Prognostic Aspects, Survival Rate, and Predisposing Risk Factors in Patients with Fournier’s Gangrene and Necrotizing Soft Tissue Infections: Evaluation of Clinical Outcome of 55 Patients

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Key Words
Necrotizing soft tissue infection · Fournier’s gangrene · Necrotizing fasciitis · Gas gangrene · Hyperbaric oxygen therapy

Abstract
Objective: To determine predisposing or prognostic factors and mortality rates of patients with Fournier’s gangrene compared to other necrotizing soft tissue infections (NSTI).

Material and Methods: Data of 55 intensive care patients (1981–2010) with NSTI were evaluated. Data were collected prospectively. Results: 43.4% of the patients were in septic condition and 27.3% were hemodynamically unstable. Half of the patients showed predisposing factors (52.7%). The lower extremity (63.2%), abdomen (30.9%), and perineum (14.5%) were most affected. Polymicrobial infections were frequent (65.5%, mean 2.8, range: 1–4). The mortality rate was 16.4% (n = 9). An increase was shown for diabetes mellitus (20%), cardiac insufficiency (22.3%), septic condition at presentation (33.3%), abdominal affection (47.1%), and hemodynamic instability (46.7%). Comparing survivors and nonsurvivors, statistical significance was seen with age (p < 0.001), septic condition at admission (p < 0.001), hemodynamic instability (p < 0.001), low blood pressure (p < 0.001), and abdominal affection (p < 0.001). In laboratory findings, an increase of creatine kinase (p < 0.001) and lactate (p < 0.001) and a decrease of antithrombin III (p < 0.007) and the Quick value (p < 0.01) proved to be significant. Conclusion: Patients with Fournier’s gangrene do not differ in all aspects from those with other NSTI. Successful treatment consists of immediate surgical debridement, broad-spectrum antibiotic treatment, and critical care management. Supportive hyperbaric oxygen therapy should be considered.

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Introduction

Necrotizing soft tissue infections (NSTIs) constitute a spectrum of diseases of any layer within the soft tissue compartment that is associated with necrotizing changes, characterized by fulminate, widespread necrosis of soft tissue, systemic toxicity, and high mortality. Although no clear definition exists, the disease can clinically be subdi-
vided in superficial infections (necrotizing cellulitis) confined to the cutis and subcutis, and those reaching deeper regions [1]. Necrotizing fasciitis is a severe NSTI involving primarily the superficial fascia and subcutaneous tissue. In the perineal, genital, and perianal regions, it is often referred to as Fournier’s gangrene. Gas gangrene, on the other hand, is caused by Clostridia. Despite advances in antibiotic therapy and intensive medical treatment, these infections still pose a serious challenge. The disease is characterized by a rapid aggravation and the frequent loss of extremities, as well as high mortality rates of up to 76% [2]. It can appear as a result of a trauma, surgical intervention, an accidental or sometimes minor injury, or even spontaneously. Originally reported by Baurienne [3] in 1794, Jean Alfred Fournier [4], a Parisian dermatologist and venereologist, was the first to describe this fulminate infection of the subcutaneous tissue and superficial fascia to the scrotum, penis, and perineum. The first description of necrotizing fasciitis in a significant number of cases was published by Joseph Jones [5] in 1871, a surgeon in the Confederate army, who reported a mortality rate of 46% in 2,642 soldiers afflicted during the Civil War. In 1924, Meleny [6] isolated Streptococcus pyogenes as a causative organism of soft tissue infections. Streptococcus pyogenes is the most referred to cause of this disease, named ‘flesh-eating bacteria’ or ‘killerbug’ in the lay press as well as the is the most referred to cause of this disease, named ‘flesh-eating bacteria’ or ‘killerbug’ in the lay press as well as the.

