Not Just Full of Hot Air:
Hyperbaric Oxygen Therapy Increases Survival
in Cases of Necrotizing Soft Tissue Infections

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Abstract

Background: The utility of hyperbaric oxygen therapy (HBOT) in the treatment of necrotizing soft tissue infections (NSTIs) has not been proved. Previous studies have been subject to substantial selection bias because HBOT is not available universally at all medical centers, and there is often considerable delay associated with its initiation. We examined the utility of HBOT for the treatment of NSTI in the modern era by isolating centers that have their own HBOT facilities.

Methods: We queried all centers in the University Health Consortium (UHC) database from 2008 to 2010 that have their own HBOT facilities (n = 14). Cases of NSTI were identified by *International Classification of Diseases, Ninth Revision* (ICD-9) diagnosis codes, which included Fournier gangrene (608.83), necrotizing fasciitis (728.86), and gas gangrene (040.0). Status of HBOT was identified by the presence (HBOT) or absence (control) of ICD-9 procedure code 93.95. Our cohort was risk-stratified and matched by UHC's validated severity of illness (SOI) score. Comparisons were then made using univariate tests of association and multivariable logistic regression.

Results: There were 1,583 NSTI cases at the 14 HBOT-capable centers. 117 (7%) cases were treated with HBOT. Univariate analysis showed that there was no difference between HBOT and control groups in hospital length of stay, direct cost, complications, and mortality across the three less severe SOI classes (minor, moderate, and major). However, for extreme SOI the HBOT group had fewer complications (45% vs. 66%; p < 0.01) and fewer deaths (4% vs. 23%; p < 0.01). Multivariable analysis showed that patients who did not receive HBOT were less likely to survive their index hospitalization (odds ratio, 10.6; 95% CI 5.2–25.1).

Conclusion: At HBOT-capable centers, receiving HBOT was associated with a significant survival benefit. Use of HBOT in conjunction with current practices for the treatment of NSTI can be both a cost-effective and life-saving therapy, in particular for the sickest patients.

Necrotizing soft tissue infections (NSTIs) are a group of complicated skin and soft tissue infections with a necrotizing component [1]. Organisms infiltrate and migrate along the superficial and deep fascial planes with resultant vascular occlusion, ischemia, and tissue necrosis often associated with sepsis and multiple organ dysfunction syndrome. The national incidence of these life-threating infections in 2009 was estimated at 6,500 cases using the Nationwide Inpatient Sample [2]. More than 50% of these cases were seen at large academic teaching hospitals [3].

Historically, studies have shown an association between time to intervention and patient survival for those diagnosed with an NSTI [4–6]. Wheras a number of adjuvant therapies have been proposed—including specific therapies targeting bacterial toxins such as intravenous gamma globulin [7,8], plasmapheresis [9], and activated protein C [10,11] and the more generalized therapy of hyperbaric oxygen therapy (HBOT) [12,13]—there have been no universally accepted changes in the management of NSTI over the last three decades. Consequently, NSTI mortality has remained approximately 10–43% [14–20], and early diagnosis and aggressive site debridement remain the standard of care.

To date, there has been insufficient evidence to either support or refute the efficacy of adjuvant HBOT for the treatment of NSTI. Both animal and human studies have shown that rich oxygen tissue states inhibit anaerobic

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infections and increase the oxidative burst ability of human leukocytes, which aid in the killing of bacteria [12,21–25]. The theoretical basis for HBOT is two-fold. First, it creates an oxygen-rich environment that is inhospitable for bacterial growth, while secondarily increasing host defenses against foreign cells [26]. Delivering 100% oxygen at two to three atmospheres of pressure, results in arterial and tissue oxygen tension several times greater than under normal conditions [27]. This results in increased oxygen delivery to the infected host sites, inhibiting bacterial growth.

