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FUNGAL INFECTIONS OF SKIN AND SUBCUTANEOUS TISSUE (A BONIFAZ AND M PEREIRA, SECTION EDITORS)

Fungal Necrotizing Skin and Soft Tissue Infections

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Abstract

Purpose of Review This review summarizes the medical literature regarding fungal necrotizing skin and soft tissue infections (NSTI). The available epidemiologic, microbiologic, treatment, and outcome data are presented by the most common causal organisms of this disease process.

Recent Findings With the exception of cutaneous mucormycosis, which often progresses to necrotizing infection, clinical data for other fungal NSTI are largely limited to case reports and small case series. Fungal NSTI are rare but some data suggests that incidence may be increasing. These infections occur in both immunocompromised and immunocompetent hosts, especially following trauma. Mortality varies by host factors, organism, and extent of disease. Foundations of treatment include targeted antifungal therapy and aggressive surgical debridement.

Summary Fungal NSTI is a rarely described clinical entity associated with a high mortality. More study is needed to better understand the epidemiology and optimal management of these infections.

Keywords Fungal · Necrotizing skin and soft tissue infection · Necrotizing soft tissue infection · Necrotizing fasciitis · Mucormycosis · NSTI

Introduction

Necrotizing soft tissue infections (NSTI) are generally rapidly progressive infections characterized by extensive necrosis of the epidermis, dermis, fascia, and/or muscle. Cases often present with significant systemic toxicity and carry high morbidity and mortality. Classically, bacterial NSTI are categorized as either polymicrobial (type I) or monomicrobial (type II) [1•, 2]. Fungal NSTI are extremely rare infections, and the majority of cases in the literature are attributed to Mucorales fungi. The overall incidence of necrotizing soft tissue infections ranges from 0.3 to 15 cases per 100,000 people [3–7]. The incidence of fungal NSTI (either monomicrobial or polymicrobial) is difficult to estimate due to low case rates, the relative difficulty of diagnosis, and fluctuating risk of fungal NSTI between patient populations. There is likely a bias towards recovery of *Candida* spp. from these infections due to its comparative ease to grow on routine culture media. Though limited by small sample sizes, several series have described a 2 to 11% incidence of concurrent fungal involvement in type I NSTI [8–11]. In the largest single institution case series describing rates of fungal involvement in NSTI, fungal organisms were recovered from intraoperative cultures in 21 of 197 (10.7%) cases. *Candida albicans* was the most commonly isolated fungus in 57%, with the remainder including other *Candida* spp., unspeciated yeast, and *Apophysomyces.* Eighteen of the cases growing yeast were polymicrobial, most commonly isolated with *Escherichia coli* and *Bacillus fragilis*, while three patients had surgical cultures only positive for fungi (two *C. albicans* and one *A. trapeziformis).* [12••]. Monomicrobial necrotizing soft tissue infections caused by non-Mucorales fungi including *Aspergillus*, *Cryptococcus*, and *Candida* among others are rare and are primarily represented within the medical literature as case reports complicating an estimate of incidence. There is a more robust literature regarding mucormycosis as compared to other fungal NSTI. In a systematic review of 929 cases of mucormycosis from 1940 to 2003, 176 were associated with

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cutaneous disease, which was the third most common disease presentation [13••]. There is data, primarily from patients with hematologic malignancy, to suggest that the incidence of mucormycosis is increasing [14, 15] and Mucorales-associated NSTI has been reported more frequently in the literature in more recent reviews [13••, 16•, 17, 18••].

Fungal NSTI Risk Factors

The risk factors for fungal NSTI are difficult to specifically describe given the infrequency of this disease entity. There is likely overlap with factors that predispose to bacterial NSTI including trauma or other cutaneous or mucosal barrier breach, surgery, obesity, diabetes, immunosuppression, neutropenia, and malignancy [19–21]. As noted by Horn et al., elevated BMI and prior abdominal surgery were independent risk factors for the isolation of fungal organisms (predominantly *Candida*) among NSTI. Diabetes was comorbid in 43%, alcohol use in 19%, moderate to severe liver disease in 5%, and metastatic solid tumor malignancy in 5% of cases of NSTI with fungal involvement, and these comorbidities were not significantly different from rates in bacterial NSTI. Other immunosuppression, defined as either primary immunodeficiency, organ transplant, or chronic corticosteroid use, was present in 10% of cases [12••].