The study included all patients presenting at our hospital with necrotizing infections of the skin and the subcutis with or without necrosis of the muscle which showed a systemic progression and who were in need of intensive care. Patients treated on peripheral wards were not included. Thus, we look at a selected group of patients with an advanced stage of the disease. From 1981 to 2009, the medical records of 55 patients were reviewed for demographics, age, gender, predisposing factors, clinical and laboratory findings, anatomic site of infection, surgical interventions, additional treatment, clinical outcome, and mortality. A statistical evaluation was performed to identify predisposing and prognostic factors. The patient cohort consisted of 34 male patients (61.9%) and 21 female patients (38.1%), ranging in age from 14 to 82 years, with a median age of 48 years. Sepsis was diagnosed on the basis of the definitions issued by the American College of Chest Physicians/Society of Critical Care Medicine (ACCP/SCCM) Consensus Conference Committee in 1992 [12], i.e. when: (1) an infection was clinically or microbiologically detected, and (2) a systemic host reaction was present (hypothermia <36.0°C or hyperthermia >38.0°C, tachycardia >90 beats/min, leukocytosis >12,000/l or leukenopenia <4,000/l or tachypnea >20 breaths/min), and infection-induced organ dysfunction was detected [metabolic acidosis (pH <7.36), acute encephalopathy, thrombocytopenia (<60,000/l), arterial hypotension (<100 mm Hg systolic), or renal dysfunction (serum creatinine >1.5 mg/dl or oliguria <500 ml/day)]. All patients were treated with immediate surgical debridement. Nonviable and infected tissue was excised until healthy tissue was reached. Repeated debridements were performed in cases with worsening clinical parameters, recurrent tissue necrosis, or delayed wound recovery. Broad-spectrum antibiotics were immediately started and later adapted according to microbiological results. Hyperbaric oxygen therapy (HBO) was administered according to the 'Boerema-Schema TS 300-90', i.e. 300 kPa/3 bar for 90 min, while continuing the intensive care [11]. The data were collected prospectively and analyzed retrospectively. A commercially available statistical software package (SPSS Inc., Chicago, Ill., USA) was used for the statistical analyses, performing the Mann-Whitney U test and Fisher’s exact test. p < 0.05 was considered significant.

Approximately half (52.7%) of the patients showed predisposing factors, about a third (32.7%) of the patients had a cardiac insufficiency NYHA II and higher, and 27.3 and 25.4% suffered from diabetes mellitus and hypertension,

Patients and Methods

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Results

Approximately half (52.7%) of the patients showed predisposing factors, about a third (32.7%) of the patients had a cardiac insufficiency NYHA II and higher, and 27.3 and 25.4% suffered from diabetes mellitus and hypertension,
respectively. Arteriosclerosis was found in 23.6%. At the time of admission, 52.7% of the patients received controlled respiration, 43.6% were already septic, and 27.3% showed hemodynamic instability, necessitating the application of vasopressors. All patients (100%) showed local reddening, swelling, and necrosis. All addressable patients (n = 17, 30.9%) complained of severe pain. The typical crepitation was found in 73.6% of all cases. The lower extremities were most frequently affected (63.2%), followed by the abdominal wall (30.9%) and the perineum (14.5%). In the other 11, NSTI was found on the hand (n = 2), forearm (n = 3), neck (n = 2), and thorax (n = 6). Two or more areas were affected in 18 cases. Muscular affection could be found in 32.7% of the cases. The number of bacteria isolated in each patient varied from 1 to 4 species. The most frequent pathogen was *Clostidium perfringens* (67.3%), followed by *Enterobacter cloacae* (30.9%), *Streptococcus* group A (30.9%), and *Staphylococcus aureus* (25.4%). Polymicrobial infections were found in 65.5% of all patients (mean 2.8). The surgical procedures included repeated debride-ments in 78.2% and amputations and excarticulations in 25.4% of the cases (mean number of interventions: 3). During intensive care treatment, controlled respiration was necessary in 74.5% of all cases and the application of vasopressors was necessary in 50.9%. All patients received combined intravenous antibiotic therapy. The average stay on the intensive care unit was 11.8 days. Supportive HBO was performed in nearly all cases (96.4%). As the hyperbaric chamber is included in our intensive care unit, unproblematic continuation of intensive care treatment was possible. The average number of hyperbaric oxygen treatments was 7.5. Our mortality rate was 16.4% (n = 9). An increase in the mortality rate could be seen in patients with diabetes mellitus (20%), cardiac insufficiency (22.3%), a septic condition at presentation (33.3%), muscular involvement (38.9%), and above all if the abdomen was affected (47.1%) or the disease had already caused hemodynamic instability (46.7%). Taking into account changes in intensive care management and available antibiotics, we divided the cohort into three decade groups (1981–1990, 1991–2000, and 2001–2010). We found an improvement in mortality rates of 20% (3/15), 15.8% (3/19), and 14.3% (3/21).

