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Review

Invasive Fungal Infections Secondary to Traumatic Injury

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ABSTRACT

Invasive fungal infection (IFI) is a rare but serious complication of traumatic injury. The purpose of this article is to review the epidemiology, natural history, mycology, risk factors, diagnosis, treatment, and outcomes associated with post-traumatic IFI in military and civilian populations. The epidemiology of post-traumatic IFI is poorly characterized, but incidence appears to be rising. Patients often suffer from severe injuries and require extensive medical interventions. Fungi belonging to the order *Mucorales* are responsible for most post-traumatic IFI in both civilian and military populations. Risk factors differ between these cohorts but include specific injury patterns and comorbidities. Diagnosis of post-traumatic IFI typically follows positive laboratory results in the appropriate clinical context. The gold standard of treatment is surgical debridement in addition to systemic antifungal therapy. Patients with post-traumatic IFI may be at greater risk of amputation, delays in wound healing, hospital complications, and death as compared to trauma patients who do not develop IFI. More research is needed to understand the factors surrounding the development and management of post-traumatic IFI to reduce the significant morbidity and mortality associated with this disease.

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Introduction

Invasive fungal infections (IFI) are a rare but serious complication of traumatic injury characterized by fungal angioinvasion and resultant vessel thrombosis and tissue necrosis (Alonso et al., 2006; Spellberg et al., 2005). In contrast to other settings, post-traumatic IFI occurs through direct inoculation of tissue with spores at the site of injury (Bilal et al., 2016). Fungi may then take advantage of an acidemic, iron-rich environment to proliferate and invade vessels through hyphae growth. Patients with post-traumatic IFI suffer poor outcomes from the aggressive nature of the infection and from delays in diagnosis and appropriate management (Neblett Fanfair et al., 2012). Significant gaps in the literature exist, with large-scale cohorts and comparative studies curbed by the scarcity of cases. Nevertheless, a growing body of evidence drawn from case series, cohorts, and case-control studies has accumulated over the past several decades such that clinicians and researchers can begin to gain an understanding of the clinical course and consequences of developing post-traumatic IFI.

The aim of this review is to summarize the epidemiology, clinical presentation, microbiology, diagnosis, management, and clinical outcomes in military and civilian trauma patients with IFI. When possible, we will focus on IFI occurring as a direct result of soft tissue injury rather than delayed or chronic progressing infection, as the latter group likely represents a different pathogenic pathway. Additionally, we will highlight areas lacking attention in the literature to inform future research on this subject.

Epidemiology

Military

During the wars in Iraq and Afghanistan, IFI emerged as a significant complication of combat-related injury. A review of the U.S. Department of Defense Joint Theater Trauma Registry identified fungal infection by ICD-9 codes in 0.44% of combat trauma patients, although these codes were not specific to IFI and candidiasis, both invasive and non-invasive, accounted for the majority of infections (Murray et al., 2011). Subsequently, analyses of combat-injured military personnel evacuated from Afghanistan found an overall IFI incidence rate of 6.8% (Rodriguez et al., 2014a), with incidence increasing over the period of observation (Warkentien et al., 2012). These data were based on the Trauma Infectious Disease Outcomes Study (TIDOS), representing a subset of 1,133 injured soldiers evacuated from Afghanistan between 2009 and 2011. The improved sensitivity and accuracy of IFI identification afforded by TIDOS likely contributed to these starkly different incidence estimates.

Demographically, the military population affected by IFI is consistent with the underlying population of young healthy adult soldiers (Table 1). Cohort patients were all male, with a median age between 22 and 24 years old, and most had no underlying medical conditions (Paolino et al., 2012; Lloyd et al., 2014).

Civilian

The epidemiology of post-traumatic IFI in the heterogeneous civilian population is less well-defined. Observational studies have varying IFI definitions and patient characteristics, and many are confined to cases of mucormycosis only, which have an annual incidence of approximately 0.43–1.7 cases per million persons (Bitar et al., 2009; Bouza et al., 2006; Torres-Narbona et al., 2007). Traumatic injury accounts for up to 21% of these cases overall and 59% of primary cutaneous mucormycosis (Llorente et al., 2011; Skiada et al., 2011; Pagano et al., 2009; Lanternier et al., 2012; Roden et al., 2005; Skiada and Petrikkos, 2009; Skiada et al., 2012; Kaushik, 2012). Incidence of post-traumatic IFI due to all organisms, however, is poorly characterized. A prospective study in Lebanon found that the rate of fungal infection in patients injured by cluster munition explosions was 2.6% (Fares et al., 2013). Two retrospective studies found IFI to occur in 3.1% of upper extremity wounds and 15% of corn picker injuries (Moran et al., 2006a; Obradovic-Tomasev et al., 2016). These studies, however, were circumscribed to a specific injury type and are not likely to be generalizable. Vitrat-Hincky et al. (2009) identified 75 cases of post-traumatic filamentous fungal infection in the literature and their own hospital records between 1985 and 2008, most often due to either traffic accidents (41%), agricultural accidents (25%) or natural disasters (12%). Unfortunately, overall incidence from this study cannot be ascertained due to lack of a reasonable denominator.

