Injury 50 (2019) 2234–2239

Contents lists available at ScienceDirect

Injury

journal homepage: www.elsevier.com/locate/injury

Severe fungal infections following blunt traumatic injuries: A 5-year multicenter descriptive study

Constance McGraw[a,b,c,d,e,f], Matthew Carrick[g], Francie Ekengren[h], Gina Berg[h], Mark Lieser[i], Alessandro Orlando[a,b,c,d,e,f], Robert Madayag[j], Allen Tanner, II[k], Michael Kelly[k], Kaysie Banton[l], David Bar-Or[a,b,c,d,e,f,*]

[a] Medical City Plano, Trauma Research Department, Plano, TX, United States
[b] Wesley Medical Center, Trauma Research Department, Wichita, KS, United States
[c] Research Medical Center, Trauma Research Department, Kansas City, MO, United States
[d] St. Anthony Hospital, Trauma Research Department, Lakewood, CO, United States
[e] Penrose Hospital, Trauma Research Department, Colorado Springs, CO, United States
[f] Swedish Medical Center, Trauma Research Department, Englewood, CO, United States
[g] Medical City Plano, Trauma Services Department, Plano, TX, United States
[h] Wesley Medical Center, Trauma Services Department, Wichita, KS, United States
[i] Research Medical Center, Trauma Services Department, Kansas City, MO, United States
[j] St. Anthony Hospital, Trauma Services Department, Lakewood, CO, United States
[k] Penrose Hospital, Trauma Services Department, Colorado Springs, CO, United States
[l] Swedish Medical Center, Trauma Services Department, Englewood, CO, United States

ARTICLE INFO

Article history:
Accepted 12 October 2019

Keywords:
Post-traumatic
Fungal infection
Blunt trauma
Risk factors
Management

ABSTRACT

Introduction: The aggressive and timely treatment of post-traumatic fungal infections is the most efficacious way to reduce morbidity and mortality. Compared to the military trauma population, studies reporting on fungal infections in civilian trauma are not well described. The purpose of this study was to describe characteristics of civilian trauma patients who developed fungal infections and to identify common risk factors and report any delays between injury and treatment.

Methods: This was a five-year (1/1/2013–3/1/2018) retrospective, descriptive study across six level 1 trauma centers. All consecutively admitted trauma patients (≥18 years) with laboratory-confirmed fungal wound infections were included. Patients with solely candida wound isolates were excluded. Patient demographics, clinical wound and infection characteristics, organisms cultured, treatment modalities, length of stay, in-hospital mortality, and any diagnostic or treatment delays were described.

Results: Of the 54,521 trauma patients screened for fungal infection, 12 were identified. All patients suffered major injuries after blunt trauma (abbreviated injury score 3–5) and sustained wound contamination, and in nine patients, the cause of injury was motor vehicle. Six had open wounds/fractures on admission. The geographical region with the highest rate of fungal infection was Texas ($n = 7$), followed by Kansas ($N = 3$), then Missouri ($N = 2$). First symptoms of infection (leukocytosis or fever ($n = 10$)) presented a median of 6.3 (4.1–9.8) days after injury. Wound management entailed a combination of debridements ($n = 8$), negative pressure wound therapy ($n = 9$), amputation ($n = 6$), and antifungal treatment ($n = 10$). All fungal isolates identified from the wound site were hyphomycetes. A median of 2.1 (1.8–4.0) days passed from diagnosis to first antifungal treatment, and 3 patients died.

Conclusions: Our study shows the challenges surrounding diagnosis and treatment of fungal infections secondary to trauma. Non-specific fungal infection symptoms, such as leukocytosis and fever, typically presented a week after injury. Vigilance for investigating risk factors and infection symptoms may help clinicians with more timely management of trauma patients with a severe fungal infection.

Introduction

Post-traumatic fungal infections are an uncommon (2–17% of all fungal infections are post-traumatic), yet life threatening complica-

* Correspondence author at: Trauma Research Department, Swedish Medical Center, 501 E. Hampden Ave, Rm 4-454, Englewood, CO 80113, United States.
E-mail address: davidbme49@gmail.com (D. Bar-Or).

https://doi.org/10.1016/j.injury.2019.10.027
0020-1383/

tion secondary to major traumatic injury, that develop when fungal spores inoculate damaged tissue at the injury or wound site, leading to aggressive proliferation of spores and potential angioinvasion [1–5]. Sometimes characterized as a concomitant condition of a major traumatic injury, post-traumatic fungal infections can compromise the immune system, rapidly causing vessel thrombosis and tissue necrosis from a wound site or systemically [1,6–8]. It is well recognized that management of post-traumatic fungal infections are time sensitive to prevent infection spread, and even with prompt medical attention, patients are frequently subjected to significant morbidity and high mortality rates [1,9,8].