The comparison between the survivors and the non-survivors shows a statistical significance for the factor age (43.7 vs. 64.6 years, p < 0.001), a septic condition at presentation (88.9 vs. 34.8%, p < 0.001), hemodynamic instability (77.8 vs. 17.4%, p < 0.001), low systolic blood pressure (92.8 vs. 120.8 mm Hg, p < 0.001), abdominal affection (88.9 vs. 19.6%, p < 0.001), and muscular involvement (77.8 vs. 4.3%, p < 0.001).

The increase of creatine kinase (383 U/l vs. 501 U/l, p < 0.001) and lactate (2.2 vs. 10.7 mmol/l, p < 0.001) as well as a decrease of the antithrombin III parameter (62.1 vs. 47.6%, p < 0.007) and the Quick value (73.3 vs. 47.6%, p < 0.01; corresponding to the INR) at time of admission also proved to be a significant factor for a fatal prognosis.

The cohort included 8 patients with Fournier’s gangrene (male-to-female ratio 5:3) in need of intensive care medicine. Additional to the scrotal/penile infection, an affection of the perineum was found in all of these patients. Muscular involvement could be found in 3 patients. One patient (with muscular affection) in this group died. Patients with Fournier’s gangrene did not show significant differences concerning any item compared to other localizations of NSTI (table 1).

### Discussion

Severe NSTIs are life-threatening diseases with high mortality rates of 16.9–34% in larger clinical studies and even reaching 76% in smaller studies [2, 9]. An incidence
of 0.4/100,000 inhabitants has been reported [13]; in the USA the incidence has been determined to be 0.04 cases per 1,000 person-years in a larger study, using insurance databases from various states [11]. When Stephens et al. [14] specifically reviewed Fournier’s gangrene in 1993, 449 cases were reported from 1979 to 1988, giving a mean of 45 cases per year. Since then from 1989 to 1998, 973 cases have been reported in the English literature, giving a mean yearly incidence of 97 cases [15]. Death is usually not caused by the often extensive tissue defect, but by the systemic effects of severe sepsis, coagulopathy, acute renal failure, diabetic ketoacidosis, adult respiratory distress syndrome, mesenteric ischemia, aspirations pneumonia, myocardial infarction, hepatic failure, bone marrow failure, and adrenal insufficiency, leading to multiorgan failure [2, 8, 9]. Untreated, the mortality of gas gangrene approaches 100%; surgical treatment alone may reduce the rate to 38% and a combination of all therapeutic options (surgical debridement, antibiotics, critical care medicine, and HBO) may reduce it to 13–19% [11, 16]. Without surgical treatment, necrotizing fasciitis has mortality rates of 100% [13], and overall mortality rates of about 30% [8]. McHenry et al. [2] showed a cumulative mortality rate in nearly 700 patients with Fournier’s gangrene of 34%. In smaller studies, a mortality rate of 7.5–40% was reported [9, 16, 17]. In the biggest study with 1,726 reviewed cases, Eke [15] stated that the mortality rate associated with Fournier’s gangrene is lower than that of other forms of necrotizing fasciitis, varying from 3 to 45%, with an overall mortality of 16%. In our study, we achieved a mortality rate of 16.4% by combining aggressive surgical debridement, antibiotics, critical care management, and HBO in a selected group of patients in an advanced stage, and even reducing it to 14.3% in the last decade.

Early diagnosis of NSTI requires a high level of suspicion and familiarity with the clinical findings [16]. Establishing the diagnosis at the earliest time-point presents the major challenge [17]. Typical clinical findings are severe painful swelling, erythema, and blisters [8]. Sometimes only pain, tenderness, and local hyperthermia may initially be observed, making it difficult to distinguish NSTI from cellulitis [1]. Once the infection progresses, the more typical signs and symptoms including tense edema beyond the area of compromised skin, skin discoloration, bullae, or crepitation can be identified [1, 18]. As the infection spreads along the fascial planes and deeper areas, painless black ulcers may appear. With progressive infection, vascular occlusion, ischemia, and tissue necrosis may occur. As a result, superficial nerves may be damaged, producing localized anesthesia [1] before patients complain about pain [8]. Symptoms may develop over a period of a few hours, but the process can also take several days. Disproportional pain should especially alert the clinician [1].

