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Contemporary Trends in Necrotizing Soft Tissue Infections in the United States

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Abstract

Background—Necrotizing soft tissue infections (NSTI) are rare, potentially fatal surgical emergencies. We studied a national cohort of patients to determine recent trends in incidence, treatment, and outcomes for NSTI.

Methods—We queried the Nationwide Inpatient Sample (1998–2010) for patients with a primary diagnosis of NSTI. Temporal trends in patient characteristics, treatment (debridement, amputation, hyperbaric oxygen therapy (HBOT)), and outcomes were determined using Cochran-Armitage Trend Tests and Linear Regression. To account for trends in case mix (age group, sex, race, insurance, Elixhauser index) or receipt of HBOT on outcomes, multivariable analyses were conducted to determine the independent effect of year of treatment on mortality, any major complication, and length of stay for NSTI.

Results—We identified 56,527 weighted NSTI admissions; incidence ranging from approximately 3,800–5,800 cases annually. The number of cases peaked in 2004 and then decreased for an overall statistically significant decrease between 1998 and 2010 ($p < 0.0001$). The percentage of female patients decreased slightly over time (38.6 to 34.1%, $p < 0.0001$). Patients were increasingly in the 18–34 year old (8.8 to 14.6%, $p < 0.0001$) and 50–64 year old age groups (33.2 to 43.5, $p < 0.0001$), Hispanic (6.8 to 10.5%, $p < 0.0001$), obese (8.9 to 24.6%, $p < 0.0001$), and admitted with >3 co-morbidities (14.5 to 39.7%, $p < 0.0001$). The percentage of patients requiring only one surgical debridement increased (43.2 to 46.2%, $p < 0.0001$) while the utilization of HBOT was rare and decreasing (1.6 to 0.8%, $p < 0.0001$). The percentage of patients requiring operative wound closure decreased (23.5 to 20.8%, $p < 0.0001$). Although major complication rates increased (30.9 to 48.2%, $p < 0.0001$), LOS remained stable (18–19 days) and mortality decreased (9.0 to 4.9%, $p < 0.0001$) on univariate analyses. On multivariable analyses each one-year incremental

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increase in year was associated with a 5% increased odds of complication (OR 1.05), 0.4 times decrease in hospital LOS (coefficient -0.41), and 11% decreased odds of mortality (OR 0.89)

Conclusions—There were significant national trends in patient characteristics and treatment patterns for NSTI between 1998 and 2010. Importantly, though patient acuity worsened and complication rates increased, LOS remained relatively stable and mortality decreased. Improvements in early diagnosis, wound care, and critical care delivery may be the cause.

Keywords

Necrotizing Fasciitis; Necrotizing Soft Tissue Infection; Gas Gangrene; Fournier's gangrene

Introduction

Necrotizing soft-tissue infections (NSTIs) are a collection of rapidly advancing, often fatal infections of the subcutaneous tissues and fascia. Mortality for NSTI has been reported to range from 21–43% in single center studies[1, 2]. Larger studies have shown a mortality as high as 34%[3] but more recently there appears to have been a decline in mortality to 10–12%[4–6]. These epidemiological studies on NSTIs have provided some data on treatment modalities such as hyperbaric oxygen therapy (HBOT)[7, 8] and the association between a number of co-morbidities such as chronic alcoholism, obesity, diabetes, and immunocompromised status on the development of NSTIs[9]. Only two of these studies have examined a national cohort of NSTI patients[4, 5].

It appears that the basic principles of treatment for NSTI have remained unchanged over the past several decades. Early diagnosis and treatment have been the only consistently proven predictors of outcomes for NSTI[10, 11]. Aggressive antibiotic therapy with prompt, often serial, surgical debridement of all necrotic tissue is paramount to reduce morbidity and mortality[2, 12]. We undertook this study to examine recent national trends in incidence, treatment, and outcomes for NSTI from a large representative sample of the US population.

Methods

The Nationwide Inpatient Sample (NIS) (1998–2010) was queried for all patients with a primary diagnosis of NSTI (International Classification of Diagnosis ninth revision [ICD-9] codes 728.86 [necrotizing fasciitis], 040.0 [gas gangrene], or 608.83 [Fournier's gangrene] and at least one surgical debridement (ICD-9 procedure codes defined in Appendix 1) or at least one amputation (ICD-9 procedure codes defined in Appendix 1). The NIS is a dataset from the Healthcare Cost and Utilization Project and represents the largest all-payer inpatient database in the United States. The NIS contains approximately 8 million admission records per year and represents a 20% stratified sample of all acute care hospital admissions nationally [13].