Estimating temporal incidence trends is similarly challenging, and data is only available for post-traumatic mucormycosis, of which the frequency of published case reports has increased significantly between 1993 and 2013 (Lelievre et al., 2014). In an analysis of all-cause mucormycosis rates in French hospitals, overall IFI incidence, but not IFI in immunocompetent patients, increased between 1997 and 2006, suggesting that the rising incidence of post-traumatic mucormycosis may be attributed to an increasing proportion of immunocompromised individuals within this population. Indeed, up to 25% of patients with post-traumatic IFI may be immunocompromised to some extent (Skiada et al., 2011; Lelievre et al., 2014).

Post-traumatic IFI may exhibit seasonal and geographical fluctuations. Two case series in France and Lebanon observed higher rates of infection in rural areas (Fares et al., 2013; Bitar et al., 2009), which could be related to differences in hospital resources

Table 1
Comparison of civilian and military post-traumatic IFI populations by demographic information, injury patterns, and medical interventions. Values are reported as proportions of the cohort (%), mean, median, or ranges based on one or more studies. Abbreviations: IED, Improvised Explosive Device; LE, Lower Extremity; UE, Upper Extremity; ICU, Intensive Care Unit; LOS, Length Of Stay.

	Civilian	Military
Demographic information		
Average* age, years	27–48 Fares et al. (2013),Neblett Fanfair et al. (2012)	22–24 Lloyd et al. (2014), Paolino et al. (2012)
Sex (% male)	46–93% Fares et al. (2013), Neblett Fanfair et al. (2012)	100% Lloyd et al. (2014)
Underlying disease (%)	18–38% Moran et al. (2006a), Neblett Fanfair et al. (2012)	–
Common injury settings	Motor vehicle accidents Agriculture-related Natural disasters	IED during dismounted patrol
Injury patterns		
Bone fracture (%)	34–85% Lelievre et al. (2014), Neblett Fanfair et al. (2012)	80% Lewandowski et al. (2016)
Open bone fracture (%)	–	70% Lewandowski et al. (2016)
LE amputation (%)	–	79–85% Lewandowski et al. (2016), Rodriguez et al. (2014a)
UE amputation (%)	–	15% Lewandowski et al. (2016)
Clinical characteristics		
Fever (%)	20–100% Arnaiz-Garcia et al. (2009), Obradovic-Tomasev et al. (2016)	95% Warkentien et al. (2012)
Leukocytosis (%)	50–100% Austin et al. (2014), Obradovic-Tomasev et al. (2016)	97% Warkentien et al. (2012)
Common wound characteristics	Necrosis Ulceration	Necrosis Purulence Fibrinous exudate
Clinical interventions		
ICU admission (%)	56–77% Lelievre et al. (2014), Neblett Fanfair et al. (2012)	86–98% Warkentien et al. (2012), Warkentien et al. (2015)
Surgical amputation (%)	12–83% Lelievre et al. (2014), Vitrat-Hincky et al. (2009)	19–77% Warkentien et al. (2015), Weintrob et al. (2015)
Average* hospital LOS, days	34 Moran et al. (2006a)	48–69 Lloyd et al. (2014), Warkentien et al. (2012)
Massive transfusions, >20 units/24 hours (%)	–	65% Lewandowski et al. (2016)
Average ICU LOS, days	–	2–11 Rodriguez et al. (2014b,c), Warkentien et al. (2012)
Average diagnostic and treatment delay in days*		
Injury to diagnosis	10–19[a] Austin et al. (2014)	3–0 Lloyd et al. (2014), Warkentien et al. (2012)
Injury to first positive culture	14 Neblett Fanfair et al. (2012)	6 Warkentien et al. (2015)
Injury to first surgical debridement	1–16[a] Neblett Fanfair et al. (2012)	–
Injury to start of antifungal therapy	–	7–15 Lloyd et al. (2014), Paolino et al. (2012)
Sample acquisition to start of antifungal therapy	0.5–3.4 Neblett Fanfair et al. (2012), Rüping et al. (2009)	4 Warkentien et al. (2012)

Reference citations refer to the original list of references in the full manuscript.
* Average refers to either mean or median values as reported by individual studies.
[a] These values represent ranges rather than averages.

or physician awareness, but also may reflect a higher density of organic material harboring fungi in rural environments (Richardson, 2009). Seasonal patterns are more complex. In some cases, IFI has been diagnosed more frequently during the summer and autumn months, although the majority of these infections are due to inhalation rather than trauma (Richardson, 2009; Petrikkos et al., 2012). Accelerated organic decay during warm, dry periods may precipitate rapid fungal growth and higher atmospheric spore concentrations, explaining this observation. In contrast, a 6-year (1994-2004) retrospective Texan study of 16 patients, 4 with known trauma, reported a clustering of mucormycosis cases in February and March, prior to the rainy season and with average high temperatures rarely exceeding 25 °C (Sims and Ostrosky-Zeichner, 2007). Given that most fungi prefer temperatures in the range of 12 °C to 30 °C (Garcia-Solache and Casadevall, 2010), the relatively hot Texan climate may explain the shift in peak incidence.

