ORIGINAL ARTICLE

Hyperbaric Oxygen Treatment and Survival From Necrotizing Soft Tissue Infection

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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.

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THE TERM *NECROTIZING SOFT tissue infection* (NSTI) refers to a spectrum of disease entities whereby necrosis of the deeper soft tissue is precipitated by an infective microorganism.[1-3] The necrotic reaction involves liquefaction of the deep tissues and fascia, with spread along these tissue planes. Myonecrosis may occur, and there is variable involvement of overlying skin. While histologic features are consistent, clinical progression is unpredictable and may be indolent or fulminant with severe systemic sepsis. This condition has variously been labeled necrotizing fasciitis, Meleney ulcer, Cullen ulcer, bacterial synergistic gangrene, Fournier gangrene, gas gangrene, and, more sensationally, "flesh-eating bug disease." All of the diagnoses share similar management strategies: early surgical debridement, intensive medical support, and antibiotic therapy directed by identification of the causative organism. Distinguishing between the different diagnoses offers little advantage when clinical manifestations overlap and management is essentially the same. The term *NSTI* recognizes these similarities, amalgamating the many diagnoses under 1 descriptive label and allowing a practical review of manifestation and management.

Review articles have summarized the many case series published in the last 60 years for this condition, with mortality rates ranging from 9% to 76%, although most are in the region of 30%.[1,4] There is no evidence to suggest a trend in mortality rate during this period. There are no prospective controlled data to establish best clinical practice, and most articles have used a combination of surgery and antibiotics. Hyperbaric oxygen (HBO_2) therapy has been suggested as an adjunctive strategy in the management of NSTI.[5]

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Hyperbaric oxygen therapy involves placing the patient in an environment of increased ambient pressure while breathing 100% oxygen, resulting in enhanced oxygenation of the arterial blood and tissues. Hyperbaric oxygen therapy has a number of biological actions that may be of benefit to patients with NSTI. A retrospective case note review was undertaken for patients admitted to the Royal Adelaide Hospital, Adelaide, Australia, with NSTI. Clinical features at the time of hospital admission and management strategies were analyzed according to their association with outcome. For patients who survived to hospital discharge, follow-up was undertaken to determine long-term survival.

METHODS

The research ethics committee approved a retrospective case note review for a 5-year period between 1994 and 1999. Treatment records of the Hyperbaric Medicine Unit and the hospital's *International Classification of Diseases, Ninth Revision* coding records were searched to identify potential cases using the terms *necrotizing fasciitis*, *Fournier gangrene*, and *gas gangrene*. Because the intent of this study was to examine the influence of management decisions on outcome, any patient admitted in extremis and offered only palliative care was excluded from further analysis.

A diagnosis of NSTI was defined by case note documentation during surgical debridement of necrosis of fascia and/or muscle along with variable skin and subcutaneous tissue, supported by clinical and laboratory confirmation of an infective process. Data were collected from medical record entries and investigations performed during the period of hospital stay with NSTI. Factors included presence of comorbidities (medical record entry stating presence of other medical conditions, smoking history, obesity, or excessive alcohol consumption), clinical features at the time of hospital admission (temperature, systolic blood pressure, and results of initial blood investigations), site and presumed etiology of infection, and microbiological characteristics. Management strategies were documented with regard to surgery, antibiotics, intensive care unit admission, and HBO_2 therapy. Studies have suggested that poor outcome was more likely with increased time between hospital admission and first surgical debridement.[1,2] Estimating the time from symptom onset to the patient's hospital admission and then the time from hospital admission to first surgical debridement were calculated to assess the influence of this factor. The primary end point was death during hospital stay. The secondary end point was requirement for limb amputation.

For those patients who survived to hospital discharge, an assessment of long-term survival was made by documented reattendance in the hospital's medical record or a notified date of death. For case notes that did not provide this information, reference was made to updated information distributed by the Registrar of Births, Deaths, and Marriages. These data were used to perform statistical tests for survival analysis.

