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Fungal Infections Increase the Mortality Rate Three-Fold in Necrotizing Soft-Tissue Infections

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Abstract

Background: Necrotizing soft-tissue infections (NSTIs) result in significant morbidity and mortality rates, with as many as 76% of patients dying during their index admission. Published data suggest NSTIs rarely involve fungal infections in immunocompetent patients. However, because of the recent recognition of fungal infections in our population, we hypothesized that such infections frequently complicate NSTIs and are associated with higher morbidity and mortality rates.

Methods: A prospectively maintained Acute and Critical Care Surgery (ACCS) database spanning 2008–2015 and including more than 7,000 patients was queried for patients with NSTIs. Microbiologic data, demographics, and clinical outcomes were abstracted. Risk factors and outcomes associated with NSTI with positive intra-operative fungal cultures were determined. Frequencies were compared by χ^2 and continuous variables by the Student *t*-test using SPSS. Because the study included only archived data, no patient permission was needed.

Results: A total of 230 patients were found to have NSTIs; 197 had intra-operative cultures, and 21 (10.7%) of these were positive for fungi. Fungal infection was more common in women, patients with higher body mass index (BMI), and patients who had had prior abdominal procedures. There were no significant differences in demographics, co-morbidities, or site of infection. The majority of patients (85.7%) had mixed bacterial and fungal infections; in the remaining patients, fungi were the only species isolated. Most fungal cultures were collected within 48 h of hospital admission, suggesting that the infections were not hospital acquired. Patients with positive fungal cultures required two more surgical interventions and had a three-fold greater mortality rate than patients without fungal infections.

Conclusions: This is the largest series to date describing the impact of fungal infection in NSTIs. Our data demonstrate a three-fold increase in the mortality rate and the need for two additional operations. Consideration should be given to starting patients on empiric anti-fungal therapy in certain circumstances.

Necrotizing soft-tissue infections (NSTIs) have been recognized as a clinical entity since at least the 5th Century B.C.E., when they were described by Hippocrates [1]. The first modern report was published in 1871 when it was reported by a Confederate Army surgeon who described 2,642 cases of ''hospital gangrene'' [2]. Wilson later coined the term ''necrotizing fasciitis'' to emphasize the characteristic fascial involvement [3]. More recently, the term ''necrotizing soft-tissue infection'' has been used to encompass disease, not just of the fascia, but also of associated skin, adipose tissue, and muscle [4, 5]. The infection remains rare, with an estimated 3,800–5,400 cases in the United States annually [6].

Historically, the mortality rate from NSTI has been as high as 76%, but recent evidence suggests the overall mortality rate has decreased to 4.9%–12% [6–10]. This large decrease in deaths may be related to an emphasis on early recognition, operative debridement, broad-spectrum antibiotics in patients with suspected NSTIs, and advances in critical care [11–13].

Traditionally, NSTI has been categorized as Type I (polymicrobial) or Type II (monomicrobial), with occasional reference to Type III (*Vibrio vulnificus* or other marine-dwelling gram-negative organisms) [5,12,14, 15,16]. Cases of NSTI attributed to fungal species have been reported, usually in immunocompromised or injured individuals [17–19].

Necrotizing soft-tissue infections attributed solely to fungi have been described in case reports implicating species of *Aspergillus, Candida,* and *Cryptococcus* [20–23]. Although the majority of these cases occurred in immunocompromised

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individuals, a significant number of immunocompetent individuals also have been affected [24,25]. Moreover, cases of NSTI attributable to fungi such as *Apophysomyces* and *Rhizopus* have been documented in cases of natural disaster, as well as in India, where its occurrence appears to be more prevalent [19, 26, 27]. In these series, as many as 85% of patients were either at higher risk for infection (immunosuppressed, history of diabetes, etc.) or had suffered penetrating trauma [28–30].

Retrospective and prospective series of NSTI patients have reported occurrences of fungal growth in Type I NSTIs at rates from 2% to 10.9%, albeit with relatively small samples [10,15,31,32]. There remains little analysis of the risk factors for and impact of fungal involvement in NSTI, and neither the Surgical Infection Society (SIS) nor the Infectious Disease Society of America (IDSA) recommends empiric anti-fungal treatment [33, 34]. We hypothesized that fungal species frequently complicate NSTI and are associated with increased morbidity and mortality rates.