Demographically, IFI occurs over a wide range of ages, with the mean age in civilian trauma patients between 27 and 48 years (Table 1) (Neblett Fanfair et al., 2012; Fares et al., 2013; Moran et al., 2006a; Lelievre et al., 2014). This age distribution is roughly comparable to that of the general trauma population and reflects occupational age patterns (Heim et al., 2014; Alghnam et al., 2014; Allen et al., 2015). Most studies observe a male predominance consistent with both general IFI and trauma populations (Neblett Fanfair et al., 2012; Nance et al., 2013).

Clinical Course

Military

The vast majority of soldiers with post-traumatic IFI are injured by explosions during dismounted patrol, leading to severe injuries and intensive medical interventions (Table 1) (Radowsky et al., 2015; Lewandowski et al., 2016; Warkentien et al., 2015). Description of wound characteristics in these patients is often limited to the presence or absence of necrosis, and recurrent necrosis was a requirement for inclusion in most studies to better

capture true IFI cases (De Pauw et al., 2008; Rodriguez et al., 2014b). Other common physical exam findings include purulence and fibrinous exudates (Warkentien et al., 2012).

Delays between injury, diagnosis, and treatment are well-described as significant drivers of patient outcomes. In the military setting, the average time between injury and date of first positive culture was six days, corresponding to an average delay of 3–10 days between injury and diagnosis (Paolino et al., 2012; Lloyd et al., 2014; Warkentien et al., 2015). Meanwhile, 7–15 days passed between injury and initiation of antifungal therapy; this delay was reduced to four days when measured from sample acquisition (Warkentien et al., 2012; Paolino et al., 2012; Lloyd et al., 2014).

Civilian

In contrast to military patients, a multitude of injury types and settings may be seen in civilians with IFI (Table 1). The most commonly reported antecedent injuries are motor vehicle accidents, incidents associated with agricultural equipment, natural disasters, and to a lesser extent, falls (Neblett Fanfair et al., 2012; Lanternier et al., 2012; Roden et al., 2005; Vitrat-Hincky et al., 2009; Ingram et al., 2014; Jain et al., 2006). The lower extremities are the most common site of infection, with the exception of near-drowning events that precipitate infection in the lungs and CNS (Katragkou et al., 2007). Almost all post-traumatic IFIs are categorized as cutaneous, while disseminated and rhinocerebral infections may occur in rare instances (Lanternier et al., 2012; Vitrat-Hincky et al., 2009; Bala et al., 2015; Millon et al., 2016; Rao et al., 2006).

In general, most infectious symptoms, commonly including fever and leukocytosis, develop within 30 days of injury (Obradovic-Tomasev et al., 2016; Lelievre et al., 2014; Vitrat-Hincky et al., 2009; Arnaiz-Garcia et al., 2009; Austin et al., 2014; Jacobo et al., 2010; Rodríguez-Lobato et al., 2016; Almaslamani et al., 2009; Chander et al., 2015). Necrosis is the most common physical exam finding, occurring in 40–100% of cases, although its use as an inclusion criteria may artificially inflate this figure in certain studies (Lelievre et al., 2014; Ingram et al., 2014; Jain et al., 2006; Arnaiz-Garcia et al., 2009; Austin et al., 2014; Chander et al., 2010; Rajakannu et al., 2006; Petrikkos et al., 2003). Ulceration is the second-most common finding, occurring in 19-57% of patients (Lelievre et al., 2014; Chander et al., 2015). Erythema, edema, induration, purulent discharge, cellulitis, and visible mold may also be evident, although estimation of frequencies is limited by small sample sizes (Neblett Fanfair et al., 2012; Lelievre et al., 2014; Vitrat-Hincky et al., 2009; Austin et al., 2014; Rodríguez-Lobato et al., 2016; Fang et al., 2016; Kaushik et al., 2012; Li et al., 2013).

The timing of clinical interventions has thus far only been reported in a small number of civilian studies. In patients injured during a tornado in Joplin, Missouri, the time between injury and diagnosis ranged from 10 to 19 days, with a median of 14 days between injury and collection of the culture that led to diagnosis (Neblett Fanfair et al., 2012; Austin et al., 2014). In a small case series, Jacobo et al. (2010) described a 3-day delay between first symptoms and treatment initiation. Two additional studies found an average of 0.5 and 3.4 days between acquisition of the sample leading to diagnosis and initiation of antifungal therapy (Neblett Fanfair et al., 2012; Rüping et al., 2009). However, these estimates included non-traumatic IFI and patients who were treated prior to definitive diagnosis. Overall, when compared to military cohorts, civilians appear to have a more delayed diagnosis, possibly due to postponement of sample acquisition, while initiation of antifungal therapy after sample collection is comparable between the two populations.