The NIS contains data on patient characteristics including demographics (gender, age, insurance status, and race) and co-morbidities (measured by the Elixhauser Index)[14], hospital characteristics (geographic region, urban vs. rural location, and teaching status), interventions (up to 15 procedures classified), and outcomes (complications recorded in up to 14 secondary diagnoses, length of stay, mortality).

For each year of data, we determined proportions in patient characteristics as well as interventions and outcomes using descriptive statistics. Interventions were classified as debridements, amputations, wound care, wound closure, and HBOT (see Appendix 1). Complications were divided into categories including cardiac, pulmonary, neurologic, thromboembolic, renal, and infectious (see Appendix 2). Complications were also measured

as a dichotomous variable indicating any major complication and a continuous variable counting the total number of complications out of these six categories. These national point estimates were calculated using the NIS survey weights and sampling frame. Trends over time in these estimates were then determined using the Cochrane-Armitage trend tests for dichotomous variables and linear regression for continuous variables.

In order to determine if observed epidemiologic trends in outcomes were due to simultaneous trends in case mix or receipt of HBOT, we also conducted multivariable analyses of all patients in our cohort to determine predictors of mortality, any major complication, and LOS for NSTI. Co-variables in the model included year of treatment, age group, sex, race, insurance, Elixhauser index, and HBOT treatment. The models for mortality and LOS also included total major complications. The model for LOS included only those patients who survived hospitalization.

All analyses were performed using SAS statistical software (version 9.2; SAS Institute, Inc, Cary NC). P-value <0.05 for trend tests and co-efficients in multivariable models were considered significant. This study was deemed exempt by the University of Massachusetts Medical School Institutional Review Board.

Results

Incidence

During the thirteen-year study period there were 56,527 weighted NSTI admissions in the United States with the annual incidence ranging from approximately 3,800–5,800 admissions per year. The number of cases peaked in 2004 and then decreased for an overall statistically significant decrease between 1998 and 2010 ($p<0.0001$).

Demographics

Table 1 depicts the basic demographics for the entire study population. Although the proportion of patients missing race data improved over time from 21.2 to 15.4% ($p<0.0001$), race data was far from complete. However, among those with race data recorded, the about half of patients were white (50.1–52.2%) with the percentage of Hispanics increasing (6.8 to 10.5%, $p<0.0001$) while the proportion of blacks decreased (19.6 to 18.6%, $p<0.01$) during the study period. While there were fewer women (38.6 to 34.1%, $p<0.0001$), an increasing percentage of NSTI patients were in the 18–34 year old (8.8 to 14.6% $p<0.0001$) and 50–64 year old age groups (33.2 to 43.5, $p<0.0001$). The proportion of patients on Medicaid also increased during the study period (17.6 to 20.1, $p<0.0001$).

Co-Morbidities

Patients admitted with NSTIs were more likely to be obese (8.9 to 24.6%, $p<0.0001$), have uncomplicated diabetes (30.4 to 33.0%, $p<0.0001$), and chronic liver disease (1.0 to 4.0%, $p<0.0001$) during the study period. Overall, patients had more preexisting co-morbidities (Elixhauser index > 3 increased from 14.5 to 39.7%, $p<0.0001$). (see table 2 and figure 1)

Treatment

Trends in treatment of NSTI are detailed in Table 3. The percentage of patients requiring only a single surgical debridement or multiple debridements (>3) increased (43.2 to 46.2%, $p<0.0001$ and 13.5 to 15.9%, $p<0.001$ respectively) while those needing two and three surgical interventions decreased (29.5 to 26.4%, $p<0.0001$ and 13.4 to 11.1%, $p<0.0001$ respectively). Amputations were rare and ranged from 1.2%–1.9% (reported in three year intervals per the NIS data use agreement). HBOT (reported in three year intervals per the NIS data use agreement) was rarely used and its utilization decreased nationally during our

study period (1.6 to 0.8%, $p<0.0001$). Over the study period, there was increased utilization of wound therapy (12.7 to 14.5%, $p<0.0001$) and less need for complex wound reconstruction (23.5 to 20.8, $p<0.0001$).

Outcomes

Table 4 lists major complications associated with NSTI. The proportion of patients having any major complication increased over the study period (30.9 to 48.2%, $p<0.0001$). Patients, on average, experienced a total of 0.4 to 0.7 major complications during their hospital stay. LOS remained stable at 18–19 days while overall mortality decreased (9.0 to 4.9%, $p<0.0001$). (see figure 1). On multivariable analyses, we found that age, sex, insurance, and Elixhauser index were predictors of any major complication; age, race, insurance, Elixhauser index, HBOT treatment, and number of major complications were predictors of LOS; and age, race, insurance, and number of major complications were predictors of mortality. After accounting for these significant confounders, each one-year incremental increase in year was associated with a 5% increased odds of complication (OR 1.05), 0.4 times decrease in hospital LOS (coefficient -0.41), and 11% decreased odds of mortality (OR 0.89) (see table 5).