Trauma is known to be a risk factor for fungal NSTI including among immunocompetent individuals. Soil-contaminated wounds may result in polymicrobial necrotizing fungal infections. In a series of 54 invasive fungal wound infections among 37 American military personnel with combat-related blast injuries, necrosis or myonecrosis was present in 81% of injuries. Thirty-one patients had at least one mold species cultured from their wound, with a Mucorales organism growing in 16 patients, *Aspergillus* growing in 16 patients, and *Fusarium* in 9 patients [22•]. Host factors associated with fungal NSTI will be described further by organism type in the sections below.

Fungal NSTI by Organism

Candida

Candida spp. are yeasts that are normal constituents of the human microbiome, colonizing the skin, respiratory, gastrointestinal, and genitourinary tracts. *Candida* are common opportunistic pathogens in the immunocompromised and critically ill and cause local disease in the setting of cutaneous or mucous membrane barrier breakdown or imbalances in host flora. While there are at least 15 species of Candida known to cause disease in humans, *C. albicans*, *C. glabrata*, *C. tropicalis*, *C. parapsilosis*, and *C. krusei* are responsible for greater than 90% of infections [23••]. Despite the relative frequency of invasive candidiasis, *Candida* is uncommonly implicated in NSTI [12••]. Further, necrotizing skin and soft tissue infections though to be caused by *Candida* spp. alone are extremely rare and represented by only several case reports [24–30].

In Horn et al., *Candida* spp. were isolated from culture in 13 of 197 (7%) of culture positive type I NSTI cases (12 *C. albicans*, 1 *C. dubliniensis)*. An additional 8 of 197 (4%) of cases grew a yeast not further identified, a large proportion of which are presumed to have been *Candida* spp. Female sex, higher BMI, and previous abdominal surgery were associated with increased risk of fungal NSTI culture positivity. Patients with fungi growing from operative cultures were significantly more likely to require additional debridement and had increased mortality (24% vs. 7%) [12••]. This series is limited by a lack of histopathologic data to evaluate for invasive fungal elements to help discern whether the yeast may have been pathogenic or a local colonizer.

We identified seven case reports in the English language medical literature of monomicrobial NSTI attributed to *Candida* spp. Of these cases, three were related to trauma or gunshot wound, three were consistent with Fournier's gangrene, and one case was a cervicofacial NSTI following a dental infection. Two patients (29%) had associated fungemia. All but one case (86%) were diagnosed both via culture and histopathology. The remaining case only specified positive cultures from head and neck debridement. Four patients (57%) had some underlying immunocompromising condition (one renal transplant recipient with diabetes mellitus; three other patients with diabetes). *C. albicans* was the most commonly isolated species and was recovered in four cases (57 %). Among these, *C. tropicalis* also grew in two cases. *C. glabrata*, *C. parapsilosis*, and *Candida* spp. unspecified were each cultured in a single case. None of these cases reported bacterial growth or histopathology suggestive of concurrent bacterial or alternative fungal infection. At least one debridement was performed in all cases. All patients were treated with antifungal agents and in at least five cases broad-spectrum antibacterials were also utilized. None of the patients in these case reports died as a result of fungal NSTI [24–30].

Cryptococcus

Cryptococcus spp. are encapsulated basidiomycetous yeasts with a global distribution. They are a relatively common cause of opportunistic disease in immunocompromised hosts, including patients with HIV, transplant recipients, and patients on chronic immunosuppressive medications like glucocorticoids. The Cryptococci most commonly pathogenic to humans can be divided into two species, one with two variants: *Cryptococcus neoformans* var. *grubii* (estimated to cause 95% of clinical infections), *Cryptococcus neoformans* var.

neoformans, and *Cryptococcus gattii* [31, 32]. *Cryptococcus laurentii* and *C. albidus* are emerging pathogenic species that have been implicated in cutaneous infections, although to our knowledge, these species have not been reported in the context of necrotizing infections [33–35]. Initial infection by these organisms generally occurs through inhalation of basidiospores that may cause primary pulmonary infection with further potential for dissemination throughout the body, including to the central nervous system. It is estimated that 10–20% of cases of disseminated Cryptococcal disease have cutaneous involvement. Cryptococcal NSTI appears to occur far less commonly [31, 32, 36•].