Mycology

Military

Post-traumatic IFI in military patients is most often caused by *Mucorales, Aspergillus* and *Fusarium* species, accounting for 34%, 31% and 22% of infections, respectively (Table 2) (Weintrob et al., 2014). However, *Mucorales* growth is most predictive of recurrent necrosis and IFI diagnosis (Lloyd et al., 2014; Rodriguez et al., 2014c). Within the order *Mucorales*, *Mucor* species are the predominant organisms, followed by *Saksenaea* and *Rhizopus*. The most common *Aspergillus* species are *A. terreus* and *A. flavus*, accounting for 10% and 9% of all infections, respectively, with *A.*

Table 2
Fungi isolated from wounds of civilian and military trauma patients diagnosed with IFI.

Civilian		Military	
Mucorales	*Aspergillus spp.*	*Mucorales*	*Aspergillus spp.*
Actinomucor spp.	*A. flavum*	*Apophysomyces spp.*	*A. flavum*
A. elegans	*A. fumigatus*	*Lichtheimia spp.*	*A. fumigatus*
Apophysomyces spp.	*Candida spp.*	*Mucor spp.*	*A. niger*
A. elegans	*Exserohilum spp.*	*Rhizopus spp.*	*A. terreus*
A. trapeziformis	*E. rostratum*	*Saksenaea spp.*	
A. variabilis	*Fusarium spp.*	*S. erythrospora*	*Acrophialophora spp.*
Cunninghamella spp.	*Scedosporium spp.*	*S. vasiformis*	*A. fusispora*
C. bertholletiae	*S. apiospermum*		*Alternaria spp.*
Lichtheimia spp.			*Beauveria spp.*
L. corymbifera			*Bipolaris spp.*
L. ramosa			*Candida spp.*
Mucor spp.			*Fusarium spp.*
M. circinelloides			*Graphium spp.*
M. racemosus			*Paecilomyces spp.*
Rhizomucor spp.			*Penicillium spp.*
R. variabilis			*Pythium spp.*
Rhizopus spp.			*P. aphanidermatum*
R. microsporus			*Scedosporium spp.*
R. oryzae			*S. prolificans*
Saksenaea spp.			*Ulocladium spp.*
S. erythrospora			
S. vasiformis			
Syncephalastrum spp.			
S. racemosum			

fumigatus constituting about 1% of infections (Warkentien et al., 2015). Other organisms cultured from IFI wounds include *Lichtheimia, Apophysomyces, Aspergillus niger, Bipolaris, Penicillium, Alternaria, Scedosporium, Graphium,* and *Candida* (Murray et al., 2011; Warkentien et al., 2012; Paolino et al., 2012; Radowsky et al., 2015).

Co-infections by both bacteria and other fungi are common. Bacterial and yeast co-infections occur in 55% of IFI, with 27% of infections involving MDROs (Lewandowski et al., 2016). The most common bacteria are *Enterococcus* and *Acinetobacter* (Warkentien et al., 2012). Compared to those without IFI, bacterial co-infections in IFI wounds occur at a significantly higher rate (Lewandowski et al., 2016). Meanwhile, co-infection with other molds occurs in 27-67% of patients (Paolino et al., 2012; Radowsky et al., 2015; Warkentien et al., 2015; Akers et al., 2015).

Civilian

Similar to the military population, post-traumatic IFI in civilian patients is most often due to fungi in the order *Mucorales* (Table 2). As a result, most studies detailing species-level identification of infectious agents in this population have been purposefully limited to cases of mucormycosis. These studies illustrate a predominance of *Apophysomyces, Lichtheimia* (previously *Absidia*), *Rhizopus*, and *Mucor,* whereas infection due to *Rhizomucor, Cunninghamella,* and *Cokeromyces* genera are relatively rare (Gomes et al., 2011). At the species level, commonly identified organisms include *Rhizopus oryzae*, *Lichtheimia corymbifera, Apophysomyces elegans, Apophysomyces trapeziformis, Mucor racemosus,* and *Saksenaea vasiformis* (Neblett Fanfair et al., 2012; Lelievre et al., 2014; Millon et al., 2016; Arnaiz-Garcia et al., 2009; Chander et al., 2010; Li et al., 2013). Although *Rhizopus oryzae* accounts for ~70% of all mucormycosis infections, post-traumatic IFI in general appears to be caused by a more heterogeneous collection of *Mucorales* organisms (Kaushik, 2012; Lelievre et al., 2014; Bilal et al., 2016). *Aspergillus* (esp. *fumigatus*), *Scedosporium* (esp. *apiospermum*), and *Fusarium* are also prevalent pathogens, occasionally overcoming mucormycosis in frequency (Obradovic-Tomasev et al., 2016; Vitrat-Hincky et al., 2009; Slavin et al., 2015). Although *Candida* has been cultured from traumatic wounds (Obradovic-Tomasev et al., 2016), the role of this pathogen in IFI remains uncertain.