Studying the use of HBOT as an adjuvant treatment in NSTI over the years has proved difficult for many reasons. Because NSTIs are relatively rare, rapidly progressive, and often lethal, an adequately powered, randomized controlled trial is essentially impossible. The vast majority of studies examining the utility of HBOT are small, single-institution series that are underpowered to detect a survival benefit. Furthermore, HBOT is not available readily at all medical centers and the degree of critical illness accompanying NSTIs often precludes access to HBOT [28,29]; thus, retrospective studies of the benefits of HBOT are influenced strongly by selection bias. To address this bias and understand the true benefits of HBOT for the treatment of NSTI, we examined the utility of HBOT for the treatment of NSTI in the modern era by focusing on only those centers that have their own HBOT facilities.

Patients and Methods

Our dataset was obtained from the University Health Consortium (UHC). The UHC is an administrative data gathering collaborative, with participation from more than 90% of all US academic centers and over 200 of their affiliated hospitals, focusing on optimization of quality of care while containing cost [30].

The UHC clinical data base resource manager (CDB/RM) captures 100% of the patients treated at these centers and provides the following information: De-identified hospital and surgeon variables including specialty, unique patient visit identifiers, patient demographics, financials, and procedural and diagnostic information. Morbidity is defined using the UHC morbidity profiler [31]. Both cost and charge information are reported in UHC. Charges are reported by each center and cost is calculated using institutional specific cost: charge ratios obtained from the department-level Medicare cost reports. Federally reported area wage indexes are used to account for regional and center-specific cost variations that are not attributable directly to a center.

The UHC severity of illness (SOI) score has been used previously for both risk adjustment and predicted resource allocation [32]. This method of risk assessment has been verified and validated by the Agency for Healthcare Research and Quality (AHRQ) [33]. Severity of illness accounts for a number of patient variables and weights them in the context of patient illness, including other co-morbid conditions, age and diagnoses [34–41].

We identified all UHC centers from 2008 to 2010 that have their own HBOT facilities (n = 14) by the presence of *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9 CM) code (93.95). Centers that had third-party HBOT facilities would have been unable to bill for the treatment and were not searchable in UHC. Internet search and phone calls to these facilities were then used to confirm the existence of a HBOT facility. Because our primary objective was to understand the role of HBOT on outcomes for NSTI, we excluded centers without HBOT facilities in order to minimize the effect of barriers to inter-facility transfer on our analyses, as such barriers could have caused some unmeasured delay in access to HBOT. Furthermore, to determine that each of these 14 centers were potentially using their HBOT facilities to treat NSTIs, we ensured at least one NSTI patient was treated with HBOT there during the study period (see definition below).

We queried the charge description master for all cases of NSTI at these 14 facilities. Cases were identified by the presence of an ICD-9 diagnosis code for NSTI (Fournier gangrene [608.83], necrotizing fasciitis [728.86], or gas gangrene [040.0]) and at least one surgical debridement defined by ICD-9 procedure codes (86.04, 86.09, 86.22, 86.28, 83.09, 83.44, 83.45, 83.49; Appendix A). Patients who were transferred from another hospital were excluded due to the absence of data on duration and type of care provided at the transferring facility. Thus, we ensured that all patients had the same starting time of admission.

These NSTI patients were stratified according to whether or not they had received the primary intervention, HBOT. Receipt of HBOT was identified by the presence of ICD-9 CM code 93.95. Additional de-identified patient variables used in the analysis were: Age (years), gender, ethnicity (Caucasian, African American, Hispanic, Asian, and other), insurance status (private, Medicaid, Medicare, government and other), and co-morbidities (see Appendix B). Outcome variables included number and types of procedures, hospital length of stay (LOS), admission to an intensive care unit (ICU), in-hospital mortality, morbidity and hospital cost. We risk-stratified and matched these two cohorts in both univariate and multivariable analyses using UHC's proprietary and validated SOI score: Minor, moderate, major, and extreme.