Discussion

NSTI, though decreasing in mortality, is a highly morbid disease. Our national, thirteen year analysis elucidates recent trends in the incidence, treatment, and outcomes for this high acuity surgical illness. We have found that there have been significant national trends in patient population, treatment patterns, and outcomes. Patients have been increasingly from Hispanic and publicly insured groups and overall co-morbidities have risen sharply along with complication rates. Despite worsening acuity, length of stay has been relatively stable and mortality has decreased by nearly 50%.

Our study found demographic changes in the NSTI population, with Hispanics accounting for a greater proportion of patients. A likely explanation for this finding is the rapid expansion of the United States Hispanic population. According to the United States Census Bureau greater than half of the total population growth within the United States during the 2000 to 2010 decade was due to increases in the Hispanic population. This segment grew 43% during this time, seeing an increase of 15.2 million persons[13]. We also found that the proportion of Medicaid patients also increased during our study period. The fact that Hispanics and Medicaid patients are being affected by this morbid infection at such increasing rates raises further questions concerning etiologies, access to care, and prevalence of risk factors that warrants further investigation. Given our findings it is important for clinicians caring for patients of diverse backgrounds to consider NSTI in their differential diagnosis for patients who present with signs and symptoms of soft tissue infection in order to ensure that all patients benefit equally from early diagnosis, aggressive debridement, and improved wound therapy.

Our results suggest, however, that even after diagnosis disparities not explained by factors such as age and co-morbidities may persist. When controlling for these possible confounders, we found that both Hispanics and Medicaid patients have an odds of mortality 1.6 times higher than white patients and privately insured patients, respectively. Meanwhile, Medicaid patients have higher odds of complications and increased lengths of stay compared to patients with private insurance. Black patients also suffer more complications than their white counterparts with NSTI. There is a growing body of evidence that patients in the United States get differential treatment based on race/ethnicity and socioeconomic status. The causes of these healthcare disparities are multiple and the source of much debate[14–17]. One explanation for increased lengths of stay with Medicaid patients may be that their

insurance is not favorable for discharge to rehabilitation or skilled nursing facilities[18]. Hospital factors may also be the source of differences in complication rates as a number of studies have shown that hospitals that treat more minority and/or indigent patients have worse outcomes[19–21]. When resources and access are otherwise equitable across groups, differences in outcomes by race, ethnicity, or socioeconomic status may be due to unconscious bias[22].

The percentage of NSTI patients who were obese tripled during the study period. This follows the trend of increasing obesity among the general United States population over the past several decades. The current lifetime risk of an American becoming overweight or obese exceeds 50% and 25%, respectively[23]. Given the alarming rates of obesity in our population, the overall importance of obesity on the NSTI population may be becoming more significant. While obesity prevention initiatives have traditionally focused on reducing risk of cardiovascular disease and certain types of cancer, the association between obesity and NSTIs is an important public health concern. Meanwhile, clinicians faced with an obese patient with seemingly subtle cellulitis with pain out of proportion to exam should have a high index of suspicion for a NSTI. Given the difficulty in diagnosis, this patient population in particular may benefit from contrast enhanced computed tomography to aid in diagnosis[24].

Early and aggressive debridement remains the mainstay of surgical management for NSTIs. During our study period there were simultaneous increases in the proportion of patients requiring only a single debridement (nearly half in 2010) and the proportion of patients requiring multiple debridements (approximately 16% in 2010). Thus, while a certain percentage of patients appear to be benefiting from early diagnosis and aggressive single debridement, the number of patients with severe, progressive disease has also increased although the proportion of patients who need amputation is very small. Notably, the decrease in non-primary skin closure along with increases in wound care procedures suggests that more recent advances in wound therapy such as negative pressure wound therapy may be benefiting NSTI patients in the modern era. More research is needed to understand the role of different wound care options on the management of NSTI patients after all necrotic tissue has been debrided. However, clinicians should consider employing such methods prior to subjecting patients to an additional donor site wound as would be needed for complex reconstructions.

Despite the many reports regarding the utility of HBOT in the treatment of NSTI[7, 8, 25, 26], including several that report a survival advantage[8, 26], the use of HBOT in the United States is rare. This is likely because HBOT is a specialized treatment not readily available at all hospitals. Patients who did receive HBOT saw no improvements in complication rates or mortality but their hospital LOS was nearly 3.5 days higher than patients who did not undergo HBOT. Thus, we cannot recommend HBOT as an adjunct treatment for NSTI even when readily available.