Meanwhile, rates of bacterial co-infection in cases of mucormycosis vary from 20% to 100% (Neblett Fanfair et al., 2012; Obradovic-Tomasev et al., 2016; Lelievre et al., 2014; Arnaiz-Garcia et al., 2009; Austin et al., 2014; Chander et al., 2010) with involvement of diverse organisms including *Staphylococcus aureus*, *Escherichia Coli*, *Pseudomonas*, and *Enterococcus*. Fungal co-infection, most notably by *Candida* and other molds, is less common, occurring in 6-67% of IFI wounds (Neblett Fanfair et al., 2012; Lelievre et al., 2014; Vitrat-Hincky et al., 2009).

Patient and environmental characteristics may influence species frequency. In their cohort of 929 individuals with mucormycosis, Roden et al. (2005) found a higher rate of *Lichtheimia* and *Apophysomyces* infections in males. The reason for this observation was unclear, but such a pattern may reflect sex-specific frequencies of underlying conditions or possible organism-hormone interactions. Species-specific geographical clustering was demonstrated by Neblett Fanfair et al. (2012), who found that all thirteen cases of mucormycosis following the Joplin tornado were due to *Apophysomyces trapeziformis*. The authors posited that spores from one or more environmental sources along the tornado path were aerosolized and inoculated into injured individuals. Similarly, Lu et al. (2009) found that all six cases of *Rhizomucor variabilis* reported in China since 1991 occurred in three adjacent provinces.

Risk Factors

Military

Risk factors specific to military personnel are largely derived from a case-control analysis within the TIDOS cohort which found that massive transfusion (>20 U/24 hours), blast injury, dismounted status, and above-knee amputations were associated with IFI (Table 3) (Rodriguez et al., 2014a). These risk factors may partially explain why the majority of IFI cases during this time period were clustered in the southern region of Afghanistan, where injury severity and massive transfusion requirements were greater (Tribble et al., 2015). Compared to other regions of the country, southern Afghanistan has a lower elevation and more temperate climate (average annual mean temperature 18.8 °C), suggesting a possible environmental component driving IFI in this population as well (Tribble et al., 2015). Furthermore, although the frequency of underlying conditions in this population is extremely low, the high severity of injuries and subsequent need for interventions such as ICU admission and broad-spectrum antibiotics may have contributed to a temporary immunosuppressed state. In addition, severe trauma itself may produce local and systemic immunosuppression as a result of dysregulated immune responses (Kimura et al., 2010).

Civilian

Immunosuppression in the civilian population is well-known to predispose patients to IFI (Cornely, 2008). Investigation of risk factors associated with post-traumatic IFI in previously immunocompetent patients, however, is limited (Table 3). In a case-control study of patients injured during the Joplin tornado, patients with IFI had a greater number of wounds, were more likely to have penetrating wounds, and were more frequently diagnosed with rhabdomyolysis on admission compared to controls with broken skin but no evidence of IFI (Neblett Fanfair et al., 2012). Larger wound burden may represent increased injury severity, while penetrating wounds may be at greatest risk of inoculation by fungal elements (Hajdu et al., 2009). Acidosis, which occurs in severe rhabdomyolysis, is known to impair phagocyte function and cause release of free iron from sequestering proteins (Spellberg et al., 2005).

Other predisposing factors may be inferred from observational studies. Wound contamination, for example, is considered a prerequisite for post-traumatic IFI based on the proposed pathogenic mechanism (Richardson, 2009). Ingram et al. (2014) found that all motor vehicle accidents leading to IFI involved either motorcyclists or unrestrained passengers, who presumably were at

Table 3
Risk factors associated with post-traumatic IFI development. Included are factors associated with IFI in single civilian (Spellberg et al., 2005) and military (Neblett Fanfair et al., 2012) case-control studies and factors that were qualitatively associated with IFI in non-comparative observational studies (Lanternier et al., 2012; Skiada et al., 2012; Lewandowski et al., 2016; Gomes et al., 2011).