Despite the importance of its timely and aggressive surgical treatment, very few studies on post-traumatic fungal infections report on timing of clinical interventions. The majority of published literature on (time to treatment) include military populations, who have established their own screening protocols and treatment guidelines [1]. Consequently, any standardized nomenclature or management was developed for combat-personnel and is limited in the civilian trauma population [1,10–12,5,13]. Additionally, the majority of studies reporting on post-traumatic fungal infections are confined to case studies of mucormycosis, and often do not differentiate between systemic or localized fungal infections, making it challenging to estimate incidence across all organisms [14–16,1]. The small number of fungal infection cases reported in the civilian trauma population and varying definitions across studies, limits proper understanding and treatment, often resulting in delays to diagnosis and poor outcomes [1].

The current study provides a detailed description of civilian blunt trauma patients who developed a severe fungal infection. The primary aims of this study were to 1) describe the incidence, demographics, clinical characteristics, treatment modalities, geographic region, and mortality of patients with post-traumatic fungal infections, and 2) calculate any delays between injury, first procedure, symptom, diagnosis, and treatment of patients with post-traumatic fungal infection.

Methods

This retrospective, multicenter descriptive study, identified the study population by matching all patients with a positive fungal culture from the infectious disease database, to the Trauma Registry. Study inclusion criteria consisted of 1) adult trauma patients $\geq$ 18 years, 2) admitted to a trauma surgical service between 1/1/2013–3/31/2018, 3) with confirmation of a fungal wound culture infection from the infectious disease or microbiology lab. Patients with positive fungal cultures sampled from sites unrelated to the fungal incident wound sites were excluded (e.g. positive fungal culture from foot swab, not from open fracture site). Similar to other studies, the current study excluded patients (n = 20) with Candida-only culture results (*Candida: albicans,* n = 18; *glabrata,* n = 3*; tropicalis,* n = 2; *parapsilosis,* n = 2). [1] Microbial cultures were collected from the wound site with the strongest suspicion of infection and processed by standard microbiological procedures, using direct microscopy and culture to identify the isolate. If the isolate's structure was unable to be identified, it was sent for DNA sequencing. Six level I trauma centers across four states participated in this study and all sites obtained Institutional Review Board approval with a waiver of informed consent.

The following demographic and clinical characteristics were abstracted on all patients from the trauma registries: injury date and time, arrival date and time, sex, age, race, injury severity score (ISS), mechanism of injury (motor-vehicle crash (MVC) w/ ejection, motor vehicle accident (MVA) vs. tree, MVA rollover, motorcycle crash (MCC) vs. parked car, MCC no helmet, MCC w/ helmet, MVA vs. 18-wheeler, MVA, Machinery crush,)), abbreviated injury scale 3–5 (AIS), hospital length of stay (HLOS), total ICULOS, number of days on mechanical ventilation (MV), trauma type, injury diagnoses, hospital discharge destination, in-hospital mortality, and history of smoking, hypertension (HTN), anticoagulant use, diabetes (DM), congestive heart failure (CHF), and alcohol abuse (ETOH).

The following infection wound management information was abstracted from the electronic medical record: antibiotic and antifungal treatments, anatomical region of infected wound(s), infection dispersion (local vs. disseminated), infection symptoms (leukocytosis, fever, inflammation), number and type and timing of medical procedures performed to manage the incident wound (packed red blood cells [PRBCs], fresh frozen plasma [FFP], platelets [PLTs], cryoprecipitate [CRYO], debridement, irrigation, amputation, skin grafting, and negative pressure wound therapy [NPWT]). All data encompassing fungal and bacterial isolates were abstracted from each participating trauma center's microbiology or infectious disease laboratory databases.

We described the following variables: incidence, demographics, clinical presenting characteristics, fungal and bacterial isolates, (surgical) management, antifungal treatment, and in-hospital mortality of patients. We also calculated time from injury to first symptom, diagnosis (first clinical suspicion of fungal infection prompting culture order), antibiotic treatment, and procedure; and time from diagnosis to infection resolution (last day of in-hospital antifungal treatment). Continuous data were expressed using means (standard deviations) or medians (interquartile ranges), and categorical data as counts and percentages. Unadjusted generalized linear modeling was used to examine any associations between total days on antifungal treatment and as covariates, time from injury to diagnosis and time from injury to first symptom. SAS version 9.4 (Cary, NC) was used on all analyses.

Results

After screening 54,521 trauma patients, there were 12 (0.02%) patients, identified over five years who developed a post-traumatic fungal infection; only three hospitals ultimately contributed data after screening (Fig. 1). The majority were male, around 40 years of age, and presented with an ISS $\geq$ 16 (Table 1). Six patients suffered from an injury after an MVA/MVC and all 12 patients experienced blunt trauma. Injury patterns included open fracture/open wound (n = 6), followed by abrasion/friction burn (n = 4), and then traumatic amputation (n = 2). Fungal infections most frequently developed from an open wound on the leg (n = 5) and had an AIS between 3 and 5. Patients experienced a mean (SD) HLOS of 42.6 (24.7) and a median (IQR) ICULOS of 17 (7–28) days.