Overall, the mortality rate of NSTI has declined to 4.9% nationally over the past decade. This is considerably lower than similar national studies using both NIS and NSQIP data (10.9% and 12% respectively)[4, 5]. We found that increasing age was associated with more complications and higher mortality. And, while higher co-morbidity burden increased complications and LOS, this had no effect on mortality. Importantly, however, each added complication increased LOS by almost 9.5 days and resulted in a 2.7 increased odds of mortality when controlling for confounders. This suggests that patients who may have previously died from NSTI now surviving with some measure of morbidity. Possible explanations for the stable LOS and reduced mortality despite the trend toward increased baseline co-morbidities and greater complications during treatment course include increased

awareness and early diagnosis by local physicians, improvements in intensive care and resuscitative efforts, better wound care options, and improved antibiotic coverage. Our findings have implications for surgeon patient discussions at the time of diagnosis of NSTI. What in the past may have been a discussion about the very high likelihood of death despite aggressive interventions is today more appropriately a detailed discussion of a reasonable chance of survival that comes after a long hospital course involving multiple trips to the operating room for removal of affected tissue and wound care and many potential complications.

This study has a number of important limitations. The NIS is an administrative dataset reliant upon UB-40 billing sheets generated by sampled hospitals. Relying on administrative data may result in underestimation of true NSTIs. However, we believe our selection strategy, combining at least one surgical debridement with a diagnosis code for NSTI, would minimize this effect. Previous research on NSTI has detailed changes in microbiology with single organism infections more prevalent in the past and polymicrobial infection more prevalent in the modern era[10]. Unfortunately, the NIS does not provide any clinical data on wound microbiology or choice of anti-microbial therapy. Without access to clinical data, administrative databases are also subject to misclassification/underestimation errors for both measures of co-morbidity and complication severity. The Elixhauser Index, though validated and commonly used in studies using administrative data[27–34], simply measures presence or absence of co-morbid conditions without gauging the individual severity of each co-morbidity with the possible exception of diabetes (see Appendix 3). Furthermore, there has been recent criticism of Elixhauser's method but this newer application has yet to be applied widely to the literature due to a delay in implementation of ICD-10 codes in US administrative data[27]. Similarly, we are also unable to measure complication severity using common, validated metrics such as the Accordion Severity Grading System of Surgical Complications, Acute Physiology and Chronic Health Evaluation (APACHE) score or the Sequential Organ Failure Assessment (SOFA) score that rely upon actual clinical data points that are not available in the NIS. Additionally, factors not captured by the administrative database may lead to an underestimation of complication rates due both to limitations on the total number of fields available for coding complications and lack of readmission data (NIS treats each admission as a stand-alone event). Our finding of increased co-morbidity burden over the study period may have been due to up-coding by billing specialists or improved documentation by providers rather than a true increase in pre-existing conditions among NSTI patients. However, based on other studies on the overall health of the US population we believe that our findings represent a true change in patient characteristics[35, 36]. It is also possible that increases in complications were attributable to similar "improvements" in coding. It is well known that race is coded poorly in administrative data, thus our demographic findings may also be at risk for misclassifications; however, we know of no other large national dataset which would provide more precise race data for NSTI patients. Finally, the overall use of HBOT and amputations was very low and our ability to judge trends in these treatments was thus limited.

Despite these limitations, this nationwide analysis of NSTI is, to our knowledge, the largest population-based sample of NSTI in the US population and has shown that demographics and co-morbidity shifts have occurred and complications have increased. Meanwhile, however, LOS has been relatively stable and mortality has decreased. This suggests improvements of our modern health care system during this study period may be at play. Further research is needed to determine which aspects of anti-microbial treatment, critical care, surgical debridement, and wound management provide these improvements in the overall outcomes of NSTI patients. Future studies looking at NSTI risk factors including socioeconomic status, access to health care, and underlying disease are also necessary to better understand this disease and increasing our ability to prevent, diagnose, and treat it.

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Figure 1.
Trends in Elixhauser > 3, incidence of any major complication, and mortality among NSTI patients 1998–2010 (N=56,527)

Table 1

Trends in patient characteristics 1998–2010 (N=56,527)