For all continuous patient-level data, means, medians, variances, and standard deviations were calculated. For univariate analyses, continuous data were evaluated for variations in central tendency using Kruskal-Wallis non-parametric analysis because they were not normally distributed or had multiple extreme outliers [42,43]. We used the Hodges-Lehmann estimator (HLE) to predict the median difference or "pseudo-median" between cohorts [44,45]. It is particularly helpful when trying to estimate cost differences between two groups. The HLE has previously been used in numerous medical studies to accurately estimate the median difference [46–49]. Categorical data were analyzed using Chi-Square tests and Fisher Exact tests when appropriate [50–52]. Multivariable analyses were undertaken to determine the effect of HBOT on outcomes. Covariates included patient demographics, insurance status, co-morbid conditions, and SOI.

All analyses were conducting using JMP 9 Pro and SAS 9.2 statistical packages. This study complies with the UHC data usage agreement and was deemed exempt by our institutional review board (IRB), as all data are de-identified.

Results

Cohort

Over three years (2008–2010), these 14 HBOT-capable centers saw 1,583 cases of NSTI; 117 (7%) of these cases received adjuvant HBOT. Table 1 summarizes the demographic

TABLE 1. DEMOGRAPHIC CHARACTERISTICS OF PATIENTS
WITH NECROTIZING SOFT TISSUE INFECTIONS TREATED
AT CENTERS WITH HYPERBARIC OXYGEN TREATMENT
(HBOT) FACILITIES

Characteristics	HBOT treated (N=117)	Control (N=1,466)	p value*
Female gender	34	33	0.89
Age	56	54	0.67
	IQR (50–64)	IQR (44–64)	
Race			
Caucasian	66	64	0.91
African-American	31	27	0.56
Hispanic	3	6	0.46
Asian	<1	2	1.00
Other	<1	1	1.00
Co-morbidity			
Peripheral vascular disease	26	29	0.55
Hypertension	44	52	0.37
Obesity	69	71	0.71
Alcohol abuse	18	17	0.78
Other	91	79	0.12
Severity of illness			
Minor	<1	3	0.35
Moderate	12	6	0.16
Major	22	45	0.01
Extreme	66	46	0.03
Insurance			
Private	47	32	0.08
Medicaid	28	23	0.47
Medicare	16	33	0.04
Other Government	6	9	0.59
Uninsured	3	3	0.96
Diagnosis			
Fournier gangrene	69	69	0.91
Necrotizing fasciitis	16	18	0.73
Gas gangrene	15	13	0.58

*Chi^2 test or Fisher Exact test of association for categorical variables.
HBOT = hyperbaric oxygen treatment; IQR = interquartile range.

characteristics of each cohort. There was no difference in the median age of the HBOT cohort (56 y; interquartile range [IQR], 50–64) compared to the control cohort (54 y; IQR, 44–64; p = 0.67). There was a male predominance in both cohorts, (HBOT 66% vs. no HBOT 67%; p = 0.89). There were no racial differences between the groups. Both cohorts were comprised of primarily Caucasians, 66% and 64%, and African-Americans, 31% and 27% for the HBOT and control cohorts, respectively. There were fewer Medicare patients in the HBOT cohort vs. control cohort (16% vs. 33%, p = 0.04). The HBOT cohort had a greater number of aggregate medical co-morbidities than the control cohort (5 vs. 3; p = 0.03). Appendix B provides a complete list of co-morbidities counted. There were no differences when looking at the following specific co-morbidities peripheral vascular disease (PVD), hypertension, obesity, and alcoholism, which have been shown previously to be associated with increased incidences of and worse outcomes for NSTI [53,54]. The majority of patients from either cohort had a SOI score consistent with either major or extreme. The SOI score distributions were significantly different between the two cohorts. Twenty-two percent of the HBOT cohort had an SOI score of "major" compared to 45% for the control cohort (p = 0.01). Whereas 66% of the HBOT cohort had an SOI score of extreme compared to 46% for the control cohort (p = 0.03).