Most patients (n = 8) were initially managed with either debridements, irrigation, and/or NPWT and nine patients received a median of 10 (9–13) PRBCs within the first 24 h of injury (results can be found in Supplementary Table S1). These initial procedures frequently happened prior to diagnosis of fungal infection to remove wound contaminates collected during injury.

The majority of patients had disseminated infections (n = 6) and infection symptoms frequently presented as leukocytosis or fever (n = 10) (Supplementary Table S1) a median (IQR) of 6.3 (4.1–9.8) days after injury (Table 2). At the incident wound site, visible mold growth was observed in six patients, local inflammation of incident wound or wound dehiscence in four, and, three patients developed necrotic tissue. All fungal isolates identified were hyphomycetes and included fungi from the phylum Ascomycota (*Aspergillus, Curvularia, Fusarium*) (n = 7), and Zygomycota (*Mucor, Rhizopus*) (n = 6). Additionally, three patients had concurrent yeast, three had more than one filamentous fungal isolate, and six had bacterial isolates identified from the incident wound (refer to Table S1 for more information on fungal and bacterial isolates identified).

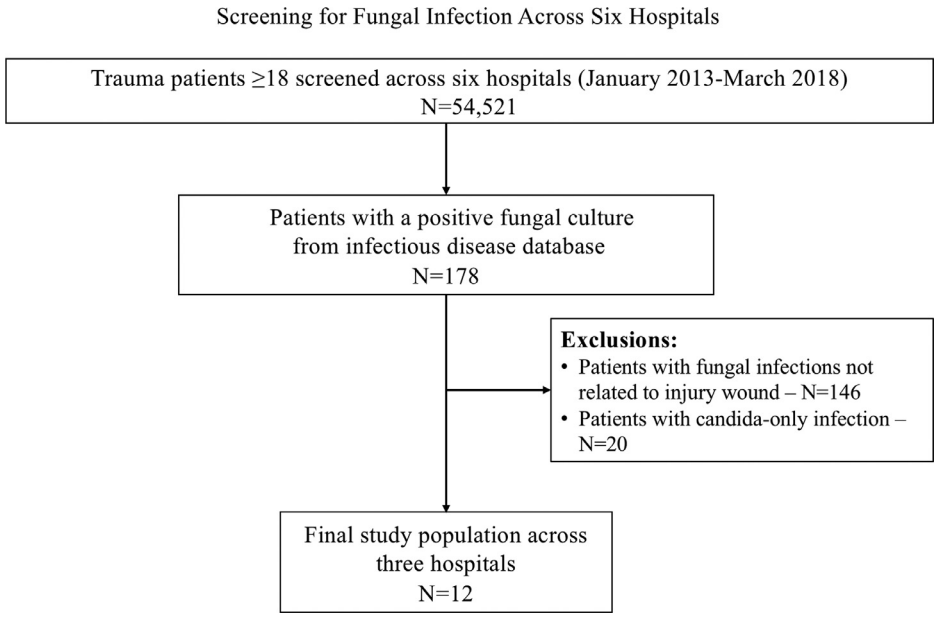

Fig. 1. Represents the screening process to identify fungal infection patients, starting with the total number of trauma patients screened across six hospitals.

Diagnoses were made a median (IQR) of 10.8 (6.3–16.2) days after injury (first sample acquisition from suspected wound site) (Table 2). Nearly all patients ($n = 10$) received antifungal treatment. Five patients received voriconazole or posaconazole as their first line of treatment, two patients received amphotericin B, two patients received fluconazole, and one received micafungin (Table S1). Overall, three patients died in-hospital, a median of 17.9 (15.3–34.2) days after injury. In one patient who died, amphotericin B was the first line of treatment, after necrotic tissue was observed. In the other two patients, fluconazole was the first antifungal prescribed.

When observing patient timelines from injury to final antifungal treatment (Fig. 2), many patients ($n = 7$) had a procedure to remove foreign debris on the same day as their injury and presented with their first fungal infection symptom nearly one week after injury. Additionally, patients who died experienced a significantly longer median (IQR) time between injury and diagnosis, compared to patients who lived (18.4 days (14.4–30.9) vs. 8.0 days (6.2–10.9) $p = 0.04$). No associations existed in the unadjusted linear model examining total days on antifungal treatment and time from injury to diagnosis or time from injury to first symptom.