Variable	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	p-value
	n=4262	n=3850	n=4307	n=4355	n=4557	n=5089	n=5815	n=4653	n=4307	n=3925	n=4033	n=3591	n=3783	<.0001
Age (%)														
18–34yo	8.8	11.0	10.8	12.1	11.3	11.5	10.3	10.3	13.1	8.8	10.3	12.7	14.6	<.0001
35–49yo	34.2	31.9	31.0	29.9	31.3	29.0	32.1	34.7	29.0	30.6	31.8	28.7	25.6	<.0001
50–64yo	33.2	33.1	34.8	33.6	35.6	36.0	36.5	37.0	38.7	40.3	39.8	41.7	43.5	<.0001
>64yo	23.8	24.0	23.4	24.5	21.8	23.5	21.2	18.0	19.2	20.3	18.2	16.8	16.2	<.0001
Female (%)	38.6	41.4	39.2	41.9	39.5	39.3	37.4	41.3	35.3	34.2	40.4	37.5	34.1	<.0001
Race														
White	50.1	50.4	52.5	48.0	43.7	46.0	49.5	44.3	45.7	42.9	52.1	54.1	52.2	0.24
Black	19.6	15.2	13.7	12.9	15.2	14.9	13.0	11.2	13.6	15.3	10.7	16.0	18.6	0.01
Hispanic	6.8	6.8	11.7	10.2	11.3	10.2	9.2	14.9	11.3	11.9	9.8	9.2	10.5	<.0001
Other	2.3	4.1	3.7	3.6	3.8	2.4	2.7	2.7	4.2	4.5	5.0	5.4	3.3	<.0001
Missing	21.2	23.6	18.4	25.3	26.1	26.6	25.6	26.9	25.2	25.5	22.4	15.3	15.4	<.0001
Insurance (%)														
Medicare	33.1	33.0	32.5	33.3	31.5	33.0	32.6	26.9	31.4	29.0	26.6	26.9	26.1	<.0001
Medicaid	17.6	18.3	13.4	16.2	17.1	17.4	16.6	17.9	17.2	16.3	17.8	22.3	20.1	<.0001
Private	31.1	33.2	34.7	32.7	31.4	33.7	29.6	32.4	29.7	33.6	34.2	26.8	29.7	<.0001
Self-pay	10.1	8.2	10.4	10.8	11.3	9.6	13.5	13.8	11.7	12.6	12.0	15.7	16.6	<.0001
No charge/Other*	8.2	7.4	8.9	7.0	8.7	6.3	7.7	9.0	10.0	8.4	9.4	8.3	7.5	0.02

* Includes Federal, Military, and Other

Table 2

Trends in specific patient co-morbidities 1998–2010 (N=56,527)

Variable	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	p-value
Individual Co-morbidities*														
Obese (%)	8.9	11.6	11.2	12.4	16.4	14.5	12.7	13.7	15.7	16.5	20.4	30.0	24.6	<.0001
Diabetes Type 2 (%)														
w/Chronic Complication	17.6	17.3	13.7	14.8	14.0	13.8	13.2	14.5	14.1	15.9	14.4	14.3	14.0	<.0001
w/o Chronic Complication	30.4	32.4	34.2	32.4	36.8	32.4	31.6	35.3	34.0	32.5	33.8	39.7	33.0	<.0001
Alcohol abuse (%)	5.9	4.8	4.4	4.5	5.1	5.9	5.1	4.8	5.9	6.1	4.3	6.5	5.7	0.02
Liver disease (%)	1.4	2.3	3.3	3.3	3.9	4.3	4.1	4.0	5.6	3.7	4.5	4.2	4.0	<.0001
Peripheral Vascular Disease (%)	6.9	6.3	5.3	5.0	6.0	6.8	5.4	4.8	4.5	5.8	5.9	7.4	5.7	0.47
Aggregate Co-morbidity Measure†														
Elixhauser Index (%)														
0	12.5	13.0	10.9	11.2	11.1	10.7	12.3	10.6	10.1	7.9	8.9	5.7	8.8	<.0001
1	27.2	22.3	25.9	24.4	20.4	19.8	19.6	19.2	17.4	17.7	15.4	12.9	14.4	<.0001
2	28.2	28.5	28.3	27.1	25.7	26.5	26.6	23.3	23.4	23.1	23.2	20.1	20.1	<.0001
3	17.6	20.6	21.2	20.1	21.7	23.5	21.8	23.4	22.4	23.2	22.3	20.8	17.0	0.08
> 3	14.5	15.7	13.7	17.1	21.2	19.4	19.7	23.5	26.6	28.2	30.3	40.6	39.7	<.0001

* These individual co-morbidities have been shown in the literature to be associated with NSTI. See Appendix 3 for a list of all co-morbidities measured by the Elixhauser Index.

† See Elixhauser, Steiner, Harris, and Coffey, Med Care, 1998;36(1):8–27.