Outcomes

Univariate analyses showed that the cost and resources consumed by the HBOT cohort was greater than the control cohort (Table 2). The HBOT cohort experienced longer hospital LOS (16 d vs. 14 d; p < 0.05), compared with the control cohort. The hospital direct cost associated with the HBOT cohort was more ($35,808 vs. $27,504; p < 0.01), compared with the control cohort. However, the HBOT cohort had a significantly lower in hospital mortality rate, compared with the control cohort (5% vs. 12%; p < 0.05).

Stratified univariate analyses by SOI revealed that there were no differences in hospital direct cost and LOS for each of the four SOI categories, minor, moderate, major, and extreme (Table 3). Only the most severely ill patients, SOI extreme, showed statistically significant differences for the HBOT cohort compared to the control cohort in mortality (4% vs. 23%; p < 0.01) and complications (45% vs. 66%; p < 0.01), while there were no differences seen in either LOS or hospital direct cost.

Multivariable analysis

On multivariable analysis of mortality, patients who did not receive HBOT were more likely to die during that hospitalization (odds ratio [OR], 10.6; 95% CI 5.2–25.1). SOI, PVD, and insurance status also were found to be significant predictors of mortality (Table 4). Each incremental increase in SOI carried with it an increased risk of death (OR, 7.6; 95% CI 3.55–18.7), as did the presence of PVD (OR, 2.22; 95% CI 1.7–5.85) and Medicare or Medicaid for insurance (OR, 5.7; 95% CI 2.4–14) and (OR, 8.6; 95% CI 1.4–44), respectively.

Discussion

Our study examined patients admitted directly to centers with HBOT facilities. With presumed equal access to HBOT treatment, patients diagnosed with a NSTI and who had adjuvant HBOT were more likely to survive their index hospitalization with fewer complications and without significant differences in hospital direct cost or LOS in this study. The previous literature on the effectiveness of HBOT has been limited by small numbers of patients, lack of availability of HBOT, and unknown clinical information on treatment rendered prior to transfer. This lack of availability and unknown utilization were perhaps why so many studies had come up with conflicting conclusions about the efficacy of HBOT in treating NSTI. Our study addressed this weakness in the existing literature by selecting 14 centers from a comprehensive national database known to have HBOT facilities and including only patients originally admitted to one of these centers. This allowed us to acquire data on a large cohort for an otherwise rare disease and reduce confounding due to lack of access or unknown time to HBOT.

We also utilized UHC's unique, validated risk-stratification methodology to compare outcomes across treatment groups. By risk-stratifying our cohort, we were able to better control for co-morbidities, insurance, diagnosis, and demographic variables [32] To our knowledge no study has risk-stratified

TABLE 2. UNIVARIATE OUTCOMES UNADJUSTED FOR SEVERITY OF ILLNESS

	HBOT treated	Control	p value	Hodges-Lehmann estimator
Length of stay (median days)	16 IQR [11–23]	14 IQR [8–23]	0.049*	2
Hospital direct cost (median)	$35,808 IQR [$23K - $65K]	$27,504 IQR [$14K – 51K]	<0.01*	$8,958
Morbidity	30%	24%	0.14	
In-hospital mortality	5%	12%	0.028*	

HBOT = hyperbaric oxygen treatment; IQR = interquartile range.

their treatment groups previously, in part because of the small numbers. We found that HBOT was associated with greatest benefit with the least amount of additional costs in only the most severe risk group, SOI "extreme."

Before risk stratification, there was a statistically significant survival benefit associated with HBOT treatment (5% vs. 12%). However, this observed relationship came with increased cost and hospital resource utilization. Once risk-stratified, these differences in cost and resource utilization were no longer statistically significant. There was no apparent difference between those who received HBOT in the lesser three SOI groups of minor, moderate, and major in the univariate analysis.