Statistical analysis was performed using Statistica software (version 6; StatSoft, Tulsa, Okla). Explanatory variables were analyzed for their association with outcome during that hospital stay. Categorical explanatory variables in 2×2 tables were analyzed using a 2-tailed Fisher exact test; the median test was used for 3×2 tables. Continuous explanatory variables were analyzed using the Mann-Whitney *U* test. Explanatory variables suggesting an association with outcome on univariate analysis ($P \leq .10$) were included in a logistic regression model and examined for the best subset.

Hyperbaric oxygen therapy was provided using a steel-hulled multiplace hyperbaric chamber (Cowan Manufacturing Pty Ltd, Warners Bay, Australia; Fink International Pty Ltd, Melbourne, Australia). Treatment was provided at 2.8 atm absolute for 60 minutes with a 30-minute decompression. Three treatments were provided in the first 24 hours and twice a day thereafter until the infection was controlled. A combination of clinical parameters and appearance of the wound at surgical review determined control of infection. A trained nurse attendant was present within the chamber at all times. For intubated patients, ventilation was maintained using a Dräger Hyperlog (Drägerwerk, Lobeck, Germany).

RESULTS

Forty-four cases of NSTI were identified during the 5-year period, with 6 deaths (14%). Two cases involved elderly patients who were severely shocked on hospital admission and offered only palliative care; they were excluded from further analysis.

For patients with NSTI, several preexisting conditions appeared to be prevalent; diabetes was present in 15 (34%) of 44 patients, documented history of alcohol abuse in 11 (25%) of 44 patients, and current steroid use in 6 (14%) of 44 patients. None of these conditions revealed any association with outcome.

Microbiological examination revealed a polymicrobial infection in 36 cases (82%). A single microorganism was cultured in only 7 cases (16%): *Streptococcus pyogenes* in 4 cases, *Staphylococcus aureus* in 2 cases, and *Escherichia coli* in 1 case. No microorganism was identified in 1 case. The most frequently cultured organisms were mixed anaerobes (13 cases [30%]), *Staphylococcus aureus* (9 cases [20%]), *Escherichia coli* (9 cases [20%]), *Enterococci* (8 cases [18%]), coliforms (6 cases [14%]), *Staphylococcus pyogenes* (6 cases [14%]), *Pseudomonas* (5 cases [11%]), and *Clostridium* (4 cases [9%]).

OUTCOME

Comorbidity, features at hospital admission, and management were analyzed with regard to their association with death during hospital stay (**Table 1** and **Table 2**). Nonsurvivors tended to be older and had a higher serum creatinine concentration. All 6 of the deaths occurred in patients whose NSTI developed as a presumed idiopathic process, that is, not preceded by surgery or recognized trauma. Number of surgical debridements and days of ventilation were increased in survivors.

Improved survival was noted in the group receiving HBO_2 therapy. Mortality was 2 of 33 patients (95% confidence interval [CI], 1%-20%) in the HBO_2 group and 4 of 11 patients (95% CI, 11%-69%) in the non-HBO_2 group ($P = .03$). The incorporation of HBO_2 therapy in the management of NSTI was associated with a reduction in the relative risk of death by 83% and corresponds to a number needed to treat of 3.

The factors of age, serum creatinine level, and HBO_2 therapy were used as variables in a logistic regression model of survival. There was no meaningful way to include etiology of infection in the logistic regression model because of the zero frequencies in the surgery and trauma

categories.[6] Number of debridements and duration of ventilation were not included in the logistic regression model because they both were considered a reflection of opportunity in the survival group. The full model was of the form:

$$\text{Logit(survival)} = \beta_0 + \beta_1 \text{HBO}_2 + \beta_2 \text{AGE} + \beta_3 \text{CREATININE}.$$

The most parsimonious model was selected by best subset regression with regression parameters reported as odds ratios, summarized in **Table 3**. The best subset model included the single independent variable of HBO_2 therapy with a survival odds ratio of 8.9 (95% CI, 1.3-58.0).