All of our patients showed typical symptoms. A crepitation of the soft tissue could be perceived in the majority of the cases. The bacterial synergism involves the production of exotoxins whose activities result in necrosis and synthesis of gases that produce the repulsive stench and crepitis, pathognomonic of anaerobic infection [15]. The finding of crepitus and soft tissue air on plain radiography are pathognomonic, although these signs are present in only 37 and 57%, respectively [19]. The localizations of NSTI in our study are comparable to others [20]. We found involvement of the abdominal wall to be a significant factor for mortality.

In a study of Heitmann et al. [8], 4–6 patients with involvement of the trunk died, but none with peripheral affection. Pessa and Howard [18] also state that affection of the abdominal wall leads to higher mortality rates. Czymek et al. [9], however, found no statistical relationship between the involvement of a particular anatomical region and the need for surgical procedures. Additionally, the percentage of body surface affected failed to be a statistically significant parameter [2, 21]. Although NSTI may affect all ages and both sexes, most studies, as well as our results, show a preference of male sex and a median age of about 48–59 years [2, 4, 5, 13, 22]. Increased age has been shown to be a statistically significant factor for the mortality of patients in the studies of McHenry, Eke and Sorensen, Unalp (age >60 years) and Yanar (age >55 years), which is in accordance with our results [2, 9, 14, 15, 21]. Gender does not seem to influence the prognosis, as stated before in other studies [22].

Various pre-existing conditions are associated with an increased risk of NSTI. In the literature, diabetes mellitus, chronic alcohol abuse, peripheral vascular disease [2, 16], chronic renal failure, hepatic dysfunction [15, 22], heart disease, acquired immunodeficiency syndrome, malignant disease [1, 16, 23], nonsteroidal anti-inflammatory drugs [22], drug abuse (specifically injection of drugs), trauma, decubitus ulcer, immune impairment [21], chronic obstructive lung disease, cortisone use [16], obesity, and malnutrition [2] have been reported as risk factors. In our study, 52.7% of the patients showed comorbidities. McHenry et al. [2] stated that the presence of peripheral vascular disease was a factor that approached statistical significance in the patients who died from NSTI. In the study of Czymek et al. [9], all patients who died had pre-existing cardiac conditions (chronic cardiac
insufficiency, coronary heart disease, arterial hypertension). Yanar et al. [16] reported cardiac disorders in 31% of their patients. Sorensen et al. [24] found congestive heart failure and hypertension to be a significant mortality predictor.

Diabetes mellitus was seen in 27.3% of our patients and was associated with a higher mortality rate. This has been confirmed by other studies. Unalp found diabetes mellitus as the most common predisposing factor in patients with Fournier’s gangrene (35.3% of 68 patients), associated with a significantly higher mortality rate (29.1 vs. 10.3%) [22]. Diabetes mellitus clearly is a risk factor for NSTI with a reported prevalence of 39–64% in the published literature [9, 16, 25, 26]. Furthermore, the presence of diabetes has an adverse effect on the survival of the patient [20]. Renal failure and coagulopathy were also significantly associated with higher mortality rates [24].

The existence of one or more comorbidities should raise the physicians’ suspicion of NSTI. Our patients presented with signs of sepsis in 43.4%, and in a hemodynamically unstable condition 27.3%; mechanical ventilation was necessary in 52.7%. Faucher et al. [17] reported similar rates (46% septic shock, 47% mechanical ventilation), and most other studies showed a lower percentage of critically ill patients [14, 21]. Like others, we found that a septic condition and hypotension at the time of admission were significant predicting factors for mortality and outcome [14, 16, 21, 27]. Furthermore, our study shows that an increase of creatine kinase and lactate parameters, as well as a decrease of antithrombin III parameter and the Quick value (corresponds to INR), are significant parameters for predicting an unfavorable outcome. In the literature, systemic acidosis, low hematocrit and albumin levels, high serum creatinine, elevated alkaline phosphatase [21], and elevated urea [20, 21] were also significantly related to mortality.