Patients and Methods

An Institutional Review Board-approved, prospectively maintained, Acute and Critical Care Surgery (ACCS) database spanning 2008–2015 and including more than 7,000 patients was queried for patients having a diagnosis of necrotizing fasciitis, gas gangrene, or Fournier's gangrene (International Classification of Disease (ICD) 9 codes 728.86, 040.0, and 608.83 respectively). All patients with ICD 9 diagnoses of NSTI were evaluated by an investigator to confirm the accuracy of coding information. Sites of infection, transfer data, microbiologic data, history of abdominal surgery, social history, immunosuppression, demographics, and clinical outcomes were abstracted. The Charlson/Deyo Comorbidity Index (CCI) was applied, and the Laboratory Risk Indicator for Necrotizing Fasciitis (LRINEC) score was calculated as previously described [35,36].

Microbiologic data were obtained solely from intra-operative tissue or fluid cultures. Transfer was defined as transfer from any hospital, rehabilitation facility, long-term acute-care hospital, or skilled nursing facility. Abdominal surgery was defined as any operation that violated the peritoneal cavity. Immunosuppression was defined as innate immunodeficiency, organ transplant requiring immunosuppressive drug use, or chronic corticosteroid use. Human immunodeficiency virus (HIV) and malignancy requiring chemotherapy were not included, as they are Charlson co-morbidities [35].

At our institution, intra-operative tissue samples are transported in sterile containers and embedded directly in culture medium. Fluid cultures are collected with flocked nylon swabs and transported in Liquid Amies medium [37]. The swab and medium are then vortexed and plated. All fungal samples are plated on blood heart infusion and inhibitory mold agars. Non-sterile specimens also are embedded or plated in Sabouraud dextrose agar with chloramphenicol. Plates are incubated for 28 d at 30°C and checked daily. Once grown, yeast species are identified via matrix assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF MS). Molds are identified with light microscopy (Melanie Yarbrough, PhD; oral communication, February 25, 2017).

Risk factors for fungal infections were assessed by univariable analysis. Frequencies were compared by Pearson's χ^2 and continuous variables by the Student *t*-test. Following univariable analysis, multivariable logistic regression of statistically significant predictors was used to determine independent factors predictive of fungal infection. Outcomes of the patients with fungal infection were then compared with those of patients without fungal infection. All data were analyzed in SPSS version 23.

Results

A total of 230 patients were found to have NSTIs; 197 had intra-operative cultures available and were included in the analysis. Of these 197 patients, the average age was 50.4 y; 104 (57.8%) were male. The most common site of infection was the groin and perineum (49.2%); the average age-adjusted CCI was 3.2, and 21 (10.7%) of the NSTIs had positive intra-operative fungal cultures. The demographics and univariable analysis data are shown in Table 1.

Fungal infection was more common in women (71% vs. 44%; $p = 0.019$), in patients with a higher BMI (41.36 ± 18.14 standard deviation [SD] vs. 34.36 ± 12.69; $p = 0.025$), and in patients with previous abdominal surgery (61.9% vs. 27.3%; $p = 0.001$). There were no significant differences in other patient demographics, co-morbidities, sites of infection, transfer status, or LRINEC score [36], although there was a trend toward an abdominal site of infection. On multivariable analysis, higher BMI (odds ratio [OR] 1.04 per kg/m^2; 95% confidence interval [CI] 1.0–1.1) and prior abdominal procedures (OR 4.6; 95% CI 1.60–13.4) were independent risk factors for fungal infection (Table 2).

Of the positive fungal cultures, 12 (57.1%) grew *Candida albicans*, one (4.8%) grew *Candida dubliniensis*, one (4.8%) grew *Apophysomyces trapeziformis*, and eight (38.1%) grew unspeciated yeasts. The majority of patients with positive fungal cultures had a mixed fungal and bacterial infection (18/21). Of the 18 patients with mixed infections, one had *Candida dubliniensis*, eight had unspeciated yeast, and 10 had *Candida albicans*. The most common bacterial species isolated were *Escherichia coli* and *Bacillus fragilis*. Complete microbiology findings in the patients with mixed fungal and bacterial NSTIs are shown in Table 3.