Civilian	Military
Number of wounds	Massive transfusion (> 20 units/24 hr)
Penetrating wounds	Blast injury
Rhabdomyolysis	Dismounted status
Wound contamination	Above-knee traumatic amputation
Synthetic clothing	Base deficit ≥ 10 mcg/L[a]
	Shock index ≥ 1.5[a]
	Temperate climate

Reference citations refer to the original list of references in the full manuscript.
[a] These factors were found to be statistically significant in univariate analyses conducted by Rodriguez et al. (2014a) but were subsequently removed from the multivariate analysis due to collinearity with the transfusion variable.

high risk of wound contamination by soil, plant matter, and gravel. Likewise, Lelievre et al. (2014) found that 100% of IFIs due to minor injury occurred in wounds with gross soil contamination. Fares et al. (2013) qualitatively observed that patients wearing synthetic fabric at the time of injury were more likely to develop IFI compared to those wearing cotton, possibly due to increased warmth and moisture on the skin. Finally, underlying conditions (older age, diabetes, medication use, chronic end-organ disease), medical interventions, and severe trauma conferring additional immunosuppression should theoretically increase the risk of developing IFI.

Diagnosis

Military

Diagnosis of post-traumatic IFI is standardized in the military literature and requires clinical and laboratory measures (Table 4) (Warkentien et al., 2012; De Pauw et al., 2008). Laboratory confirmation of IFI is a critical component of diagnosis, but current methods may give rise to missed diagnoses or delays in treatment. Positive culture is obtained in 82-91% of cases, while histopathology specimens are positive 83% of the time (Warkentien et al., 2015; Rodriguez et al., 2014c; Warkentien et al., 2012). In one study, positive histopathology during the initial hospital admission was predictive of an IFI diagnosis, whereas culture positivity was not, perhaps due to a higher false positive rate associated with fungal culture (Lloyd et al., 2014).

Early diagnosis is critical in the management of IFI. New techniques may provide a more rapid diagnosis, but widespread implementation is often hindered by cost and decreased sensitivity or specificity. For example, frozen sections have a positive predictive value of 92% and negative predictive value of 87% when compared to permanent sections (Warkentien et al., 2012; Heaton et al., 2016). Protocols for early screening may provide an alternate avenue to minimize delays between injury, diagnosis, and treatment. Implementation of the “Blast” screening guideline triggering biopsy for histopathology and culture in high-risk patients in a German military hospital accelerated time to diagnosis and treatment, with suggested improvements in clinical outcomes including mortality (Lloyd et al., 2014). In this setting, “at-risk” patients were defined as those with bilateral lower extremity amputation secondary to blast injury, large amputation burden, more than expected soft tissue necrosis, extensive wound contamination, and/or required significant amputation revision.

Civilian

IFI diagnosis in civilians is subject to a high degree of interpretation across institutions and studies, but typically requires laboratory confirmation of infection in the appropriate clinical context. Laboratory analysis often involves culture and histopathology as seen in military hospitals, but may also include direct microscopic examination with special stains and molecular methods such as polymerase chain reaction (PCR). Meanwhile, the threshold for clinical suspicion is not standardized (Montagna et al., 2013). Studies may include patients based on International Classification of Diseases (ICD) codes, which could lead to the inclusion of patients without true IFI (Bitar et al., 2009).

In case series, histopathology is the most common method of laboratory diagnosis, followed by culture (Neblett Fanfair et al., 2012; Roden et al., 2005; Obradovic-Tomasev et al., 2016; Jain et al., 2006; Arnaiz-Garcia et al., 2009; Austin et al., 2014; Jacobo et al., 2010; Almaslamani et al., 2009; Chander et al., 2015; Chander et al., 2010; Rajakannu et al., 2006; Slavin et al., 2015; Yue et al., 2013; Marques et al., 2012). Independently, neither method is completely satisfactory. Cultures are positive in 20-100% of patients, as compared to 82-91% in military cohorts (Vitrat-Hincky et al., 2009; Arnaiz-Garcia et al., 2009). This wider distribution may result from less restrictive definitions of IFI as well as greater variation in protocols for specimen collection. Meanwhile, false negative cultures occur in 17-56% of wounds with positive histopathology, and 11% of histopathology samples from wounds with positive culture are negative (Lanternier et al., 2012; Vitrat-Hincky et al., 2009; Jain et al., 2006). While histopathology can often be used to identify the fungus, misdiagnosis is not uncommon. In a comparison of surgical pathology reports to microbiological culture results, 10 (21%) cases were misdiagnosed by histopathology - eight misclassified by division (e.g. *Aspergillus* vs. *Rhizopus*) and two by genus (e.g. *Mucor* vs. *Rhizopus*) (Sangoi et al., 2009). Together, these data support the simultaneous use of histopathology and culture to maximize accurate diagnoses.

As previously discussed, IFI is a time-sensitive diagnosis. In the civilian literature, histopathology is commonly available within 24 hours of sample acquisition (Moran et al., 2006a), while culture growth occurs on average 2 to 7 days after the initial wound debridement (Moran et al., 2006a; Ingram et al., 2014). PCR may provide the most rapid diagnosis, with positive results obtained an average of 9 days before sample collection for culture or histopathology (Millon et al., 2016). Unfortunately, no data for the use of PCR in post-traumatic IFI is available, and the sensitivity is relatively low (56-81%) in patients with mucormycosis of any cause (Millon et al., 2016; Rüping et al., 2009). Therefore, while more frequent use of molecular methods could speed diagnosis, issues of test validity, cost and pre-test clinical suspicion remain. Although earlier screening of high-risk patients improved time to diagnosis in military settings, the authors are not aware of similar protocols being applied in civilian trauma care. Implementation of screening protocols for civilians would be an inexpensive and potentially effective method for reducing delays in diagnosis and improving outcomes. However, a modified definition for an “at-risk” patient would be required to accurately reflect the different patterns of injury seen in military and civilian settings.