The multivariable model of mortality showed that receipt of HBOT and decreasing SOI were both associated with increased survival. Although diabetes mellitus, PVD, alcoholism and obesity have all been identified as increased risk factors for the development of NSTI, it was surprising to see

that only PVD was associated with an increase in mortality in our study [55–57].

A number of previous studies on conditions ranging from peripheral vascular disease to colon cancer have demonstrated that uninsured or under-insured patients present later and with more advanced disease than patients with private insurance resulting in disparities in disease outcomes [58–65]. Timely access to care is particularly important to optimize outcomes for acute conditions in need of rapid definitive treatment such at stroke and myocardial infarction [58,59]. Given the need for early and aggressive treatment of NSTI, it is not surprising that our study patients with government-supported insurance or those without any insurance were less likely to survive the index hospitalization compared to privately insured patients. However, it is possible that the environment or health behaviors of uninsured

TABLE 3. ADJUSTED UNIVARIATE OUTCOMES BY SEVERITY OF ILLNESS

Treatment group	HBOT treated n = 4	Control n = 76	p value
Severity of Illness: minor			
Length of stay (median days)	12	6	0.480
Hospital direct cost (mean)	$22,105	$10,516	0.316
At least one complication	50%	14%	0.122
In-hospital mortality	<1%	2.5%	0.900
Severity of illness: moderate	N = 20	N = 149	
Length of stay (median days)	13	10	0.510
Hospital direct cost (mean)	$27,578	$18,694	0.120
At least one complication	55%	43%	0.348
In-hospital mortality	17.6%	4.9%	0.115
Severity of illness: moderate	N = 44	N = 642	
Length of stay (median days)	14	13	0.68
Hospital direct cost (mean)	$29,005	$24,517	0.088
At least one complication	41%	54%	0.117
In-hospital mortality	2.3%	5.9%	0.376
Severity of illness: extreme	N = 49	N = 579	
Length of stay (median days)	23	19	0.147
Hospital direct cost (mean)	$58,382	$42,635	0.156
At least one complication	45%	66%	0.004*
In-hospital mortality	4.2%	23%	<0.01*

HBOT = hyperbaric oxygen treatment.

TABLE. 4 MULTIVARIABLE ODDS RATIOS

Covariates	Odds ratio	95% Confidence interval
Hyperbaric Oxygen Therapy		
HBOT (Referent)		
Control	10.60	5.23–25.1*
SOI (per unit change in regressor)	7.62	3.55–18.7*
Age (per unit change in regressor)	0.99	0.97–1.02
Sex		
Female (referent)		
Male	0.65	0.32–1.30
Race		
White (referent)		
Non-white	0.80	0.38–1.60
Comorbidities		
Diabetes mellitus	0.85	0.41–1.72
Peripheral vascular disease	2.22	1.67–5.85*
Hypertension	0.90	0.42–1.91
Obesity	1.16	0.56–2.35
Insurance		
Private (referent)		
Medicaid	1.50	0.49–4.6
Medicare	0.87	0.24–1.4
Uninsured	8.60	1.4–44.0*
Other	2.60	0.52–10.6

HBOT = hyperbaric oxygen therapy; SOI = severity of illness.

or under-insured patients put them at greater risk for more aggressive forms of NSTI.