Raw data were further examined, looking for evidence of heterogeneity between the HBO_2 and non-HBO_2 groups. Univariate analysis found no difference between the groups for all data collected, apart from serum creatinine level, which was higher in the non-HBO_2 group ($P=.005$). The HBO_2 group had a median serum creatinine level of 0.90 mg/dL (80 µmol/L) (range, 0.45-4.52 mg/dL [40-400 µmol/L]) and the non-HBO_2 group, 1.81 mg/dL (160 µmol/L) (range, 0.68-6.22 [60-550 µmol/L]).

Thirty-one patients required admission to the intensive care unit at some point during their hospital stay. For this subgroup, mortality was 2 of 24 patients (95% CI, 1%-27%) in the HBO_2 group and 4 of 7 patients (95% CI, 18%-90%) in the non-HBO_2 group ($P=.01$).

In 16 cases, the NSTI was isolated to a limb. Amputation of that limb was required for 0 of 12 patients (95% CI, 0%-26%) in the HBO_2 group and 2 of 4 patients (95% CI, 7%-93%) in the non-HBO_2 group ($P=.05$).

The 2 deaths in the HBO_2 group occurred on days 2 and 30 of hospital stay. The 4 deaths in the non-HBO_2 group occurred on days 2, 4, 16, and 26 of hospital stay (**Table 4**).

The 33 patients who received HBO_2 therapy had a median of 8 treatments and a range of 1 to 30 treatments. The high end of this range reflects that some patients received further HBO_2 therapy to assist wound closure after the infective process had been controlled.

Compression within a hyperbaric chamber normally requires the conscious performance of a Valsalva maneuver to equalize the pressure within the air space

Table 1. Categorical Variables Analyzed Against Outcome (2-Tailed Fisher Exact Test)

Variable	No. of Survivors	No. of Nonsurvivors	*P* Value
Male	27	3	.36
Female	11	3	
Diabetes			
Yes	12	3	.39
No	26	3	
Peripheral vascular disease			
Yes	2	0	>.99
No	36	6	
Coronary artery disease			
Yes	4	1	.54
No	34	5	
Steroid medication			
Yes	5	1	>.99
No	33	5	
Obese			
Yes	8	1	>.99
No	30	5	
Smoker			
Yes	13	1	.65
No	25	5	
Alcohol abuse			
Yes	10	1	>.99
No	28	5	
Myonecrosis			
Yes	16	2	>.99
No	22	4	
Hyperbaric oxygen therapy			
Yes	31	2	.03
No	7	4	
Amputation			
Yes	4	1	.54
No	34	5	
Site			
Limb	15	1	.42*
Trunk	10	3	
Perineum	13	2	
Etiology			
Trauma	14	0	.07*
Surgery	5	0	
Idiopathic	19	6	

*The median test was used instead of the Fisher exact test.

Table 2. Continuous Variables Analyzed Against Outcome*

Variable	Survivors, Median (Range)	Nonsurvivors, Median (Range)	*P* Value
Age, y	48 (22-99)	65 (45-76)	.02
Systolic blood pressure, mm Hg	120 (60-160)	110 (83-130)	.18
Temperature, °C	37.8 (34.4-40.7)	37.1 (36.2-38.7)	.26
Hemoglobin level, g/dL	11.6 (7.9-16.9)	11.9 (10.7-13.5)	.72
White blood cell count, $\times 10^3$/L	13.1 (2.3-34.0)	14.0 (4.7-19.2)	.82
Albumin level, g/dL	2.6 (1.3-2.8)	2.3 (1.8-3.4)	.54
Creatinine level, mg/dL	0.90 (0.45-6.22)	1.58 (0.68-3.96)	.10
No. of debridements	4 (1-16)	1.5 (1-5)	.07
Ventilation, d	13.5 (2-37)	5.5 (1-30)	.08
Blood transfusion, U	10.5 (0-45)	13 (0-30)	.81
Time to first debridement			
Symptom to hospital admission, d	3 (0.1-30.0)	3 (0.1-7.0)	.73
Hospital admission to surgery, h	9.5 (1-312)	6 (1-96)	>.99

SI conversion: To convert creatinine to micromoles per liter, multiply by 88.4.
*Clinical features and investigations as found at hospital admission using the Mann-Whitney *U* test.