Of the three patients with solely fungal NSTIs, two had *Candida albicans* and one had *Apophysomyces trapeziformis*. All had been admitted to another healthcare facility prior to transfer. The average time that fungal cultures were collected was hospital d 3.5; however, a majority (11 patients or 52.4%) had cultures started within one d of admission. There was no significant difference in the dates of collection between patients transferred and those who were admitted directly to our facility (3.0 ± 3.9 vs. 5.2 ± 7.5; $p = 0.56$).

Patients with fungal infections required more operations (4.62 ± 3.37 vs. 2.99 ± 2.09; $p = 0.042$) and had a significantly higher mortality rate (23.81% vs. 7.39%; $p = 0.014$). There was no significant difference in hospital length of stay (LOS), ventilator d, or intensive care unit LOS between cohorts. However, in patients with fungal infections, there was a trend toward longer ICU LOS, hospital LOS, and ventilator days (Table 4).

Discussion

Previous literature has suggested that fungal infections are rare in NSTI, although there are a number of case reports that attest to their existence. These infections often are attributed

Table 1. Demographics and Univariable Analysis of Patient Characteristics

	Fungal Infection						
	Total		*Negative*		*Positive*		P *Value*
n	197		176		21		
Age	50.44 (15.15)		49.98 (15.7)		54.23 (8.85)		0.065
Gender (%)							**0.019**
Female	93	(47.2)	78	(44.3)	15	(71.4)	
Male	104	(57.8)	98	(55.7)	6	(28.6)	
Race (%)							0.523
Caucasian	122	(62.0)	112	(63.6)	10	(47.6)	
African American	65	(33.0)	56	(31.8)	9	(42.9)	
Hispanic	1	(0.5)	1	(0.6)	0		
Native American	1	(0.5)	1	(0.6)	0		
Other	1	(0.5)	1	(0.6)	0		
Unknown	7	(0.6)	5	(2.8)	2	(9.5)	
Body mass index (SD)	**35.13 (13.51)**		**34.36 (12.69)**		**41.36 (18.14)**		**0.025**
Social (%)							
Alcohol	82	(41.6)	78	(44.3)	4	(19.0)	0.312
Illicit drug use	13	(6.6)	12	(6.8)	1	(4.8)	0.709
Tobacco	83	(42.1)	77	(43.8)	6	(28.6)	0.211
Co-morbidities (%)							
Myocardial infarction	20	(10.2)	18	(10.2)	2	(9.5)	0.920
Congestive heart failure	28	(14.2)	26	(14.8)	2	(9.5)	0.515
Peripheral vascular disease	26	(13.2)	23	(13.1)	3	(14.3)	0.876
Cerebrovascular disease	6	(3.0)	6	(3.4%)	0		0.390
Dementia	1	(0.5)	1	(0.6)	0		0.729
Chronic pulmonary disease	39	(19.8)	36	(20.5)	3	(14.3)	0.502
Connective tissue disease	6	(3.0)	6	(3.4)	0		0.390
Peptic ulcer disease	5	(2.5)	5	(2.8)	0		0.434
Mild liver disease	12	(6.1)	10	(5.7)	2	(9.5)	0.487
Moderate or severe liver disease	3	(1.5)	2	(1.1)	1	(4.8)	0.200
Diabetes mellitus	67	(34.0)	58	(33)	9	(42.9)	0.365
Diabetes mellitus + organ damage	33	(16.8)	31	(17.6)	2	(9.5)	0.348
Hemiplegia	11	(5.6)	10	(5.7)	1	(4.8)	0.862
Renal disease	22	(11.2)	21	(11.9)	1	(4.8)	0.324
Any solid organ tumor	12	(6.1)	12	(6.8)	0		0.217
Metastatic solid organ tumor	10	(5.1)	9	(5.1)	1	(4.8)	0.945
Acquired immunodeficiency syndrome	1	(0.5)	1	(0.6)	0		0.729
Age-adjusted Charlson Comorbidity Index (SD)	3.2	(2.8)	3.2	(2.8)	3.0	(2.4)	0.721
Other immunosuppression (%)	28	(14.2)	26	(14.8)	2	(9.5)	0.515
History of abdominal surgery (%)	**61**	**(31.0)**	**48**	**(27.3)**	**13**	**(61.9)**	**0.001**
Transferred (%)	113	(57.4)	97	(55.1)	16	(76.2)	0.065
LRINEC Score	4.37 (2.26)		4.39 (2.27)		4.24 (2.17)		0.522
Site of infection (%)							
Head/neck	4	(2.0)	4	(2.3)	0		0.485
Chest/upper back	11	(5.6)	9	(5.1)	2	(9.5)	0.405
Abdomen/lower back	58	(29.4)	48	(27.3)	10	(47.6)	0.053
Groin/perineum	97	(49.2)	86	(48.9)	11	(52.4)	0.761
Upper extremity	19	(9.6)	17	(9.7)	2	(9.5)	0.984
Lower extremity	86	(43.7)	78	(44.3)	8	(38.1)	0.587