Discussion

Post-traumatic fungal infections, although rare, can be a devastating event for patients. The current mortality rate varies from 25% to 41%, and patient survival often entails aggressive surgical debridements, amputations, and extended HLOS and ICULOSs [1]. Studies indicate that fungal infections seem to be increasing [1], yet there is a scarcity of research on post-traumatic fungal infections. In this multicenter study on civilian trauma patients, we calculated a fungal infection prevalence of 0.02%. Our data suggest that post-traumatic fungal infections most often developed in patients who suffered from a major open-wound injury of the leg with contamination. Additionally, nearly all patients experienced non-specific infection symptoms, that appeared to result in delays to diagnosis, antifungal treatment, and infection resolution.

The non-specific clinical symptoms of fungal infection can make diagnosis challenging. Upon presentation to the hospital, all patients had no clear signs of infection. Symptoms such a leukocytosis and fever presented a median (IQR) of 6.3 (4.1–9.8) days after injury and then antifungal treatment was started a median of 5.4 (4.0–10.0) days later, as the signs of infection progressed, culture was ordered, and antibiotics were no longer working. Delayed diagnoses and treatment of fungal infection are associated with poor outcomes in the military trauma population [17,11,18–21], yet there are few studies that report on delays in diagnosis or treatment and related outcomes in the civilian trauma population. Fanfair and colleagues reported a median (IQR) time from injury to first positive culture of 14 (10–16) days, median time from injury to first surgical debridement of 3 (2–10) days, and first positive culture to start of antifungal treatment of 0.5 (0–7) days and 38% died [22]. In contrast, we observed a median (IQR) injury to first debridement of 0.8 (0.1–4.0) days, injury to first positive culture of 10.8 (6.3–16.2) days, and first positive culture to start of antifungal treatment of 2.1 (1.8–4.0) days, and 25% died. Time from injury to diagnosis appeared to be longest in the patients who died, though we were not able to establish definitive causality.

A noteworthy finding was the 100% rate of blunt trauma wounds that developed fungal infection, and furthermore, blunt trauma commonly led to open wounds (50%), compared to much lower rates of blunt trauma wounds that led to fungal infection (0–81%) in the published literature [22,23,2]. Fanfair et al. observed that number of wounds and penetrating trauma were associated with significantly higher odds of infection compared to controls. Of the patients without open wounds, contaminated abrasions causing soft-tissue injuries may have led to infection. In the RetroZygo study examining post-traumatic mucormycosis, 18–25% of cases were related to superficial abrasion [13]. Although the pathogenic mechanism for fungal infection in the trauma population is not well described, all of the patients were involved in an unrestrained MVA/MCC, or experienced a crush injury with open wounds, presumably leading to extensive tissue damage, transient immunosuppression, and hyphal inoculation. Additionally, most patients were transfused with PRBCs within 24 h of injury and had an amputation, either traumatically or in-hospital management, which have both been reported as independent predictors of fungal infection across studies [9–11]. Despite the low incidence of fungal infec-

Table 1
Characteristics of patients with fungal infection.

Characteristics	*N* (%) = 12
Gender (Male)	10 (83%)
Age (years), Mean (SD)	39.2 (16.5)
Injury Severity Score	
1–15	4 (33%)
≥16	8 (67%)
Comorbidities	
Alcohol abuse	3 (25%)
Smoker	3 (25%)
None	4 (33%)
Trauma type (blunt)	12 (100%)
Mechanism of injury	
MVA/MVC	6 (50%)
MCC	3 (25%)
Construction equipment	2 (17%)
Agricultural-related	1 (8%)
Geographical region	
Texas	7 (58%)
Kansas	3 (25%)
Missouri	2 (17%)
Potential origin of infection	
Open fracture/open wound	6 (50%)
Abrasion/friction burn	4 (33%)
Traumatic amputation	2 (17%)
Region of incident wounds	
Head/neck	2 (17%)
Leg	5 (42%)
Arm	2 (17%)
Chest	2 (17%)
Intrabdominal	1 (8%)
Highest AIS Score for incident wound	
3	4 (33%)
4	4 (33%)
5	4 (33%)
Wound Management	
Debridement	8 (67%)
Irrigation	6 (50%)
Amputation/disarticulation	6 (50%)
NPWT	9 (75%)
Grafts	5 (42%)
Mean (SD) Hospital LOS, days	42.6 (24.7)
Median (IQR) ICU LOS, days	17 (7–28)
Mean (SD) Days on mechanical ventilation	17 (5–28)
Discharge destination	
Home/home health	6 (50%)
Rehab	3 (25%)
Expired	3 (25%)

SD, standard deviation; MVA, motor vehicle accident; MVC, motor vehicle crash; MCC, motorcycle crash; AIS, abbreviated injury scale; NPWT, negative pressure wound therapy, IQR, interquartile range; LOS, length of stay; ICU, intensive care unit.

tion following blunt trauma, both open wounds and abrasions with contamination should heighten clinical suspicion for fungal infection susceptibility.

