streptococcus: Case report and therapy update. J Pharm Pract 2002; 15 (3): 290-296.

Lucca M, Unger HD, Devenny AM. Treatment of Fournier's gangrene with adjunctive hyperbaric oxygen therapy. Am J Emerg Med 1990; 8 (5): 385-387

Mao JC, Carron MA, Fountain KR, Stachler RJ, Yoo GH, Mathog RH, Coticchia JM.: Craniocervical necrotizing fasciitis with and without thoracic extension: management strategies and outcome Am J Otolaryngol. 2009 Jan-Feb;30(1):17-23. Epub 2008 Jul 10

Marmo M, Luongo C, Fumo F, Vicario C, Chiacchio D, Mendetta L, Occhiochiuso L. La sindrome del Fournier. Un approccio multidisciplinare. [Fournier's syndrome. A multidisciplinary approach]. Chirurgia 1998; 11 (6): 392-396.

Marszal M, Bielecki K. Martwicze zapalenie skory, tkanki podskornej, powiezi glebokiej oraz miesni: klasyfikacja i leczenie. [Necrotizing dermatitis, infections of soft tissue and deep fascia: classification and treatment]. Wiad Lek 1998; 51 (1-2): 64-70

Massey PR1, Sakran JV, Mills AM, Sarani B, Aufhauser DD Jr, Sims CA, Pascual JL, Kelz RR, Holena DN. : J Surg Res. 2012 Sep;177(1):146-51. doi: 10.1016/j.j Hyperbaric oxygen therapy in necrotizing soft tissue infections ss.2012.03.016. Epub 2012 Mar 28.

Mastroeni F, Novella G, Curti P, D'Amico A, Lusardi L, Porcaro AB, Tallarigo C. Gangrena di Fournier: osservazione di due casi e revisione della letteratura. [Fournier's gangrene: report of 2 cases and review of the literature]. Arch Ital Urol Androl 1999; 71 (1): 31-34

Mathieu D, Neviere R, Lefebvre-Lebleu N, Wattel F. Les infections anaerobies des tissus mous. [Anaerobic infections of the soft tissues]. Ann Chir 1997; 51 (3): 272-287

Mathieu D. Place de l'oxygenotherapie hyperbare dans le traitement des fasciites necrosantes. [Hyperbaric oxygen for the treatment of necrotizing fasciitis]. Ann Dermatol Venereol 2001; 128 (3 Pt 2): 411-418

McHenry CR, Piotrowski JJ, Petrinic D, et al: Determinants of mortality for necrotizing soft-tissue infections. Ann. Surg. 1995;221(5):558-565

Meltzer DL, Kabongo M. Necrotizing fasciitis: a diagnostic challenge. Am Fam Physician 1997; 56 (1): 145-149

Milović N, Bancević V, Campara Z, Kosević B, Zoranović U. Fournier's gangrene. Vojnosanit Pregl. 2008 Oct;65(10):775-8. PubMed PMID: 19024125

Mindrup SR1, Kealey GP, Fallon B.: Hyperbaric oxygen for the treatment of fournier's gangrene. J Urol. 2005 Jun;173(6):1975-7.

Myslinski W, Mosiewicz J, Kazubek M, Przyszlak-Szabala M, Krupski W, Pegiel-Sicko E, Hanzlik J. The influence of nonsteroidal anti-inflammatory drugs abuse and chronic stress on the development of necrotizing fasciitis--case report. Ann Univ Mariae Curie Sklodowska [Med] 2002; 57 (2): 459-462

odonou R, Hounnasso PP, Gbessi DG, Akpo C. Les gangrenes peno-perineo-scrotales. Aspects epidemiologiques, diagnostiques et therapeutiques. A propos de 32 cas. [Penile-perineal-scrotal gangrene. Epidemiologic, diagnostic, and therapeutic features. Report of 32 cases]. Prog Urol 2000; 10 (2): 271-276.

Ouazzani A, Dequanter D, Buttafuoco F, Raynal P, Lothaire P. [Cervical necrotizing fasciitis arising from dental abscess: a rare clinical observation]. Rev Med Brux. 2009 Mar-Apr;30(2):99-105. French. PubMed PMID: 19517906

Paty R, Smith AD. Gangrene and Fournier's gangrene. Urol Clin North Am 1992; 19 (1): 149-162.