There were 16 cases of Cryptococcal NSTI published from 1990 to 2017. Of these, 14 (88%) occurred in patients with underlying immunodeficiency, most commonly among solid organ transplant recipients. All of these patients were on combination immunosuppressive medications including an equivalent of 10 mg or greater of prednisone. Six of the cases after solid organ transplantation (75%) were associated with disseminated Cryptococcal disease. Other comorbid conditions included diabetes mellitus (three patients), chronic alcoholism (one patient), and pemphigus vegetans on combination immunosuppression (one patient). No cases were described in the context of HIV infection. Of the two cases occurring in immunocompetent patients, minor trauma from a wooden splinter and an insect bite were implicated as the original sources of infection. All but two patients in this series had Cryptococcal NSTI diagnosed by both culture and histopathology, while those without positive culture had histopathology consistent with invasive *Cryptococcus*. *Cryptococcus neoformans* was isolated in 13 (93%) of culture positive cases, while *C. gattii* was isolated in one case from Singapore. Due to the recent recognition of *C. gattii* as a species, a proportion of cases before 2006 may have been improperly classified as *C. neoformans*. Initial treatment following diagnosis included amphotericin B (in either lipid or deoxycholate formulation) in all but one case. Surgical debridement was performed at least once in 13 (81%) cases. Overall mortality was 44% in this series. All three of the patients that did not undergo debridement died, as did the patient who did not receive amphotericin B therapy (initially managed with fluconazole and debridement). Six of the ten patients (60%) with disseminated disease died and two of these patients did not receive debridement. Mortality was 38% among patients with solid organ transplant, two of these patients did not receive debridement. Neither of the patients without underlying immunodeficiency died. Both underwent debridement in combination with amphotericin B therapy [31, 36•, 37–48].

Mucormycosis

Mucormycosis encompasses a diverse spectrum of infection caused by organisms within the order Mucorales. The distinctive feature of mucormycosis is vascular invasion with associated thrombosis and tissue necrosis [49, 50•]. Mucorales are filamentous fungal organisms whose sporangiospores are ubiquitous within the environment, found in decaying organic matter, soil, wood, cotton, and vegetables. The genera that most commonly cause disease in humans are *Rhizopus*, *Mucor*, *Rhizomucor*, *Cunninghamella*, *Lichthemia*, *Saksenaea*, and *Apophysomyces* [13••, 18••, 49–51]. Intact mucosal and endothelial barriers and cilia within the respiratory and gastrointestinal tract serve as defenses against tissue invasion by these organisms. When these barriers are disrupted in immunocompromised hosts, infection can occur following inhalation or ingestion of sporangiospores. In the setting of trauma, epithelial barrier destruction can allow direct inoculation of high burdens of organism, especially when there is soil contamination of wounds. Localized traumatic tissue acidosis and immunosuppression can increase the pathogenicity of Mucorales in this setting [52•]. Angioinvasion allows progression of local disease to adjacent tissues, often with significant tissue necrosis, and potentiates dissemination [49, 50•]. The typical presentation of cutaneous mucormycosis is a painful erythematous skin nodule that progresses, often rapidly, to an overtly necrotic lesion. These lesions often occur at sites of prior trauma, including minor trauma in the appropriate patient. Extension of infection and necrosis to deeper contiguous skin and soft tissue is estimated to occur in 24–84% of cases [13••, 52•, 53].

Roden et al. found cutaneous mucormycosis to be the third most common presentation of mucormycosis, in 19% of cases, following rhino-orbito-cerebral and pulmonary disease [13••]. In a more recent review of 851 cases of mucormycosis reported from 2000 to 2017, cutaneous was the second most common presentation (22% of cases) after rhino-orbital-cerebral (34%). Cutaneous mucormycosis was significantly more common among patients who had suffered trauma (69% of cases). The most common genera isolated were *Rhizopus* in 48% and *Mucor* in 14% of all cases, but, *Apophysomyces* spp. and *Saksenaea* complex were more commonly isolated among patients with cutaneous disease [18••].

Risk factors for the development of mucormycosis include diabetes mellitus, use of corticosteroids, neutropenia, hematologic malignancy, hematopoietic stem cell transplant (HSCT), solid organ transplant, treatment with deferoxamine and iron overload states, and trauma [13••, 18••, 49–51, 54–58]. Traumatic wounds have been associated with as high as 80% of cutaneous mucormycosis cases [51, 53]. The use of voriconazole antifungal prophylaxis in hematologic malignancy patients may also be an independent risk factor for the development of mucormycosis [59].