Table 3. Logistic Regression of Survival Against All Variables and Best Subset

Model Used	*P* Value	Explanatory Variable	Parameter Estimate, Odds Ratio (95% Confidence Interval)	*P* Value
		Age	1.03 (0.97-1.09)	.23
All variables	.07	Creatinine level	0.61 (0.0002-1800.0000)	.90
		HBO_2 therapy	6.7 (0.76-58.00)	.09
Best subset	.02	HBO_2 therapy	8.9 (1.3-58.0)	.02

Table 4. Characteristics of Nonsurvivors of Necrotizing Soft Tissue Infection

Day of Death	Sex	Age, y	Comorbidity	Circumstances of Death
HBO_2 group				
Day 2	Male	76	Smoker; alcohol	Overwhelming sepsis
Day 30	Female	70	Colonic malignancy	Transfer from another institution for HBO_2 therapy on day 25 of illness; respiratory failure; withdrawal of therapy
Non-HBO_2 group				
Day 2	Female	45	Obese; diabetes	Overwhelming sepsis
Day 4	Male	58	Steroid medication	Overwhelming sepsis
Day 16	Female	75	Diabetes	Multiorgan failure; withdrawal of therapy
Day 26	Male	60	Diabetes; ischemic heart disease	Renal failure; cardiac arrest

Abbreviation: HBO_2, hyperbaric oxygen.

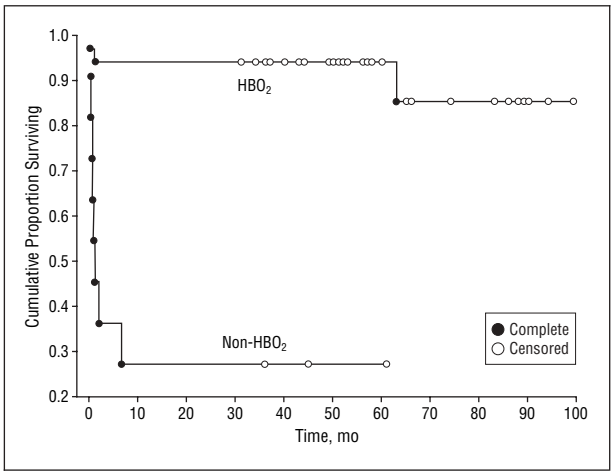

Figure. Kaplan-Meier survival curve for hyperbaric oxygen (HBO_2) and non-HBO_2 groups commencing from the time of hospital admission with the diagnosis of necrotizing soft tissue infection.

of the middle ear. Failure to equalize middle ear pressure may result in a barotrauma injury to the middle ear. As a prophylactic measure, 4 patients had a surgical procedure performed prior to commencing HBO_2 therapy (3 tympanostomy tube insertions, 1 myringotomy) and subsequently had uneventful treatment. Of the other 29 patients receiving HBO_2 therapy, 8 cases of middle ear barotrauma were reported; these were mild to moderate in severity (teed grade, 1-3). Of these 8 patients, 6 required a surgical procedure (tympanostomy tube insertion) to facilitate middle-ear equalization and continuation of treatment. As a manifestation of a toxic reaction of the central nervous system to oxygen, 2 cases of grand mal seizure were reported. These were treated with intravenous benzodiazepine, and HBO_2 treatment was continued with no reoccurrence of seizure. Although patients were accompanied by a trained attendant at all times, confinement within the chamber precipitated a report of claustrophobia in 4 cases. Treatment with benzodiazepine for anxiolysis, often as an oral premedication, allowed continued HBO_2 treatment.