Table 3

Trends in Treatment of NSTI 1998–2010 (N=56,527)

Variable	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	p-value
Surgical Intervention														
Any debridement (%)	99.6	99.3	99.4	99.2	99.6	99.5	99.3	99.6	99.9	99.9	99.5	99.6	99.6	NS
Amputation (%) *	1.9				1.7			2.0			1.2		--	0.004
Number of debridements (%)	43.2	41.3	41.4	40.4	43.2	43.3	44.1	44.2	44.1	45.5	47.2	48.7	46.2	<0001
1	29.5	32.3	31.1	32.2	27.9	29.5	29.0	28.6	29.6	28.8	27.0	25.7	26.4	<0001
2	13.4	13.9	14.8	14.2	15.0	14.6	15.3	13.0	13.5	12.2	11.8	12.5	11.1	<0001
3	13.5	11.8	12.1	12.4	13.5	12.2	10.9	13.7	12.6	13.4	13.6	12.6	15.9	0.0004
More than 3														
Wound Therapy														
HBOT (%) *	1.6				1.6			1.3			0.8		--	<0001
Wound care (%)	12.7	10.3	9.7	10.6	11.5	12.7	10.4	9.3	11.9	15.1	11.9	11.2	14.5	<0001
Wound closure (%)	23.5	18.7	17.0	20.2	16.9	15.5	17.1	17.2	17.9	16.3	14.6	14.1	20.8	<0001

* Per the data use agreement with the Healthcare Utilization Project, we cannot display results with less than 10 patients represented in the aggregate value, thus these have been collapsed into 3 year intervals from 1998 to 2009 and not shown for 2010.

Table 4

Trends in Overall NSTI Outcomes 1998–2010 (N=56,527)

Variable	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	p-value
Complications														
Any Major Complication (%)	30.9	30.5	29.1	34.0	33.8	35.8	34.7	34.5	36.9	38.5	40.6	45.5	48.2	<.0001
Specific Complications														
Cardiac (%) *	1.3			1.4				1.4			1.4		*	0.72
Pulmonary (%)	16.2	13.9	14.2	17.7	16.9	17.6	18.0	18.3	18.3	20.1	19.0	22.0	22.8	<.0001
Neurologic (%) *	0.8				0.8			0.6			0.6		-	0.02
Thromboembolic (%)	3.1	2.1	3.0	2.5	3.1	4.0	3.8	2.6	4.3	4.7	4.3	4.1	7.2	<.0001
Renal (%)	11.6	13.3	14.6	16.3	16.3	15.3	17.5	18.5	20.3	22.9	23.1	29.7	31.1	<.0001
Infectious (%)	8.2	8.1	5.6	7.5	8.0	8.6	7.4	7.5	8.2	7.9	9.5	7.9	9.1	0.0003
Total major complications (mean sum)	0.41	0.40	0.40	0.46	0.47	0.48	0.49	0.49	0.53	0.58	0.58	0.65	0.73	<.0001
Outcomes														
LOS (mean days)	19.4	19.2	18.1	19.4	18.8	17.9	17.7	17.7	18.5	18.5	18.6	18.2	18.1	0.12
LOS (median days)	13.3	13.2	11.8	13.1	13.1	12.5	12.0	12.2	12.0	12.4	11.6	12.2	11.9	0.10
Mortality (%)	9.0	10.5	10.2	11.1	10.0	7.4	8.5	5.4	6.3	5.7	4.6	5.7	4.9	<.0001

* Per the data use agreement with the Healthcare Utilization Project, we cannot display results with less than 10 patients represented in the aggregate value, thus these have been collapsed into 3 year intervals from 1998 to 2009 and not shown for 2010.

Table 5

Predictors of Outcomes for NSTI in Multivariable Analyses *

Outcome of interest Variable	Any Complication		Hospital Length of Stay		Mortality	
	OR	95% CI	Coefficient	95%CI	OR	95% CI
Year	1.05	(1.04, 1.07)	-0.41	(-0.49, -0.32)	0.89	(0.87, 0.91)
Age						
18–34yo	ref		ref		ref	
35–49yo	1.30	(1.12, 1.52)	1.29	(0.39, 2.19)	1.35	(0.95, 1.92)
50–64yo	1.69	(1.45, 1.97)	2.07	(1.15, 3.00)	2.05	(1.46, 2.88)
>64yo	1.85	(1.54, 2.22)	1.65	(0.41, 2.89)	3.03	(2.07, 4.44)
Sex						
Male	Ref		ref		ref	
Female	1.19	(1.09, 1.29)	0.46	(-0.16, 1.08)	1.01	(0.86, 1.18)
Race						
White	Ref		ref		ref	
Black	1.13	(1.00, 1.27)	0.38	(-0.56, 1.33)	0.97	(0.77, 1.23)
Hispanic	0.99	(0.86, 1.14)	0.92	(-0.09, 1.93)	1.57	(1.23, 2.00)
Asian/Pacific Islander/Native American/Other	1.04	(0.84, 1.30)	0.92	(-0.59, 2.43)	1.77	(1.25, 2.51)
Missing/Unknown	1.04	(0.94, 1.15)	-1.29	(-1.99, -0.60)	1.14	(0.94, 1.38)
Insurance						
Private	ref		ref		ref	
Medicare	1.42	(1.26, 1.60)	0.35	(-0.56, 1.26)	1.64	(1.30, 2.06)
Medicaid	1.24	(1.10, 1.40)	3.76	(2.82, 4.70)	1.55	(1.21, 1.97)
Self-pay	0.72	(0.62, 0.83)	1.58	(0.68, 2.49)	1.50	(1.12, 2.00)
No charge/Other *	0.85	(0.72, 1.00)	1.94	(0.88, 3.00)	1.19	(0.85, 1.69)
Elixhauser Index						
0	ref		ref		ref	
1	1.54	(1.30, 1.83)	0.92	(-0.06, 1.90)	1.10	(0.80, 1.52)
2	1.76	(1.49, 2.08)	2.37	(1.39, 3.35)	1.07	(0.78, 1.46)