To our knowledge, this is the first study to broadly examine fungal infections secondary to traumatic injury in the United States across different geographical regions. We screened for fungal infections at hospitals in Texas, Missouri, Kansas, and Colorado, and found the highest rates of infection in Texas ($n = 7$), followed by Kansas ($n = 3$), and then Missouri ($n = 2$). Interestingly, there were no fungal infections identified in Colorado. The United States Environmental Protection Agency reports that mold growth can start around 60% relative humidity (RH) [24]. In contrast to the other states, Colorado's climate is arid with an annual average RH of 51% across associated-hospital locations [25], which may not be able to support the level of moisture in the air required for fungal development. On the other hand, three of the cities in the central United States across Texas, Missouri, and Kansas have higher yearly RHs of 69%, 64%, and 63%, respectively, which may be more formidable environments for mold growth [24,25]. Collecting data from different regions in the United States, we also observed a more diverse fungal profile than previous studies primarily focused on mucormycosis in the civilian trauma population [26,22,27,28]. In the current study, culture isolates included four *Aspergillus*, three *Mucor*, two *Rhizopus,* two *Fusarium*, and one *Curvularia* sp., which can be commonly found in soil and plants. Species from the order Mucorales have been reported to have the most aggressive and invasive forms of fungal infection and worst outcomes.

Interestingly, it was observed that two of the three patients who died had *Mucor* spp. identified from the infected wound. One of these patients had an injury to diagnosis time of 14.4 days but was only on amphotericin B 0.8 days and died shortly after. The other two in-hospital mortalities also had lengthy times from injury to diagnosis and were prescribed fluconazole or micafungin, which are broad-spectrum antifungals traditionally used to treat yeast infections, potentially contributing to mortality. Though we do not have exact cause of death, complications seemed to be related to both the trauma and the extent of the fungal infection. One patient's incident chest wound dehisced, revealing heavy fungal growth confirmed to be *Aspergillus* sp. The other patient's autopsy revealed extensive diffuse necrosis with multiple fungal organisms throughout the brain, kidneys, heart, and lungs, confirmed to be *Aspergillus* and *Mucor* sp. The third patient had fungal sepsis, necrotic tissue, mucormycosis in the abdominal wall, and acute respiratory failure, in addition to other complications.

The patients who lived experienced injury to first antifungal treatment of 11 days (compared to the 16 days for patients who died) and four had an average time from first symptom to first diagnosis of 1 day, potentially leading to more directed antifungal treatment and faster time to infection resolution. The other three patients who had antifungal treatment experienced an average delay of 4.5 days between first symptom and diagnosis, which appeared to result in longer time to infection resolution. One patient was started on micafungin and then switched to amphotericin B, after cultures were returned and initial broad-spectrum antifungal treatments were not affective. However, in nearly all cases, targeted antifungals were the first line of treatment prescribed, due to clinical signs and symptoms of infection, and prior to return of cultures and confirmation of fungal species involved.

The primary limitation of this study is that, at the participating trauma centers, infection is routinely confirmed by lab cultures paired with clinical signs and symptoms, not histopathology. Although histopathology is the gold standard for determining angioinvasion, it is typically not the standard of care due to higher costs and lack of treating physician's knowledge and preference. At all centers the physician treats empirically based on the clinical signs and symptoms of infection, as well as culture results, and at one of the participating facilities, histopathology is supposed to be performed only when the initial broad-spectrum antifungal is not treating the infection. Nonetheless, we believe this epidemiological paper of post-traumatic fungal infections contributes to the literature, despite the lack of histopathological data, because it represents a trauma population that has not been sufficiently described, and because it reflects the real world practices of trauma surgeons when they are faced with a civilian trauma patient that has a severe fungal wound infection. Second, this is a small descriptive study with no control group, which made it challenging to test hypotheses or draw any valid conclusions; however, there were hypotheses generated that could be used for future studies. Third, this is a cross-sectional study across six trauma centers, and results may not be generalizable to other trauma centers. Nonetheless, we screened for fungal infection from a general trauma population across six facilities, which may help other sites calculate their rate of fungal infection. Fourth, fungal organisms do not always grow in cultures, which may have potentially influenced the