FOLLOW-UP

Survival analysis for the HBO_2 and non-HBO_2 groups was performed by adding the long-term follow-up data to the outcome of hospital stay. The HBO_2 group had a median survival time of 53 months (range, 0.07-99.00 months). The non-HBO_2 group had a median survival of 1 month (range, 0.07-61.00 months). There was significantly improved survival in the HBO_2 group compared with the non-HBO_2 group ($P = .002$; Cox F test). The Kaplan-Meier survival curve (**Figure**) illustrates the improved survival in the HBO_2 group compared with the non-HBO_2 group.

COMMENT

The incorporation of HBO_2 therapy in the management of NSTI was associated with almost 9 times increased survival.

An association with outcome was also found for the characteristics of patient age, serum creatinine level, and etiology of infection. Age and serum creatinine level were associated with outcome in a case series of 198 patients where HBO_2 therapy was part of standard management.[2] This study also found an association with outcome for the factors of female sex and delay to first debridement (not found in the current study) and body surface area of infected tissue (not recorded for the current study). Regarding etiology of infection, all deaths occurred in the idio-

pathic group and none in the posttraumatic or postsurgical groups, precluding the use of this variable in the logistic regression model. Experience with NSTI has demonstrated that the inciting event leading to infection has frequently eluded identification.[5] Consequently, a small traumatic wound may be unrecognized and lead to a default diagnosis of idiopathic. The significance of the idiopathic group in this study is debatable; other studies have not identified this association but found death just as likely in posttraumatic and postsurgical groups.[1]

The practical and clinically relevant conclusion is that age, serum creatinine level, and etiology of infection are features of manifestation and beyond the influence of the physician, whereas HBO_2 therapy is an available treatment option.

To our knowledge, no previous study has examined patient survival after hospital discharge following NSTI. While there is some evidence that HBO_2 therapy improves survival during hospital stay,[7-9] survival may have left the patient with a significant disability, which compromised life expectancy. A follow-up period beyond hospital discharge is required to establish any meaningful survival advantage. Within this study, it was noticeable that several patients in the non-HBO_2 group died in the months after hospital discharge, although no examination of the circumstances of death was possible. The survival curves for both the HBO_2 and non-HBO_2 groups appear to plateau a few months after hospital discharge, suggesting this might be a more accurate measure of survival than hospital discharge used in other studies. The survival advantage for the HBO_2 group was sustained for several years.

Although site of infection did not show a statistically significant association with outcome, mortality tended to be lower for those patients whose NSTI involved an extremity (1 death in 16 patients). Death would be a less sensitive outcome measure for this group but it was considered that requirement for amputation of the affected extremity might be a better measure of treatment efficacy. One clinical series of 65 patients for which HBO_2 therapy was not used reported no association of site of infection with survival but an amputation rate of 50% in patients with NSTI of the extremity.[1] The current study also found an amputation rate of 50% in those who did not receive HBO_2 therapy; however, there was a significant reduction in the amputation rate for the HBO_2 group.

The HBO_2 and non-HBO_2 groups were well matched for the data collected with no significant difference between the 2 groups for sex, age, comorbidity, and blood pressure, temperature, hemoglobin level, white blood cell count, and albumin level at hospital admission. Although serum creatinine level was higher in the non-HBO_2 group, the logistic regression model found that serum creatinine level, either independently or in any interaction with the other explanatory variables, did not reveal a significant association with outcome. During the 5-year period of the study, there were no fundamental changes in the management of NSTI. While most patients received HBO_2 therapy, case note review could find no documentation of a selection bias in the decision to use or not use this therapy. Not all surgical teams refer such patients for HBO_2 therapy, and the decision to use HBO_2 therapy appeared to be related to the preference of the particular surgeon rather than any specific characteristic of the patient. Clinical manifestation influenced the management plan only for the 2 elderly patients who had severe shock on hospital admission; for these patients, it seemed inappropriate to pursue an aggressive management plan and palliative care only was instituted. Both the HBO_2 and non-HBO_2 groups had early deaths due to overwhelming sepsis. No patient for whom HBO_2 therapy was requested was refused this therapy.