Trauma with wound contamination is often a critical step to the development of NSTI, and reviews of post-traumatic infections have described 40–90% of cases occurring in immunocompetent individuals [13••, 20, 22•, 51–53, 60]. In a French review, 63% of post-traumatic cases were associated with deep tissue extension and overt necrosis [51]. In another review of 122 cases of post-traumatic cutaneous mucormycosis from 1993 to 2013, overt tissue necrosis was seen in 76% and deep tissue extension in 84% of cases. Dissemination occurred in 8% of cases, although only two of these patients had a history of immunosuppression. *Apophysomyces* spp. were the most common genus identified. Bacterial co-infection was common, present in the initial wound culture in 41% of cases [52•]. Isolation of multiple fungal organisms is also not uncommon in these post-traumatic infections. In a cluster of 13 cases of *Apophysomyces trapeziformis* NSTI in immunocompetent individuals following a tornado, more than half the incident wound cultures also grew *Candida* spp., and *Aspergillus* and *Fusarium* spp. were also isolated in some cases [61].

In a review of 196 healthcare-associated cases of mucormycosis from 1970 to 2008, cutaneous localization was most common and noted in 96 cases (57%). Premature infants and surgical patients represented the predominant populations, with 23% of these patients having received a solid organ transplant. In 26% of the patients, surgical site infection was thought to be the initial site of infection (developing by an average of 19 days). Secondary dissemination in the healthcare setting is more common than in post-traumatic mucormycosis and occurred in 7% of the patients with surgical site infections up to 3 months after initial infection. *Rhizopus* spp. were the most commonly isolated Mucorales in this series [16•].

The overall mortality rate associated with mucormycosis may be in excess of 50% [13••, 18••]. Combination of antifungal therapy, which will be discussed further below, and debridement when possible is associated with improved outcomes. Delay in appropriate antifungal therapy ≥ 6 days after diagnosis has been associated with a doubling of mortality in patients with hematologic malignancy [62]. Outcomes for cutaneous mucormycosis are generally better than for other forms of disease. In both Roden et al. and Jeong et al., mortality rates were 31% for cutaneous disease [13••, 18••]. Patients with post-traumatic infections have a significantly better prognosis compared to other forms of mucormycosis with a 90-day mortality rate of 13% versus 52%, respectively [51, 52•]. This improved survival is due in part to several factors including a less immunocompromised patient population, less frequent dissemination, and more rapid diagnosis, allowing for more prompt debridement and initiation of therapy [13••, 18••, 22•, 51–53, 60].

Aspergillus

Aspergillus are environmental filamentous fungi that are common causes of opportunistic infection in immunocompromised individuals, most commonly those with hematologic malignancy, HSCT, and solid organ transplant recipients. Infection typically occurs after inhalation of conidia with subsequent tissue invasion in the setting of an impaired cellular immune response. *Aspergillus* causes a diverse spectrum of disease, most commonly involving the lungs and sinuses, but may disseminate or include infection of the CNS, bone, endophthalmitis, and endocarditis [63•]. *Aspergillus fumigatus* complex is the most commonly isolated species clinically. Within a large review of HSCT patients, *A. fumigatus* was implicated as the casual organism in 67%, *A. flavus* in 13%, *A. niger* in 9%, and *A. terreus* in 7% of infections [64]. Prolonged neutropenia and other immunocompromising conditions including high-dose glucocorticoids and other immunosuppressive medications, graft-versus-host disease, CMV infection in transplant recipients, and pre-transplant colonization are well-documented risk factors for invasive aspergillosis [63•].