Peled M, Rubin A, Laufer D. [Cervical necrotizing fasciitis]. Harefuah 1994; 126 (11): 651-4, 691

Pizzorno R, Bonini F, Donelli A, Stubinski R, Medica M, Carmignani G. Hyperbaric oxygen therapy in the treatment of Fournier's disease in 11 male patients. J Urol 1997; 158 (3 Pt 1): 837-840.

Plodr M, Vackova M. Hluboke nekrotizujici infekce mekkych tkani. Nekrotizujici fasciitida a nekrotizujici myozitida. [Deep necrotizing soft tissue infections. Necrotizing fasciitis and necrotizing myositis]. Epidemiol Mikrobiol Imunol 2002; 51 (4): 156-160

Radaelli F, Della VA, Colombi M, Bregani P, Polli EE. Acute gangrene of the scrotum and penis in four hematologic patients. The usefulness of hyperbaric oxygen therapy in one case. Cancer 1987; 60 (7): 1462-1464

Ramaswami RA, Lo WK. Use of hyperbaric oxygen therapy in Hong Kong. Hong Kong Med J 2000; 6 (1): 108-112

Rath E, Shelef I, Avinoah E, Lichtman Y, Levy O, Atar D. [Necrotizing soft tissue infection]. Harefuah 1998; 134 (9): 695-7, 750

Richard F Edlich; Kathryne L Winters; Charles R Woodard; L D Britt; William B Long: Massive soft tissue infections: necrotizing fasciitis and purpura fulminans. J Long Term Eff Med Implants. 2005; 15(1):57-65

Riegels-Nielsen P, Bang-Jensen E, Hesselfeldt-Nielsen J. Fournier's gangrene. Ugeskr Laeger 1984; 146 (40): 3022-3025

Riegels-Nielsen P, Hesselfeldt-Nielsen J, Bang-Jensen E, Jacobsen E. Fournier's gangrene: 5 patients treated with hyperbaric oxygen. J Urol 1984; 132 (5): 918-920

Ries I, J. Blaudszun, M. Baumann, R.Tauberl: Passagere Kolostomie zur Therapieoptimierung bei Fournier-Gangrän. Urologe 2001, 31: 580

Riseman JA, Zamboni WA, Curtis A, Graham DR, Konrad HR, Ross DS. Hyperbaric oxygen therapy for necrotizing fasciitis reduces mortality and the need for debridements. Surgery 1990; 108 (5): 847-850.

Rohmer D, Bianciotto E, Martin-Hunyadi C, Ebel M, Demuynck-Roegel C, Berthel M, Kuntzmann F. Gangrene de Fournier: a propos de trois cas chez la personne agee. [Fournier's gangrene: On three elderly cases]. Rev Geriatr 1996; 21 (2): 143-146.

Rouquette-Vincenti I, Petitjeans F, Villevieille T, Szymczyszyn P, Fangio P, Baranger B, Brinquin L. Gangrène gazeuse sur terrain d'obésité morbide et de diabète: un réel challenge thérapeutique. [Obesity, diabetes mellitus, and gas gangrene: A major therapeutic challenge]. Ann Endocrinol 2001; 62 (6): 525-528

Rudack C, Eikenbusch G, Stoll W, Hermann W. Therapeutisches Management nekrotisierender Weichteilinfektionen des **Halses**. [Therapeutic management of necrotizing neck infections]. HNO 2003; 51 (12): 986-992

Sawin RS, Schaller RT, Tapper D, Morgan A, Cahill J. Early recognition of neonatal abdominal wall necrotizing fasciitis. Am J Surg 1994; 167 (5): 481-484

Schlesinger NH, Friis-Møller A, Hvolris J. [Necrotizing fasciitis after arthroscopic synovectomy of an infected prepatellar bursa]. Ugeskr Laeger. 2007 Apr 30;169(18):1693-5. Danish. PubMed PMID: 17532880

Schmit JL. Enquete prospective. Erysipele et cellulites necrosantes: quelle prise en charge en milieu hospitalier? [A prospective study on erysipelas and infectious cellulitis: how are they dealt within hospital?]. Ann Dermatol Venereol 2001; 128 (3 Pt 2): 334-337

Sekeres LA. Necrotizing fasciitis. A perioperative case study. Crit Care Nurs Clin North Am 2000; 12 (2): 181-186

Shupak A, Shoshani O, Goldenberg I, Barzilai A, Moskuna R, Bursztein S.:Necrotizing fasciitis: an indication for hyperbaric oxygenation therapy? Surgery. 1995 Nov;118(5):873-8.