Outcome of interest Variable	Any Complication		Hospital Length of Stay		Mortality	
	OR	95% CI	Coefficient	95%CI	OR	95% CI
3	2.03	(1.71, 2.41)	2.49	(1.46, 3.51)	0.99	(0.72, 1.37)
> 3	2.89	(2.44, 3.43)	3.70	(2.61, 4.80)	1.01	(0.73, 1.40)
HBOT treatment	0.82	(0.57, 1.18)	3.47	(1.11, 5.84)	0.57	(0.26, 1.26)
Total Major Complications	--	--	9.46	(8.9, 10.01)	2.67	(2.47, 2.88)

* Co-variables in the model included year of treatment, age group, sex, race, insurance, Elixhauser index, and HBOT treatment. The models for mortality and LOS also included total major complications. The model for LOS included only those patients who survived hospitalization.

Appendix 1

ICD-9 Codes for Diagnosis and Treatment of NSTIs

Variable Name	ICD-9 code	ICD-9 descriptor
NSTI	728.86	Necrotizing Fasciitis
	040.0	Gas gangrene
	608.83*	Male genital vascular disease NEC
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
Amputation	885.0, 885.1 [†]	Amputation thumb
	886.0, 886.1 [†]	Amputation finger
	887.0, 887.1 [†]	Amputation below elbow, unilateral
	887.2, 887.3 [†]	Amputation above elbow, unilateral
	887.4, 887.5 [†]	Amputation arm, unilateral NOS
	887.6, 887.7 [†]	Amputation arm, bilateral
	895.0, 895.1 [†]	Amputation toe
	896.0, 896.1 [†]	Amputation foot, unilateral
	896.2, 896.3 [†]	Amputation foot, bilateral
	897.0, 897.1 [†]	Amputation below knee, unilateral
	897.2, 897.3 [†]	Amputation above knee, unilateral
	897.4, 897.5 [†]	Amputation leg, unilateral NOS
	897.6, 897.7 [†]	Amputation leg, bilateral
	84.04	disarticulation of wrist
	84.06	disarticulation of elbow

Variable Name	ICD-9 code	ICD-9 descriptor
	84.08	shoulder disarticulation
	84.13	disarticulation of ankle
	84.16	disarticulation of knee
	84.18	disarticulation of hip
HBOT	93.95	Hyperbaric oxygen therapy
Wound care	96.58	Wound catheter irrigation
	96.59	Wound irrigation NEC
	97.15	Replace wound catheter
	97.16	Replace wound pack/drain
	93.57	Dressing of wound NEC
	93.59	Immobilization/wound attention NEC
Wound closure	86.60	Free skin graft NOS
	86.62	Hand skin graft nec
	86.65	Heterograft to skin
	86.66	Homograft to skin
	86.67	Dermal regenerative graft
	86.69	Free skin graft nec
	86.70	Pedicle graft/flap nos
	83.82	Muscle or fascia graft

* used by convention for Fournier's gangrene See Mills, Am J Surg, 2010.