Cutaneous aspergillosis is uncommon. Primary cutaneous aspergillosis has been described in both immunocompetent and immunocompromised patients and can occur following trauma, burns, at the site of indwelling catheters, or occlusive dressings. Secondary cutaneous aspergillosis is more commonly seen in immunocompromised patients and occurs either via hematogenous dissemination or spread from direct extension of infected contiguous structures [65]. Cutaneous aspergillosis lesions may vary widely in appearance. Frank NSTI secondary to *Aspergillus* spp., either alone or in a polymicrobial infection, is rare. Figure 1 demonstrates an example of the appearance of NSTI complicated by *Aspergillus.* Concurrent isolation of *Aspergillus* and Mucorales has been described in post-traumatic NSTI [22•, 51, 52•, 61]. We identified seven cases of non-traumatic, non-mucormycosis-associated *Aspergillus* NSTI in the English language medical literature reported from 1990 to 2016 [66–72]. Two cases involved periorbital infection, two were associated with Fournier's gangrene, two were post-surgical (one following mandibular fracture repair and one of the abdominal wall following cesarean section), and one other case of lower extremity NSTI. Some degree of immunocompromise was recognized in 43% of cases (two with diabetes, one end-stage renal disease, one cirrhosis). Diagnosis was made by both culture and histopathology in 71% of cases. In the six culture positive cases, *A. fumigatus* was isolated in two cases, *A. flavus* in two cases, *A. niger* in one case, and *Aspergillus spp.* in one case. Concurrent bacterial infection was reported in four cases. Tissue-invasive aspergillosis was noted histopathologically in the initial surgical debridement in four of the cases (57%). All patients received antifungal therapy following diagnosis,

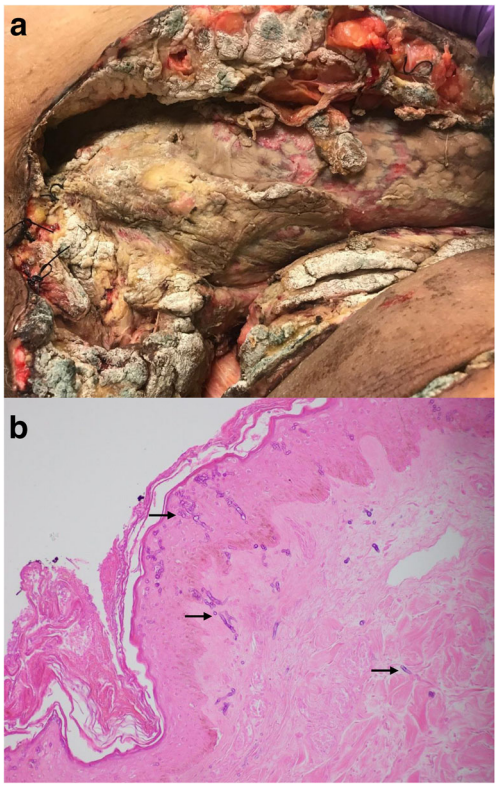

Fig. 1 **a** A representative image of polymicrobial Fournier's gangrene complicated by tissue invasive *Aspergillus fumigatus* following initial soft tissue debridement. **b** Surgical histopathology of tissue debridement from the patient pictured in **a**. The arrows highlight tissue invasive hyphae (Courtesy of Dr. Andrew Turk and Dr. Leslie Wu, Department of Pathology, Columbia University Irving Medical Center)

most commonly with amphotericin B. In one case, fluconazole, which is not active against *Aspergillus*, was the only antifungal utilized in conjunction with broad-spectrum antibiotics and debridement. Concurrent broad-spectrum antibacterial therapy was reported in six cases. At least one tissue debridement was performed in all but one case. Only one case was associated with apparent dissemination but mortality from this disease process was 57% within this series [66–72].

Other Organisms

A variety of other fungal organisms have been reported as causal organisms in the development of NSTI. These include *Fusarium* spp., *Trichosporon* spp., dematiaceous fungi such as *Exophiala dermatitidis*, and endemic mycoses including *Histoplasma capsulatum* [73–76]. Fungal NSTI due to these organisms is exceedingly rare and their description within the medical literature is limited to few case reports. These infections occur almost exclusively in profoundly immunocompromised patients and are often complicated by disseminated fungal disease. The exception to this may be NSTI attributed solely or in part to *Fusarium* spp. as this pathogen has been isolated from NSTI in the context of trauma often from contaminated wounds in immunocompetent patients [22•, 61].