Stenberg AE, Larsson A, Gårdlund B, Kumlien J, Lind F, Nordlander B. [13 cases of cervical necrotizing fasciitis--all patients survived. Surgery, antibiotics and hyperbaric oxygenation give the best results]. Lakartidningen. 2004 Jul 8;101(28-29):2336-41. Swedish. PubMed PMID: 15291312

Sugihara A[1], Watanabe H, Oohashi M, Kato N, Murakami H, Tsukazaki S, Fujikawa K.: The effect of hyperbaric oxygen therapy on the bout of treatment for soft tissue infections. J Infect. 2004 May;48(4):330-3.

Suner IJ, Meldrum ML, Johnson TE, Tse DT. Necrotizing fasciitis after cosmetic blepharoplasty. Am J Ophthalmol 1999; 128 (3): 367-368.

Tamura T, Iida K, Saito M, Shiota S, Nakayama H, Yoshida S.: Effect of hyperbaric oxygen on Vibrio vulnificus and murine infection caused by it. Microbiol Immunol. 2012 Oct;56(10):673-9. doi: 10.1111/j.1348-0421.2012.00491.x

Ugboko VI, Assam E, Oginni FO, Amole AO. Necrotising fasciitis of the head and neck: a review of the literature. Niger J Med 2001; 10 (1): 6-10

Verna G, Fava F, Baglioni E, Cannata M, Devalle L, Fraccalvieri M. Le gangrene de Fournier: remarques sur deux cas cliniques. [Fournier's gangrene: remarks on two clinical cases]. Ann Chir Plast Esthet 2004; 49 (1): 37-42

Wagner S, Greco F, Hoda MR, Kawan F, Heynemann H, Fornara P.: Is intensive multimodality therapy the best treatment for fournier gangrene? Evaluation of clinical outcome and survival rate of 41 patients. Surg Infect (Larchmt). 2011 Oct;12(5):379-83. Epub 2011 Sep 23

Waisman D, Shupak A, Weisz G, Melamed Y. Hyperbaric oxygen therapy in the pediatric patient: the experience of the Israel Naval Medical Institute. Pediatrics 1998; 102 (5): E53

Wang J, Li F, Calhoun JH, Mader JT. The role and effectiveness of adjunctive hyperbaric oxygen therapy in the management of musculoskeletal disorders. J Postgrad Med 2002; 48 (3): 226-231.

Wessells H. Genital skin loss: unified reconstructive approach to a heterogeneous entity. World J Urol 1999; 17 (2): 107-114.

Whitesides L, Cotto-Cumba C, Myers RA. Cervical necrotizing fasciitis of odontogenic origin: a case report and review of 12 cases. J Oral Maxillofac Surg 2000; 58 (2): 144-151

Wilkerson R, Paull W, Coville FV. Necrotizing fasciitis. Review of the literature and case report. Clin Orthop 1987; (216): 187-192

Wilkinson David, David Doolette: Hyperbaric oxygen treatment and survival from necrotizing soft tissue infection. Arch Surg. 2004 Dec; 139(12):1339-45

Wolf H, Ovesen T. [Necrotizing fasciitis in the **head and neck region**]. Ugeskr Laeger. 2008 Aug 18;170(34):2563-6. Danish. PubMed PMID: 18761840.

Yagi H, Takechi Y, Hiraki S, Yamaguchi A, Yoshizato M, Furuyama M. [A life saving case of Vibrio vulnificus (septic type)]. Kansenshogaku Zasshi 2003; 77 (3): 167-173

Yuen JC, Feng Z. Salvage of limb and function in necrotizing fasciitis of the hand: role of hyperbaric oxygen treatment and free muscle flap coverage. South Med J 2002; 95 (2): 255-257.

Ziser A, Girsh Z, Gozal D, Melamed Y, Adler M. Hyperbaric oxygen therapy for Fournier's gangrene. Crit Care Med 1985; 13 (9): 773-774.