NSTI requires a combined therapy consisting of early operative debridement, intensive care medicine, and combined antibiotic therapy. In 1981, Kaiser and Cerra [23] published their results with immediate surgical excision (3–4 h) of all necrotic tissue, antibiotics, aggressive nutritional support, and early skin coverage leading to a mortality rate of 8.3%, whereas treatment with antibiotics and delayed (1–3 days) excision of necrotic tissue was associated with a mortality rate of 75%.

The fascial structures of the pelvic floor and the anogenital region are of major importance for understanding the spread of Fournier’s gangrene in the pelvic floor and anogenital region. Colles’ fascia, which is the superficial fascia of the perineum, is continued as tunica dartos over the scrotum and penis. Colles’ fascia is attached to the urogenital diaphragm and merges with Scarpa’s fascia of the anterior abdominal wall. Buck’s fascia surrounds the deeper structures of the penis and periurethral region. Infection may spread from Buck’s fascia to Colles’ fascia and the dartos fascia especially in cases of injury [9]. When the penis is involved, the corpora are usually spared while the skin sloughs off. However, synchronous thrombosis of the corpus spongiosum and cavernosum has been reported [15, 28]. The male gonads are relatively well protected since they are covered by a special fascia (tunica vaginalis) and receive their blood supply from the retroperitoneum. Orchidectomy is therefore necessary only in rare cases [9]. In one study, orchidectomy was performed, at the discretion of the surgeon, in 6 patients because of the observed severe infection in peritesticular tissues; however, in the pathological review of the specimen, the testicles were not found to be involved [16]. On the other hand, a necrotic testis should always raise the suspicion of a retroperitoneal or intra-abdominal spread of the disease [9].

The mean number of debridements varies from 2 to 8 surgical procedures per patient, with absolute numbers ranging from 1 to 21; for a control of infection most studies report about 2–3 surgical measures [5, 13, 22]. Several studies failed to find a correlation between the number of debridements and the rate of mortality [15, 21]. As Faucher et al. [17] stated, initial surgery should be a true ‘search and destroy’ mission, in which all necrotic and infected tissue is resected, regardless of the wound that is created and the potential problems of complete closure, and samples should be taken for microbiologic culture [16]. Mere incision and drainage does not constitute adequate therapy [8].

Various bacteria have been identified in patients with NSTIs. The organisms are in most cases indigenous commensals and include Clostridia, Klebsiella, streptococci, coliforms, staphylococci, bacteroids, and corynebacteria. In synergism, one bacterium produces a nutrient for another, which in turn produces a leukocidal toxin, protecting both from phagocytosis. Furthermore, the aerobe produces a thriving atmosphere for the anaerobe by decreasing the oxygen tissue tension [14–16]. Fungal infections may be found, but they are rare. In our study, 65% of the cases were polymicrobial and 35% were monobacterial. Clostridium perfringens (67.3%), Streptococcus group A (30.9%) and Staphylococcus aureus (25.4%) were the most common microorganisms identified in our microbiological cultures.
Broad-spectrum antimicrobial therapy should be started empirically at once but should not delay surgical treatment as there is no proof that antibiotics can reduce the extent of surgical debridement or even stop NSTIs [1, 4]. Empirical antibiotic therapy should be a triple drug therapy, covering a polymicrobial infection with Gram-positive, Gram-negative, and anaerobic organisms [1, 5, 19]. Penicillin is recommended for streptococci, metronidazole for anaerobic organisms, and a third-generation cephalosporin (with or without gentamicin) for coliform organisms and staphylococci [15]. Combinations of penicillin (or ampicillin or third-generation cephalosporins), metronidazole, and aminoglycosides for Gram-negative aerobes have been reported [4, 5].

When the infection is acquired in the hospital, multidrug-resistant bacteria should be taken into account. The antibiotic regimen must be reassessed based on the microbiological results. Antibiotics should be continued until no further debridement is needed and the patients’ condition has improved, but no specific guideline exists as to duration of treatment. Long-term administration is not necessary and may predispose the patient to wound colonization with drug-resistant organisms [1, 25].

Physiologic support including mechanical ventilation combined with close invasive monitoring in an intensive care unit setting has to be established. Organ failure, such as acute renal failure and acute respiratory distress syndrome, requires replacement therapies. Appropriate early nutritional support, delivered enterally if possible, helps to control the catabolic response of these patients. Aggressive fluid resuscitation and blood component therapy is often required during the perioperative period. Judicious control of glucose, as well as novel therapeutic approaches for severe sepsis and septic shock, should be considered to optimize the host response to infection [19].