Principles of Management

Expeditious and accurate diagnosis are essential in the management of fungal NSTI. Diagnostic measures should include combined tissue biopsy and culture. Histopathologic evidence of invasive fungal elements is essential for definitive diagnosis given the environmentally ubiquitous nature of many fungal organisms. Further, medical therapy can be more rapidly tailored based on fungal morphology. Histologically, the agents of mucormycosis exhibit broad (5–15 micron), thin-walled, hyaline, aseptate, or pauciseptate hyphae which can be visualized under GMS and PAS staining. Grinding of tissue for laboratory processing should be avoided as this may kill Mucorales and decrease culture yield. Molecular diagnostic techniques can be performed on clinical specimens in a further effort to obtain a species level identification [77, 78]. *Aspergillus* typically exhibit narrow, septate hyaline hyphae that branch at acute angles and can be visualized under GMS and PAS staining. Combined tissue culture is also essential in the diagnosis of *Aspergillus* NSTI as other molds like *Scedosporium* spp. and *Fusarium* spp. may have similar histopathologic morphology [79]. Galactomannan antigen and other molecular diagnostics should be considered as adjunctive diagnostic measures [80]. *Cryptococcus* spp. can be visualized by GMS and PAS stain, and mucicarmine or alcian blue can stain the yeast's capsule. Both serum and CSF Cryptococcal antigen titers should be considered as adjunctive diagnostic measures [31, 32, 36•].

In all cases, treatment of fungal NSTI should include targeted antifungal therapy and broad-spectrum antimicrobials if bacterial co-infection is suspected, in conjunction with consideration of prompt and wide debridement of infected tissue. Immunosuppressive medications should be weaned as feasible and underlying comorbidities, particularly hyperglycemia in the case of mucormycosis, should be optimized. There are no data from clinical trials to specifically guide antifungal therapies in treating NSTI.

In either monomicrobial or polymicrobial NSTI with evidence of tissue invasive *Candida*, initial therapy should include an echinocandin or lipid formulation of amphotericin B. Taking into account local epidemiology and resistance patterns, stepdown to an azole may be reasonable depending on the species identified and antifungal susceptibility testing. Treatment duration needs to be tailored to the individual patient but should generally be continued for 2 weeks following resolution of signs of symptoms of infection as well as encompass concurrent appropriate management of any associated fungemia or metastatic infection [23•].

Given the high proportion of disseminated disease in the setting of Cryptococcal NSTI, even if the initial presentation is suggestive of infection localized to one anatomic area, patients with Cryptococcal NSTI should be evaluated for and managed as disseminated disease. Lumbar puncture should be considered if feasible to rule out central nervous system involvement. Treatment should include liposomal amphotericin B or amphotericin B lipid complex plus flucytosine for at least 2 weeks with subsequent transition to fluconazole suppression for 6–12 months. If flucytosine is unable to be used, a 4-week course of amphotericin should be considered [81•].

Timely initiation of antifungals and tissue debridement whenever feasible are paramount in the management of NSTI due to mucormycosis. An attempt at disease staging should be initiated via physical exam and imaging of the brain, sinuses, and chest [80, 82•, 84•]. Amphotericin B (either liposomal amphotericin B or amphotericin B lipid complex) is generally the first-line antifungal in the treatment of mucormycosis, cutaneous, and otherwise, given the limited clinical data for other regimens. Current guidelines suggest a dose of 5 mg/kg/day but optimal dosing is not known, and in vitro activity against the Mucorales can be variable [80, 81, 82•, 85]. Both posaconazole and isavuconazole have variable in vitro activity against the agents of mucormycosis [86]. Clinical data regarding the efficacy of posaconazole in the treatment of mucormycosis is limited and generally in the setting of salvage therapy [87–89]. The majority of studies used oral suspension preparations of posaconazole with limited bioavailability and difficulty achieving therapeutic serum concentrations, which may lead to treatment failure [90]. Intravenous and tablet formulations have become available with improved pharmacokinetic profiles but clinical data remains very limited [91]. Isavuconazole was approved for the treatment of mucormycosis in the USA and Europe following a study of 37 patients with mucormycosis (mostly pulmonary with no primary cutaneous cases included) and performed similarly to a historical control of patients treated with amphotericin B [92]. Combination antifungal therapy with amphotericin B plus an echinocandin has been evaluated with mixed results but not in the context of the treatment of cutaneous mucormycosis [93, 94]. Clinical data regarding triazole and amphotericin combination therapy is also limited and poorly evaluated for cutaneous or NSTI [95]. Stepdown to oral therapy with isavuconazole or posaconazole may be considered following initial favorable treatment response. The duration of therapy should be tailored to each patient and is typically continued for weeks to months until resolution of signs or symptoms of infection. If immunocompromising conditions are present and unable to be reversed, lifelong therapy may be considered [82•, 83•].