Whereas we have shown a benefit of HBOT for the most severely ill patients, there are some important limitations to this research. Administrative databases can provide invaluable information retrospectively regarding practice trends across many institutions, and allow researchers to study large cohorts of patients with an otherwise infrequent disease or intervention. Coding errors are a potential limitation of all administrative databases. However, we believe our selection strategy, combining at least one surgical debridement with a diagnosis code for NSTI, would minimize this effect. Furthermore, our study had a sufficiently large cohort over a long enough time interval to counterbalance such selection bias. This study comprised of 14 centers that offered on-campus HBOT. Whereas a great many more centers offer adjuvant HBOT for the treatment of NSTI, because of third-party ownership of these HBOT treatment centers, they are not part of the hospital charges and billing, thus not captured in UHC's database, and therefore could not be identified for inclusion in our study. Thus, our results may not be generalizable to centers that do not operate their own HBOT chambers. Similarly, because UHC is a collaborative of academic medical centers, our findings may not be generalizable to non-academic locations. Nevertheless, our study represents a large cohort for a rare disease, all of whom had access to HBOT treatment on-site. Importantly, databases reliant upon UB-40 billing data are unable to provide us with some of the key clinical variables that may go into the management of a patient, in particular the decision to provide HBOT. However, given the challenges in designing a randomized, controlled trial for HBOT, this study represents a meaningful addition to the HBOT literature in that it contains more than 1,500 cases of NSTI and 117 patients receiving HBOT, which far exceeds any of the previous studies comparing this intervention whose entire cohorts ranged from 16 to 54 with at most 24 patients treated with HBOT [13,66–71]. Finally, risk-stratification is widely regarded as paramount in comparing the efficacy and utility of medical interventions such as HBOT. However, there is controversy regarding the best method of risk-stratification. This study relied on the UHC's proprietary risk-stratification method which some have questioned, in particular when compared to chart abstracted data in the National Surgical Quality Improvement Project. However, a recent study using that database identified fewer than one-half as many patients as this study (n = 688) and had no means of identifying use of HBOT as an adjunct to surgical debridement [72,73]. The UHC's risk-stratification method has been validated by the AHRQ and has been used by a number of other researchers to adjust outcomes after various interventions [34–41,72]. Therefore, despite the possible limitations of our severity of illness measure, given the database's power to yield a relatively large cohort for a rare disease, and an ever-rarer intervention, we believe that our analysis is meaningful for clinicians considering whether or not to use HBOT to treat NSTI.

Conclusion

In this study, receiving HBOT was associated with increased survival for the sickest patients whereas for all other patients HBOT was associated with increased cost without an immediate survival benefit. Although previous studies yielded conflicting results on the utility of HBOT, our findings suggest that a clinical trial randomizing critically ill patients with NSTI to HBOT would be warranted. Meanwhile algorithms to identify patients who will benefit most, from HBOT, and organizational changes to improve access to HBOT, may save lives and decrease healthcare cost in the long run.

Author Disclosure Statement

No competing financial interests exist.

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APPENDIX: A

Category	ICD-9 code	ICD-9 definition
Necrotizing Soft Tissue Infections	728.86	Necrotizing fasciitis
	040.0	Gas gangrene
	608.83	Fournier's gangrene
Surgical Debridement	86.04, 86.09	Skin and soft tissue incision
	86.22	Soft tissue excision and debridement
	86.28	Non-excisional debridement of soft tissue
	83.09	Soft tissue incision NOS
	83.44	Fasciectomy
	83.45	Myectomy
	83.49	Other soft tissue excision
Hyperbaric Oxygen Therapy	93.95	Hyperbaric oxygen therapy

NOS=not otherwise specified.

APPENDIX: B

Code	Description
1	Congestive heart failure
2	Valvular disease
3	Pulmonary circulation disease
4	Peripheral vascular disease
5	Hypertension
6	Paralysis
7	Other neurological disorders
8	Chronic pulmonary disease
9	Diabetes with complications
10	Diabetes without complications
11	Hypothyroidism
12	Renal failure
13	Liver disease
14	Peptic ulcer disease
15	HIV/AIDS
16	Lymphoma
17	Metastatic Cancer
18	Solid tumor without metastatic disease
19	Rheumatologic disorder
20	Coagulopthy
21	Obesity
22	Weight loss
23	Fluid electrolyte disorder
24	Chronic blood loss anemia
25	Deficiency anemias
26	Alcohol abuse
27	Drug abuse
28	Psychoses
29	Depression

HIV/AIDS=human immunodeficiency virus/acquired immuno-deficiency syndrome.