The presence of fungal infection was diagnosed on the basis of intra-operative fluid or tissue culture.
Statistically significant differences are shown in **boldface** type.
SD = standard deviation.

Table 2. Multivariable Binomial Logistic Regression of Traits Associated with Fungal Necrotizing Soft-Tissue Infection

	Odds Ratio	*95% Confidence Interval*	P *Value*
Prior abdominal surgery	**4.628**	**1.600–13.389**	**0.005**
Female sex	1.649	0.557– 4.881	0.366
Body mass index (kg/m^2)	**1.039**	**1.006– 1.074**	**0.020**

Statistically significant differences are shown in **boldface** type.

Table 3. Bacteriology of Patients with Fungal Involvement

Species	*No. (%)*
Bacteroides fragilis	3 (14.3)
Enterococcus faecium	1 (4.8)
Pseudomonas aeruginosa	2 (9.5)
Staphylococcus aureus	2 (9.5)
Escherichia coli	3 (14.3)
Proteus mirabilis	1 (4.8)
Streptococcus agalactaiae	2 (9.5)
Coagulase-negative *Staphylococcus*	1 (4.8)
Acinetobacter calcoaceticus-baumannii complex	1 (4.8)
Klebsiella pneumoniae	1 (4.8)
Lactobacillus spp.	1 (4.8)
Klebsiella oxytoca	1 (4.8)
Eneterobactor cloacae	1 (4.8)
Prevotella	1 (4.8)
Mixed anaerobic micro-organisms	4 (19.0)
Mixed micro-organism	4 (19.0)
Mixed aerobic micro-organisms	4 (19.0)

Percentages sum to greater than 100% as several species occasionally were present.

to underlying trauma, immunosuppression, or foreign travel [17–19]. Although the literature suggests a rate of fungal infection between 2% and 10.9%, there has been no rigorous analysis of risk factors or outcomes in fungal NSTI [10,15,31,32]. In several studies, the culture source was not specified [10,31]. Other studies specifically looked at intra-operative cultures [15,32].We chose to look only at intra-operative cultures in order to reduce the chances of including fungemia caused by healthcare-acquired infections. Our work demonstrated a rate of fungal infection of at least 10.7% on intra-operative culture. At our institution, fungal cultures are obtained from intra-operative samples only on surgeon request, suggesting that the actual incidence of fungal involvement may be higher than reported here. We further attempted to assess whether fungi had been acquired in the hospital by evaluating the day that fungal cultures were collected. The majority (52.4%) of patients had cultures taken on hospital day 0 or 1, suggesting that the majority of patients presented with the fungal infections. We further attempted to determine if the infections were nosocomial by assessing culture days as a function of transfer status. We reasoned that if the infections were acquired in a healthcare setting, patients transferring would have positive fungal cultures sooner than those who had not been transferred. However this was not the case. Taken together, we interpret the data to suggest that most of these infections are present on admission.