In cutaneous aspergillosis, as with mucormycosis, additional examination and imaging should be performed to evaluate for metastatic sites of infection, focused on contiguous soft tissue structures and the lungs. Although there are no prospective randomized clinical data regarding antifungal therapy for *Aspergillus* NSTI, voriconazole is generally preferred over amphotericin B therapy for invasive aspergillosis [63•, 96]. Initial treatment with amphotericin B is a reasonable alternative if voriconazole use is contraindicated or there is concern for co-infection with an additional mold like the Mucorales. Both posaconazole and isavuconazole have been studied for the treatment of invasive aspergillosis, but outcomes in the setting of cutaneous disease were not specifically described [97, 98]. The combination of voriconazole and an echinocandin for the treatment of invasive aspergillosis has yielded mixed results and has also not been specifically studied in the context of cutaneous disease or *Aspergillus* NSTI. Echinocandin monotherapy is not typically recommended [63•, 99–101]. The duration of therapy for *Aspergillus* NSTI has not been studied and should be tailored to each patient. Guideline statements recommend therapy for cutaneous invasive aspergillosis on the order of 6 to 12 weeks, contingent on assessment of ongoing immunosuppression, source control, ongoing signs or symptoms of infection, and response to therapy [63•].

Several adjunctive therapies have been investigated for the treatment of fungal NSTI, predominantly mucormycosis. Though limited to case reports, topical preparations of amphotericin have been used with success in the management of cutaneous mucormycosis and can be considered especially in cases that are refractory to combination surgical debridement and systemic amphotericin. The optimal dose of topical amphotericin is not known [102, 103]. The use of Dakin's solution to irrigate and dress wounds has been advocated when fungal NSTI is suspected or diagnosed in the context of combat-related trauma [104]. Following promising preclinical data, combination therapy with the non-siderophore iron chelator deferasirox for the treatment of mucormycosis was associated with increased mortality as compared to amphotericin B alone [105]. Hyperbaric oxygen therapy (HBOT) has been explored as an adjunctive therapy for aspergillosis and mucormycosis as increased oxygen tension can increase neutrophil phagocytic ability, decrease tissue acidosis, inhibit fungal growth, and improve wound healing [106, 107]. In a review of 28 cases in mucormycosis, including only four cases of NSTI, there appeared to be a possible survival benefit associated with HBOT, but the data may be confounded by reporting and survival bias [106]. The use of statin therapy, granulocyte colony-stimulating factor, granulocyte infusion, nivolumab, and interferon infusion have also been reported as adjunctive treatments, but the majority have not been studied in the context of NSTI and all clinical data comes from isolated case reports [108–113]. Intravenous immunoglobulin (IVIG) may improve outcomes in superantigen toxin-mediated type II NSTI, in particular Streptococcal infections [114]. However, toxin production is not believed to be the primary driver of morbidity in other forms of NSTI

including fungal, and there does not appear to be a benefit of IVIG in this setting [115, 116].

Conclusions

Fungal necrotizing soft tissue infections are rare but associated with a high mortality. The most commonly isolated fungal organisms in polymicrobial NSTI include *Candida* spp. Monomicrobial fungal NSTI appears most commonly due to mucormycosis. The incidence of fungal NSTI may be increasing, although this finding could be due to increased recognition and diagnosis of this clinical entity. Concurrent immunodeficiency is often present and contributes to the development of fungal NSTI. Fungal NSTI also occurs in immunocompetent populations, particularly following trauma and is generally associated with a lower mortality. Necrotizing cutaneous or soft tissue infections that fail to improve on appropriate antibacterials in immunocompromised populations, in injured patients especially with contaminated wounds, or in patients with minor trauma in the healthcare setting should raise suspicion for fungal NSTI.

Expeditious diagnosis and treatment of fungal NSTI are essential to management. Both tissue culture and biopsy for histopathology to assess for invasive fungal organisms should be obtained if this diagnosis is considered. Treatment of NSTI includes targeted antifungal chemotherapy, surgical debridement, and attempts at immune reconstitution when possible. Depending on the fungal pathogen, a search for disseminated disease is often warranted. Given the complexity of fungal NSTI, duration of therapy should be tailored to each patient. Further research is needed to elucidate the epidemiology, microbiology, and pathogenesis of fungal NSTI as well as to guide treatment strategies in this high morbidity disease.

Compliance with Ethical Standards

Conflict of Interest Logan Bartram and Justin Aaron declare no conflicts of interest relevant to this manuscript.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
- •• Of major importance

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