Treatment

Military

Early surgical debridement and systemic antifungal therapy constitute the gold standard of treatment for IFI in both military and civilian populations (Rodriguez et al., 2014c; Gomes et al., 2011). The empirical evidence for such therapy is generally supportive, although methodological issues impede definitive conclusions. For example, although surgical debridement is often associated with a better prognosis, lack of controlled studies makes it difficult to differentiate between true improvement and confounding by indication (Lanternier et al., 2012; Bala et al., 2015; Chakrabarti et al., 2009; Shoham et al., 2010). That is to say,

Table 4
Post-traumatic IFI criteria used in military cohorts, modified from the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) IFI definitions (Murray et al., 2011; Allen et al., 2015).

Military Criteria for IFI Diagnosis
(1) Presence of traumatic wound
(2) Recurrent necrosis on ≥ 2 consecutive surgical debridements
(3) Evidence of IFI by culture or histopathology

Reference citations refer to the original list of references in the full manuscript.

surgical debridement may not be undertaken in patients with disseminated disease or risk of imminent death who are by definition predisposed to worse outcomes. Likewise, the utility of antifungal therapy has been questioned by some authors given limited wound tissue penetration in the setting of vessel thrombosis (Spellberg et al., 2005). However, observational studies have shown reduced mortality (Roden et al., 2005; Vitrat-Hincky et al., 2009; Millon et al., 2016). Despite doubts raised about the true effectiveness of these interventions, most experts support the combined surgical and pharmaceutical approach.

Treatment of IFI in the military cohort generally follows this standard. Essentially all patients underwent surgical debridement, with an average of 9 procedures per patient, and at least 84% of patients additionally received an antifungal drug, most commonly amphotericin B with or without voriconazole, for a median of 22 days (Lewandowski et al., 2016; Weintrob et al., 2014). Dakin's solution has performed well in in vitro studies and was a common adjuvant treatment, received by 32% of patients in one series (Rodriguez et al., 2014c; Barsoumian et al., 2013).

Civilian

Similar to the military cohort, greater than 90% of civilian patients undergo surgical debridement, with a large proportion requiring multiple debridements (Lelievre et al., 2014). The most common antifungal therapy given in case series is amphotericin B, either in conventional or lipid form, often followed by a triazole (i.e. posaconazole). Although liposomal amphotericin B is preferred due to lower toxicity and some, albeit mixed, evidence of improved effectiveness and survival (Sims and Ostrosky-Zeichner, 2007; Rüping et al., 2009), deoxycholate amphotericin B is commonly used because of availability and lower cost. In surviving patients, antifungal therapy is usually administered for a period of several months after diagnosis, with a median duration of treatment between 23 and 55 days in two series (Skiada et al., 2011; Lelievre et al., 2014; Arnaiz-Garcia et al., 2009). Compared to soldiers, civilians appear to receive a longer course of antifungals, possibly reflecting higher rates of comorbidities and variability in local guidelines.

Other less frequently used adjunctive therapies include hyperbaric oxygen, topical solutions such as Dakin's, deferasirox, and, most recently, immune-modulating agents such as interferon-γ and nivolumab (Roden et al., 2005; Vitrat-Hincky et al., 2009; Almaslamani et al., 2009; Yue et al., 2013; Grimaldi et al., 2017). Evidence for the effectiveness of these therapies is limited and mixed. Hyperbaric oxygen and Dakin's solution have been shown to have antifungal effects in vitro, but only a handful of lower quality studies, which suggest possible improved outcomes, have examined their use in the clinical setting (Barsoumian et al., 2013; Tragiannidis and Groll, 2009; Lewandowski et al., 2013). Adjunctive deferasirox, which theoretically reduces fungal access to iron through its chelating ability and appeared promising in open-label studies, was actually associated with a higher 90-day mortality compared to placebo in a randomized controlled trial (Spellberg et al., 2012). However, this trial was limited by small sample size, unequal baseline characteristics, and a patient population with high rates of hematologic malignancy and other immunosuppressive states that are not reflected in the post-traumatic IFI population. Immune-modulating agents are some of the newest additions to the antifungal armamentarium, but are currently only supported by success in case reports.

Unfortunately, almost no prospective trials have been conducted to compare the effectiveness of different antifungal regimens and, as a result, the optimal therapeutic approach to IFI in trauma and other populations is not known.