⁷ paired codes for simple and complicated amputations of the same location respectively

Appendix 2

ICD-9 Codes for Complications

Variable Name	ICD-9 code	ICD-9 descriptor
Cardiac *	410.00–410.91	Acute myocardial infarction
Pulmonary	507.0	Aspiration pneumonia
	481, 482, 482.0–482.9, 485.6	Acute bacterial pneumonia
	997.31	Ventilator associated pneumonia
	518.81, 518.82, 518.4, 518.5, 514	Respiratory failure
	31.1, 31.29	Tracheotomy
Neurologic	431.00–431.91, 433.00–433.91, 434.00–434.91, 436, 437.1	Acute cerebrovascular accident
Thromboembolic	453.4–453.42, 453.8, 453.9	Deep venous thrombosis
	451.11, 451.19, 451.81, 451.2	Phlebitis
	415.1, 415.11, 415.19	Pulmonary embolism
	415.0	Acute cor pulmonale
Renal	584.5–584.9	Acute renal failure
	39.95	Insertion of short term dialysis catheter
Infectious [†]	771.82, 599.0, 996.64, 996.65	Urinary tract infection
	999.31	Catheter-associated bloodstream infection

* Excludes 410.42 and 410.72

[†] Excludes pneumonia and skin/soft tissue infection

Appendix 3

Temporal trends in all co-morbidities measured by the Elixhauser Index⁷

Co-morbidity	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	p-value
CHF	1.9	2.2	2.3	3.2	3.1	2.6	2.0	3.0	2.2	3.2	7.2	6.5	8.3	<.0001
Valvular disease							*							
Pulmonary circulation disorders							*							
Peripheral vascular disorders	6.9	6.3	5.3	5.0	6.0	6.8	5.4	4.8	4.5	5.8	5.9	7.4	5.7	0.47
Hypertension	23.1	27.4	26.9	30.4	35.3	36.7	33.4	37.6	40.7	41.6	43.4	50.7	47.3	<.0001
Paralysis	3.0	3.3	2.2	3.1	2.2	2.5	2.1	2.0	1.9	2.1	2.9	3.5	3.2	0.87
Other neurological disorders	5.3	4.4	3.4	4.2	4.4	4.6	3.5	3.6	4.9	2.8	3.4	4.0	5.3	0.12
Chronic pulmonary disease	11.2	11.7	10.9	11.2	12.2	12.1	13.4	13.9	14.2	13.1	11.7	13.5	12.9	<.0001
Diabetes, uncomplicated	30.4	32.4	34.2	32.4	36.8	32.4	31.6	35.3	34.0	32.5	33.8	39.7	33.0	<.0001
Diabetes, complicated	17.6	17.3	13.7	14.8	14.0	13.8	13.2	14.5	14.1	15.9	14.4	14.3	14.0	<.0001
Hypothyroidism	2.2	2.6	3.2	4.3	4.2	3.3	4.0	3.5	2.7	4.3	4.3	5.2	5.7	<.0001
Renal failure	6.0	6.6	5.1	6.4	6.1	6.0	7.2	7.8	12.0	12.7	8.8	13.4	13.4	<.0001
Liver disease	1.4	2.3	3.3	3.3	3.9	4.3	4.1	4.0	5.6	3.7	4.5	4.2	4.0	<.0001
Peptic ulcer disease							*							
AIDS							*							
Lymphoma							*							
Metastatic cancer							*							
Solid tumor without metastasis							*							
Rheumatoid arthritis/collagen vascular diseases							*							
Coagulopathy	6.0	6.6	5.9	7.2	6.1	5.7	6.3	4.5	5.0	4.9	4.5	7.8	7.8	0.90
Obesity	8.9	11.6	11.2	12.4	16.4	14.5	12.7	13.7	15.7	16.5	20.4	30.0	24.6	<.0001
Weight loss	8.8	7.4	7.2	8.0	9.4	8.4	9.1	9.7	10.0	12.7	12.7	15.5	18.4	<.0001
Fluid and electrolyte disorders	25.5	28.4	28.0	28.1	30.0	30.9	30.7	34.1	36.2	35.9	37.2	39.3	38.0	<.0001
Blood loss anemia							*							
Deficiency anemia	12.6	14.3	15.1	15.9	14.3	16.3	15.2	16.6	17.9	18.4	21.5	24.5	22.4	<.0001
Alcohol abuse	5.9	4.8	4.4	4.5	5.1	5.9	5.1	4.8	5.9	6.1	4.3	6.5	5.7	0.02
Drug abuse	12.9	7.3	9.6	6.1	6.6	7.8	10.3	8.2	9.1	11.2	8.3	9.1	10.2	0.24

Co-morbidity	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	p-value
Psychoses	2.0	2.3	2.1	4.0	2.7	2.5	3.6	4.1	3.5	3.7	6.6	4.7	5.6	<.0001
Depression	2.1	3.2	3.6	4.0	3.6	4.6	6.0	5.8	5.7	5.8	7.3	8.8	10.2	<.0001

[†] ICD-9 codes for these co-morbidities from Elixhauser, Steiner, Harris, and Coffey, *Med Care*, 1998;36(1):8–27

* Per the data use agreement with the Healthcare Utilization Project, we cannot display results with less than 10 patients represented in the aggregate value, thus these have not shown for co-morbidities with fewer than 10 unweighted patients per year in our cohort.