Necrotizing soft tissue infection is a unifying term for several different diagnoses. Discriminating between these diagnoses has generally been determined by factors such as the identity of the infective microorganism, type of tissue affected (eg, fascia or muscle), or anatomical location of infection. It is arguable as to whether such a process provides any clinical advantage as evidenced by the following observations. Necrotizing fasciitis has previously been differentiated into type I and type II on the basis of microbiological examination[10]; however, analysis reveals such a division has no relevance to outcome.[5] The term *Fournier gangrene* refers to necrotizing fasciitis only in the specific anatomical region of the perineum, although on histologic examination it is no different from necrotizing fasciitis occurring elsewhere. Clostridial infections have been considered separately by some on the basis of a predilection for myonecrosis and gas formation[4]; however, myonecrosis and gas formation are neither sensitive nor specific for *Clostridium*. Additionally, it is accepted that the finding of clostridial species in the wound does not exclude a diagnosis of necrotizing fasciitis.[5] A detailed examination of the microbiological data and antibiotic usage from the 44 cases of this study has not been included in this article because few meaningful conclusions can be drawn. Similar to other studies, the majority of the cases from this study were polymicrobial.[1,2,7,8,11] All antibiotic therapy was commenced as broad spectrum and subsequently revised by an infectious diseases specialist. This study identified clostridial species in only 4 cases, all of which were polymicrobial. Of the 18 cases documenting clinically apparent myonecrosis during surgical debridement, only 2 identified clostridial species in microbiological cultures. There may be "textbook manifestations" of gas gangrene or Fournier gangrene in some patients; however, there is such an overlapping clinical spectrum of findings to suggest they are variants of a similar process.[8] The use of many different diagnostic terms certainly has historical and epidemiological value but has little if any practical advantage for the physician debriding a necrotizing wound. Ultimately, principles of management and outcome remain essentially the same.[2]

The use of HBO_2 therapy in NSTI continues to be a cause for debate; certainly no prospective controlled trials have been published for this life-threatening condition. Such trials would be difficult to complete because of the relatively low incidence of illness. Despite their limitations, there are 5 published, retrospective, comparative clinical studies examining the effect of HBO_2 therapy on NSTI.[7-9,11,12] There were differences in the diagnostic labels used in these 5 studies; however, when reviewed,

Table 5. Summation of Outcome Data From All Comparative Studies

Source	No. of Survivors	No. of Nonsurvivors
Gibson and Davis, 1986[9]		
HBO_2 Group	20	9
Non-HBO_2 Group	5	12
Riseman et al, 1990[8]		
HBO_2 Group	13	4
Non-HBO_2 Group	4	8
Brown et al, 1994[12]		
HBO_2 Group	21	9
Non-HBO_2 Group	14	10
Shupak et al, 1995[11]		
HBO_2 Group	16	9
Non-HBO_2 Group	9	3
Hollabaugh et al, 1998[7]		
HBO_2 Group	13	1
Non-HBO_2 Group	7	5
Current study		
HBO_2 Group	31	2
Non-HBO_2 Group	7	4
Summation		
HBO_2 Group	**114**	**34**
Non-HBO_2 Group	**46**	**42**

the patient characteristics in each showed considerable overlap supporting the use of the unified term of *NSTI*. Apart from the difference in terms, there is little to differentiate these studies in methodology. All used similar HBO_2 regimens as recommended by the Undersea and Hyperbaric Medical Society, Kensington, Md,[3] and treatment at 2.5 to 3.0 atm absolute, with 2 or 3 treatments in the first 24 hours and twice daily thereafter.

The common finding of preexisting medical conditions, such as diabetes, steroid use, and alcohol abuse, in patients with NSTI was noted in several studies.[7,8,11] Two larger case series of patients with NSTI had suggested that delay to first surgical debridement was associated with poor outcome.[1,2] The current study and that by Hollabaugh et al[7] were the only comparative studies to examine this factor, and both were unable to replicate this finding. Expeditious recognition and management would seem logical to maximize chances of survival. The inability of the current study to demonstrate this may reflect the variable and unpredictable rate of clinical progression in NSTI. There were examples of such rapid progression of disease where even early debridement was unable to prevent early death.