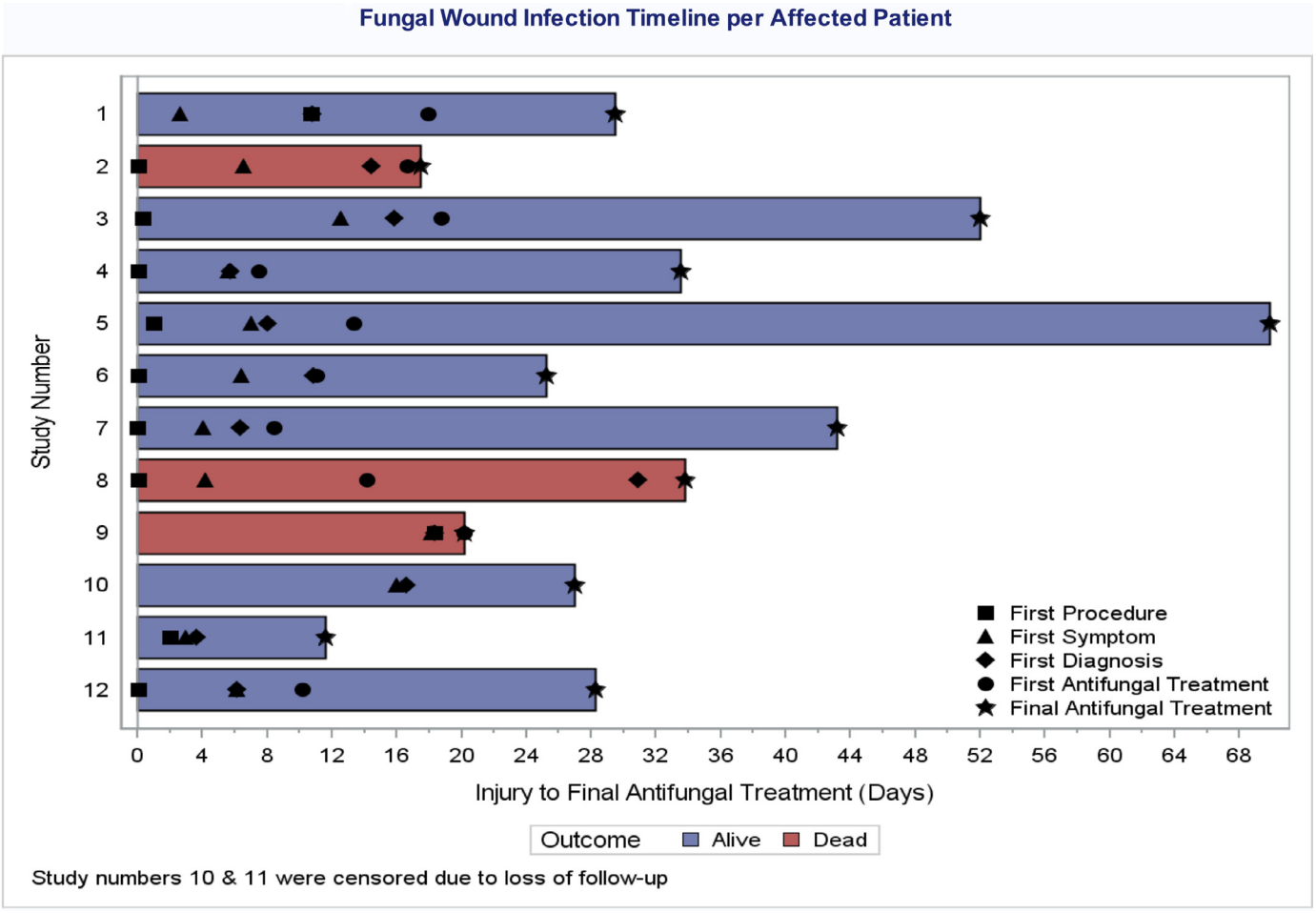

Fig. 2. Wound infection timeline beginning with injury, ending with final antifungal treatment, and including time points of first procedure, infection symptom, and diagnosis.

Table 2
Median delays between injury, diagnosis, and treatment among patients with fungal infection.

Outcome	Days[a]
Median Days from Injury to First Procedure	0.10 (0.1–2.0)
Median Days from Injury to First Antibiotic Treatment	0.4 (0.1–3.1)
Median Days from Injury to First Symptom	6.3 (4.1–9.8)
Median Days from Injury to Diagnosis (Sample Acquisition)	10.8 (6.3–16.2)
Median Days from Injury to First Antifungal Treatment	13.8 (10.2–18.0)
Median Days from First Symptom to First Antifungal Treatment	5.4 (4.0–10.0)
Median Days from Diagnosis to First Antifungal Treatment	2.1 (1.8–4.0)
Median Days from Diagnosis to Final Antifungal Treatment*	27.8 (18.7–36.8)
Median Days from Injury to Infection Resolution*	33.5 (28.3–52.0)

[a] Represented as median with interquartile range; * excludes patients who died.

screening and true incidence of fungal infection in this population. Fifth, two patients had no information available for antifungal treatment; one patient was discharged to the burn unit after trauma and no information was listed and the other patient was discharged to an outside facility of care before the fungal culture came back. Both patients, however, had other clinically meaningful data that contributed to the study. Sixth, not all fungal isolates had confirmed taxonomic organization and thus our fungal biodiversity may be underrepresented. The infection course and characteristics of these patients, however, are similar to what we have observed in the study and across many other studies of filamentous fungi. Lastly, we did not collect cause of death. In spite of this, examining the medical records of patients who died gave us a fair assessment of potential causes.