As a local infection progresses, the bacterial metabolism depletes the oxygen in the affected area. Additionally, the accumulation of metabolic products lowers the oxidation-reduction potential and tissue oxygen levels. This leads to an inhibition of phagocytosis and bacterial clearance, a decrease of fibrocytic synthesis of collagen, and a reduced effect of aminoglycosides [11, 26].

HBO has several beneficial effects on severe NSTI, especially on clostridial infections. HBO can raise the physically dissolved oxygen level in blood from 0.3 ml O₂/dl (normal atmospheric pressure) to 2.1 ml/dl (1 bar), 4.4 ml/dl (2 bar), and 6.8 ml/dl (3 bar) [29]. A pO₂ of 80–250 mm Hg stops the production of alpha-toxin and a pO₂ of 1,500 mm Hg is bactericide to Clostridia [11]. Therefore, HBO may inhibit bacterial reproduction, thus enabling the body to utilize its own host defense mechanisms. The systemic toxicity as well as the local spread of the necrosis can be reduced [28], which will reduce the probability of amputations and therefore the grade of handicap [11, 29], thus leading to better mortality rates [25].

In NSTI, the use of HBO remains disputable [8, 30]. Available data are controversial, and although the beneficial effects have been reported in the literature [9, 26], there is increasing doubt as to whether HBO has a measurable positive effect on morbidity and mortality [9, 27, 31, 32]. A review of 1,726 cases of Fournier’s gangrene concludes that hyperbaric oxygenation increases tissue oxygen tension to a level that inhibits and kills anaerobic bacteria, while also reducing systemic toxicity, limiting necrosis and enhancing demarcation of gangrene [15]. Riseman et al. [30] report of a significant reduction of mortality as well as the number of debridements due to application of hyperbaric oxygen. Korhonen et al. [33] showed in a study of patients with Fournier’s gangrene (n = 33) a very low (9%) mortality rate with HBO. In a retrospective analysis comparing patients of two clinical centers (48 with HBO vs. 30 without HBO) George et al. [32] reported no significant differences in the number of debridements, length of stay at the hospital, or duration of antibiotic therapy. Although not statistically significant, they observed a mortality rate of 13.3% in the non-HBO group and 8.3% in the HBO group [31]. In conclusion, HBO is no standard therapy but may be an important therapeutic adjunct in NSTI [11, 25].

Several scores have been published in order to predict mortality in NSTI. Wong et al. [34] created the Laboratory Risk Indicator for Necrotizing Fasciitis Score (LRINEC), identifying six independent variables associated with NSTI. Each variable, if present, gives a specific number of points towards the final score, ranging from 0 to 13, with a probability of <50% for NSTI in 5 or less points, between 50 and 75% for 6–7 points, and more than 75% if the score is 8 or more points. For the last two groups, they showed a PPV of 92% and an NPV of 96%. The Fournier’s Gangrene Severity Index (FGSI) is a numerical score to describe the acuity of the disease. Several studies proved a higher mortality rate for FGSI score >9 [24]. Hospital stay ranged 2–278 days in the biggest retrospective study of 1,726 cases [15]. Sorensen et al. [24] calculated median hospital charges for Fournier’s gangrene patients to USD 27,646 (survivors USD 26,574 vs. non-survivors USD 40,871). Faucher et al. [17] reported mean charges of USD 153,803 for survivors (mean hospital stay 26.3 days). Thirty percent of survivors required ongoing care after hospital discharge, most often for open wound closure [24].
**Conclusion**

Most importantly, early diagnosis of NSTI requires a high level of suspicion. The relative rarity of NSTI, coupled with its frequently subtle initial presentation, often presents a major diagnostical challenge. It is generally agreed that the successful therapy of severe NSTI consists of several equally important cornerstones: immediate adequate surgical debridement, intravenous antibiotic treatment (for example acylureido-penicillin + amino-glycoside + metronidazole, or carbapenem in case of an allergy to penicillin), and modern critical care management. The fourth pillar of treatment may be supportive HBO in infections with Clostridia; in other severe NSTIs, HBO should be taken into account as an additional therapeutic procedure.

**References**