The controlled study by Riseman et al[8] suggested the use of HBO_2 therapy was associated with a reduction in the number of surgical debridements. This was not a finding of the current study; the HBO_2 group had more debridements (median, 5 [range 1-16]) than the non-HBO_2 group (median, 1 [range 1-4]). This may reflect opportunity owing to the improved survival of the HBO_2 group. The case notes documented occasions where surviving patients returned daily for examination under anesthesia and when a small amount of tissue was excised, it was counted as a debridement. Brown et al[12] also found an increase in debridements, whereas the other 2 comparative studies found no difference.[7,11] It is unclear as to whether any significance can be attributed to the number of surgical debridements.

When considering the 5 previously published comparative studies, 3 report a significant survival advantage for patients undergoing HBO_2 therapy[7-9] and 2 do not,[11,12] which argues against a publication bias on this subject. With similar methods and HBO_2 treatment protocols, all measured the primary end point of death during hospital stay. Although all studies were retrospective and relatively small, it is interesting to look at the amalgamated data for mortality. This outcome data has been summarized in **Table 5** for the 5 comparative studies plus the current study. When these figures are amalgamated, overall mortality in the HBO_2 group was 34 (23%) of 148 patients compared with 42 (48%) of 88 patients in the non-HBO_2 group. There is a significant difference in mortality between the 2 groups (χ^2 $P<.001$) and corresponds to a number needed to treat of 4.

Hyperbaric oxygen therapy produces a significant increase in tissue oxygen tensions.[3,13] The increase in oxygen tension is important for a number of biological actions that can be of benefit in NSTI and has been demonstrated in laboratory and animal studies. For anaerobic infections, the tissue oxygen tensions generated will be bacteriostatic and halt production of the α-toxin of *Clostridium*,[3,4] even though the oxygen levels generated during HBO_2 therapy probably do not reach a sufficiently high level to be bactericidal. Facultative microorganisms can survive in very low–oxygen environments where neutrophil function may be compromised because of the loss of the oxidative killing mechanisms.[5] Infected tissue is known to be hypoxic through a combination of poor perfusion and edema, while HBO_2 therapy can improve neutrophil function by raising the oxygen tension within the infected tissue. Hypoxia may also reduce the effectiveness of several antibiotics (vancomycin hydrochloride and ciprofloxacin hydrochloride) while hyperoxia may potentiate the action of others (aminoglycosides cross the cell membrane of the microorganism by an oxygen-dependent pump).[14] Once the infection has been controlled, fibroblast stimulation by HBO_2 therapy may assist with wound closure.[3] More recent studies have suggested that the systemic shock seen in patients with NSTI may be precipitated in part by the release of cytokines from activated neutrophils.[5] Studies have already demonstrated the ability of streptococcal exotoxin[15] and clostridial θ-toxin[3,4] to stimulate neutrophil-endothelial interaction resulting in the release of endogenous mediators. Hyperbaric oxygen therapy has demonstrated the ability to modulate the neutrophil-endothelial interaction in a dose-dependent fashion and reduce cytokine liberation in a number of disease models,[3,16-18] although this has not been specifically demonstrated in the setting of NSTI. Fascinatingly, this effect of HBO_2 therapy on neutrophil-endothelial interaction appears to be independent of neutrophil phagocytic activity.

The principal treatment strategies for NSTI continue to be early and thorough surgical debridement and appropriate antibiotic use. Consideration of HBO_2 as an adjunctive therapy in NSTI is supported by proven biological action together with emerging clinical evidence. This study reports improved long-term survival with a median of 8 HBO_2 treatments, meaning only a few days of

therapy may be required. Hyperbaric oxygen therapy can be provided safely to patients who are intubated and require intensive care. The incidence of ear barotrauma in this study (8 of 29 patients) suggests prophylactic myringotomy should be routinely considered prior to initiating HBO_2 therapy.

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