Conclusions

This study emphasizes the challenges surrounding the diagnosis and treatment of post-traumatic fungal infections. Our data suggests that because fungal infection symptoms, diagnoses, and treatment are frequently delayed, vigilance for investigating the following risk factors should be followed to potentially reduce morbidity and mortality in this patient population: 1) polytrauma patients with major open and contaminated wounds and transient

immunosuppression, 2) injured in regions with high humidity, 3) experience multiple blood transfusions, surgical debridements, amputations, or NPWT, 4) signs and symptoms that develop up to a week after injury indicating infection, and 5) patients who are not responding to antibiotics. These risk factors may assist clinicians in earlier culture orders, diagnosis, and treatment. Further studies are warranted to better delineate the use of more precise diagnostic methods, such as histopathology in parallel with cultures, on timing of clinical treatments and outcomes for severe post-traumatic fungal infection in civilian trauma populations.

Funding

The study was investigator-initiated. Internal funding was provided by all affiliated institutions (Medical City Plano, Wesley Medical Center, Research Medical Center, Penrose Hospital, St. Anthony Hospital, and Swedish Medical Center).

Ethics approval and consent to participate

The study was approved from the Institutional review boards at each participating site with a with a waiver of informed consent: Medical City Plano: Hospital Corporation of America-IRB# 1186938; Swedish Medical Center: Hospital Corporation of America-IRB#1191387; Wesley Medical Center: Hospital Corporation of America-IRB# 18-014, St. Anthony Hospital and Penrose Hospital: Catholic Health IRB# 1188392; and Research Medical Center: Western IRB# 20180270.

Declaration of Competing Interest

All authors declare there are no conflicts of interest.

CRediT authorship contribution statement

Constance McGraw: Conceptualization, Formal analysis, Data curation, Writing - original draft. **Matthew Carrick:** Conceptualization, Data curation. **Francie Ekengren:** Data curation. **Gina Berg:** Data curation, Writing - original draft. **Mark Lieser:** Data curation, Writing - original draft. **Alessandro Orlando:** Data curation, Writing - original draft. **Robert Madayag:** Data curation, Writing - original draft. **Allen Tanner, II:** Data curation, Writing - original draft. **Kaysie Banton:** Data curation, Writing - original draft. **David Bar-Or:** Data curation, Writing - original draft.

Acknowledgements

The authors would like to thank Kathy Rodkey, Diane Redmond, Jennifer Pekarek, Shenequa Deas, Pam Colvin, Jamie Shaddix, and Carolyn Blue, for their invaluable work in abstracting data and helping to move this study forward.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.injury.2019.10.027.