On univariable analysis, female gender, obesity, and prior abdominal operations were associated with fungal infections. Although abdominal and flank involvement did not reach statistical significance, there was a trend toward more fungal involvement in infections of these sites. On multivariable analysis, increased BMI (OR 1.04 per kg/m^2; 95% CI 1.0–1.1) and prior abdominal procedures (OR 4.6; 95% CI 1.60–13.4) were independent risk factors for fungal infection. Surprisingly, immunosuppression was not associated with a higher rate of fungal infection on either univariable or multivariable analysis. We specifically evaluated prior abdominal operations as a possible source of fungal infections because of the predominance of enteric bacterial species in the patients with fungal cultures and the trend toward abdominal sites in patients with concomitant fungal infections, suggesting a gastrointestinal source. This hypothesis is supported by data showing that yeasts colonize approximately 70% of healthy adult gastrointestinal tracts [38]. Although there is a growing understanding of the mycobiome in various disease states, there still is significant uncertainty as to the role fungal species play in human disease [39].

Despite having similar co-morbidities and admission LRINEC scores, patients with fungal infections had a higher mortality rate than patients without. Although the LRINEC score was designed as a diagnostic tool, previous retrospective studies have shown higher rates of death and limb loss associated with higher scores, and as such, the score was used as a marker for greater disease severity [36,40, 41]. Despite no significant difference in LRINEC score, patients with fungal infections required two additional operative debridements. Patients with fungal infections also had a trend toward longer hospital stays and ICU LOS, although the differences did not reach statistical significance.

The overall mortality rate was 9.14%, similar to that in most modern series. However, in patients with fungal infections, our data demonstrate a three-fold increase in the mortality rate [6–10]. This is in contrast to work by Moore et al., which suggested that fungal infections are not predictive of death; this may have been secondary to a small sample [32]. It also is possible that local variation in the pathogenicity of fungal species plays a role in this difference, as the paper by

Table 4. Outcomes of Patients with Necrotizing Soft-Tissue Infection With and Without Fungal Infections

		Fungal Infection		
	Overall	*Negative*	*Positive*	P *Value*
n	197	176	21	
Length of stay	14.6 (11.14)	13.81 (9.99)	21.29 (17.01)	0.061
ICU LOS	5.82 (7.45)	5.21 (6.22)	10.95 (13.25)	0.063
Ventilator d	1.69 (4.41)	1.45 (3.88)	3.62 (7.41)	0.202
No. of operations (SD)	**3.17 (2.30)**	**2.99 (2.09)**	**4.62 (3.37)**	**0.042**
Mortality rate (%)	**18 (9.14)**	**13 (7.39)**	**5 (23.81)**	**0.014**

The presence of fungal infection was diagnosed on the basis of intra-operative fluid or tissue culture.
Statistically significant differences are shown in **boldface** type.
ICU = intensive care unit; LOS = length of stay; SD = standard deviation.

Moore et al. does not report fungal species [32]. It is unclear why previous work has not shown a difference in outcomes in patients with fungal infections. Similar-size studies have shown comparable incidences of fungal involvement [15,32]. It is possible that this can be explained by local or temporal variability in pathogenicity. Previous work has shown that local variation in causative organisms and pathogenicity, even within regions, is present and results in differences in presentation and outcomes [7], whereas other investigators have shown temporal changes in causative organisms and pathogenicity [42].

Our study has several limitations. Most notably, this was a single-center review. The use of data from a single center and the wide variability of presentation may limit wider applicability, especially in light of the local variations in causative organisms [7]. Further, although fungal infection was associated with more deaths and operative debridements, it is unclear whether the organisms are causative or simply indicative of more severe infection. Anecdotal institutional evidence suggests that treatment of fungal infection in patients with NSTI improves site healing; however, further study is required.

In summary, this was a single-center study of 197 patients with confirmed NSTI. Intra-operative cultures demonstrated fungal infection in 10.7% of patients. This is the largest series to date describing the impact of fungal involvement in NSTIs in the United States. Fungal infection was associated with a significantly higher mortality rate and a trend to a need for additional operative procedures. Prior abdominal surgery and higher BMI were independently associated with fungal involvement. These results underscore the importance of fungal cultures at index operation. Consideration should be given to starting patients on empiric antifungal therapy on presentation with NSTI until antibiotic therapy can be tailored or discontinued.

Author Disclosure Statement

No competing financial interests exist.

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