References

[1] Kronen R, Liang SY, Bochicchio G, Bochicchio K, Powderly WG, Spec A. Invasive fungal infections secondary to traumatic injury. Int J Infect Dis 2017;62:102–11. doi:10.1016/j.ijid.2017.07.002.
[2] Fares Y, El-Zaatari M, Fares J, Bedrosian N, Yared N. Trauma-related infections due to cluster munitions. J Infect Public Health 2013;6:482–6. doi:10.1016/j.jiph.2013.05.006.
[3] Obradovic-Tomasev M, Jovanovic M, Vuckovic N, Popovic A. Fungal infections in corn picker hand injury. Srp Arh Celok Lek 2016;144:52–5. doi:10.2298/sarh1602052o.
[4] Skiada A, Pagano L, Groll A, Zimmerli S, Dupont B, Lagrou K, et al. Zygomycosis in Europe: analysis of 230 cases accrued by the registry of the European Confederation of Medical Mycology (ECMM) Working Group on Zygomycosis between 2005 and 2007. Clin Microbiol Infect 2011;17:1859–67.
[5] Ingram PR, Suthananthan AE, Rajan R, Pryce TM, Sieunarine K, Gardam DJ, et al. Cutaneous mucormycosis and motor vehicle accidents: findings from an Australian case series. Med Mycol 2014;52:819–25. doi:10.1093/mmy/myu054.
[6] Alonso S, Jarque Ramos I, Salavert Lletí M, Pemán J. Epidemiology of invasive fungal infections due to Aspergillus spp. and Zygomycetes. Clin Microbiol Infect 2006;12:2–6.
[7] Spellberg B, Edwards J, Ibrahim A. Novel perspectives on mucormycosis: pathophysiology, presentation, and management. Clin Microbiol Rev 2005;18:556–69.
[8] Vitrat-Hincky V, Lebeau B, Bozonnet E, Falcon D, Pradel P, Faure O, et al. Severe filamentous fungal infections after widespread tissue damage due to traumatic injury: six cases and review of the literature. Scand J Infect Dis 2009;41:491–500.
[9] Rodriguez CJ, Tribble DR, Malone DL, Murray CK, Jessie EM, Khan M, et al. Treatment of suspected invasive fungal infection in war wounds. Mil Med 2018;183:142–6. doi:10.1093/milmed/usy079.
[10] Lloyd B, Weintrob AC, Rodriguez C, Dunne JR, Weisbrod AB, Hinkle M, et al. Effect of early screening for invasive fungal infections in US service members with explosive blast injuries. Surg Infect 2014;15:619–26.
[11] Weintrob A, Weisbrod A, Dunne J, Rodriguez C, Malone D, Lloyd B, et al. Combat trauma-associated invasive fungal wound infections: epidemiology and clinical classification. Epidemiol Infect 2015;143:214–24.
[12] Lelievre L, Garcia-Hermoso D, Abdoul H, Hivelin M, Chouaki T, Toubas D, et al. Posttraumatic mucormycosis: a nationwide study in France and review of the literature. Medicine 2014;93(24).
[13] Lanternier F, Dannaoui E, Morizot G, Elie C, Garcia-Hermoso D, Huerre M, et al. A global analysis of mucormycosis in France: the RetroZygo Study (2005–2007). Clin Infect Dis 2012;54:S35–43. doi:10.1093/cid/cir880.
[14] Singla K, Samra T, Bhatia N. Primary cutaneous mucormycosis in a trauma patient with Morel-Lavallée Lesion. Indian J Crit Care Med 2018;22:375–7. doi:10.4103/ijccm.IJCCM_343_17.
[15] Loganathan S, Ajay GAE, Thyagarajan U, Gokul RD. Invasive fungal infection in immunocompetent trauma patients – a case series. J Clin Orthop Trauma 2018;9:S10–SS4. doi:10.1016/j.jcot.2017.10.005.
[16] Castrejón-Pérez AD, Welsh EC, Miranda I, Ocampo-Candiani J, Welsh O. Cutaneous mucormycosis. An Bras Dermatol 2017;92:304–11. doi:10.1590/abd1806-4841.20176614.
[17] Warkentien TE, Shaikh F, Weintrob AC, Rodriguez CJ, Murray CK, Lloyd BA, et al. Impact of Mucorales and other invasive molds on clinical outcomes of polymicrobial traumatic wound infections. J Clin Microbiol 2015;53:2262–70.
[18] Rodriguez C, Weintrob AC, Dunne JR, Weisbrod AB, Lloyd B, Warkentien T, et al. Clinical relevance of mold culture positivity with and without recurrent wound necrosis following combat-related injuries. J Trauma Acute Care Surg 2014;77:769–73. doi:10.1097/TA.0000000000000438.
[19] Lloyd B, Weintrob AC, Rodriguez C, Dunne JR, Weisbrod AB, Hinkle M, et al. Effect of early screening for invasive fungal infections in U.S. service members with explosive blast injuries. Surg Infect 2014;15:619–26. doi:10.1089/sur.2012.245.
[20] Rodriguez CJ, Weintrob AC, Shah J, Malone D, Dunne JR, Weisbrod AB, et al. Risk factors associated with invasive fungal infections in combat trauma. Surg Infect 2014;15:521–6. doi:10.1089/sur.2013.123.
[21] Warkentien T, Rodriguez C, Lloyd B, Wells J, Weintrob A, Dunne JR, et al. Invasive mold infections following combat-related injuries. Clin Infect Dis 2012;55:1441–9. doi:10.1093/cid/cis749.
[22] Neblett Fanfair R, Benedict K, Bos J, Bennett SD, Lo YC, Adebanjo T, et al. Necrotizing cutaneous mucormycosis after a tornado in Joplin, Missouri, in 2011. N Engl J Med 2012;367:2214–25. doi:10.1056/NEJMoa1204781.
[23] Cocanour CS, Miller-Crotchett P, Johnson P, Fischer R. Mucormycosis in trauma patients. J Trauma 1992;32:12–15.
[24] Agency USEP. Mold: Mold Course Chapter 2: Why and Where Mold Grows; 2019 https://www.epa.gov/mold/mold-course-chapter-2#Chapter2Lesson2 Accessed 1 May 2019.
[25] NOAA: National Centers for Environmental Information. Accessed 30 September 2019, 2019. https://www.ncdc.noaa.gov/cdo-web/datasets.
[26] Zahoor B, Kent S, Wall D. Cutaneous mucormycosis secondary to penetrative trauma. Injury 2016;47:1383–7. doi:10.1016/j.injury.2016.03.011.
[27] Andresen D, Donaldson A, Choo L, Knox A, Klaassen M, Ursic C, et al. Multifocal cutaneous mucormycosis complicating polymicrobial wound infections in a tsunami survivor from Sri Lanka. Lancet 2005;365:876–8. doi:10.1016/s0140-6736(05)71046-1.
[28] Hajdu S, Obradovic A, Presterl E, Vecsei V. Invasive mycoses following trauma. Injury 2009;40:548–54. doi:10.1016/j.injury.2008.03.034.