Outcomes

Military

The overall mortality rate for military personnel with IFI is 7.8%, with other estimates ranging from 6% to 14% depending on case definitions. Despite relatively high survival, morbidity in surviving patients is substantial. Surgical amputation, an important patient-centered outcome, is required in 19–77% of surviving patients (Warkentien et al., 2015; Weintrob et al., 2014). The median total hospital length of stay is 48–69 days, with a median of 2 to 11 days spent in the ICU and an average of 16 days to initial wound closure (Warkentien et al., 2012; Lloyd et al., 2014).

Compared to non-infected trauma patients, patients with IFI typically have poorer outcomes. Trends towards higher mortality in IFI patients and those with higher likelihood of IFI (recurrent necrosis or proven/probable status) were apparent in several case-control studies (Lloyd et al., 2014; Lewandowski et al., 2016; Weintrob et al., 2014; Rodriguez et al., 2014c). For example, Lewandowski et al. (2016) found a 6% mortality rate in IFI cases compared to 1% for non-IFI controls. Although these differences were not significant, no study included more than 100 IFI cases, which may have masked true differences in mortality.

Morbidity in patients with IFI follows a similar pattern. Compared to non-IFI controls, patients with IFI have more surgical amputations, spend more days in the ICU, experience significant delays in initial wound closure, and are more likely to develop complications requiring repeat surgery after wound closure (Lloyd et al., 2014; Lewandowski et al., 2016; Warkentien et al., 2015). Among IFI patients, *Mucorales* infection, massive transfusions, ICU admission, and SSTIs are associated with increased time to wound closure (Lewandowski et al., 2016; Warkentien et al., 2015).

Civilian

The overall mortality rate in trauma patients is 25–41% (Neblett Fanfair et al., 2012; Skiada et al., 2011; Roden et al., 2005; Lelievre et al., 2014; Vitrat-Hincky et al., 2009), although some smaller series report survival of all patients (Yue et al., 2013; Moran et al., 2006b). Most deaths tend to occur within 2 weeks of hospital admission or diagnosis (Neblett Fanfair et al., 2012; Austin et al., 2014; Rajakannu et al., 2006; Slavin et al., 2015). Compared to combat-injured patients, the civilian mortality rate is substantially higher, perhaps reflecting differences in underlying health status. When comparing civilian patients with traumatic wounds who did and did not develop IFI, those with IFI have a 6.7 fold higher mortality rate (Neblett Fanfair et al., 2012).

As in military cohorts, morbidity is significant. The rate of amputation varies between 12% and 83%, roughly comparable to that seen in soldiers (Lelievre et al., 2014; Vitrat-Hincky et al., 2009). Although no valid comparison of amputation rates in non-IFI civilian trauma patients exists, an estimated 24% of all trauma affects the extremities, and only 1% of all trauma patients require limb amputation (Moini et al., 2009). Patients have prolonged hospital stays, with one study reporting an average of 34 days in those with upper extremity mucormycosis (Moran et al., 2006a). While the majority of surviving patients recover within 1.5 months (Chander et al., 2010; Chakrabarti et al., 2003), Moran et al. (2006a) found that only 43% of patients had returned to work after an average of 37 months of follow-up, suggesting that IFIs may have long-term implications that have not been fully captured by the present literature.

Some evidence exists for fungal species-specific outcomes, but these analyses are scarce and inconsistent. While one study of mucormycosis found that mortality rates were comparable between *Mucor/Rhizopus, Rhizomucor,* and *Lichtheimia* infections

(Millon et al., 2016), *Cunninghamella* infections were associated with a higher risk of mortality in another study not limited to trauma (Roden et al., 2005). In a series from Australia, Slavin et al. (2015) only found dematiaceous molds to be associated with reduced mortality, while no species-specific differences within the *Mucorales* order were evident.

Future Directions

Current knowledge of post-traumatic IFI leaves much to be elucidated. The literature is saturated with case series and other lower quality studies, while large comparative trials are scarce. Methodological quality hinges on consistent and reliable data collection, which is often lacking in the IFI population. Thus, to support the success of future research, improvements in IFI reporting should be undertaken. The definition of post-traumatic IFI, which is well-established in military studies, should be consistently characterized in the civilian literature. Although wound aspects such as evidence of angioinvasion and recurrent necrosis should be equivalent for military and civilian patients, the wider variety of injuries seen in civilians, including minor injuries and chronic infection development, may warrant restriction to specific injury types and time frames. Furthermore, the role of newer diagnostic modalities such as PCR and other molecular or serologic tests should be addressed. If a modified version of the EORTC/MSG criteria is to be utilized, then this definition should be validated in civilian cohorts and endorsed by experts in civilian trauma and infectious disease. In conjunction, standardized national and international protocols for reporting IFI based on these definitions will significantly improve the capacity for developing and conducting expanded studies. Civilian IFI registries are instrumental to this research because recruiting patients with a rare disease for appropriately-powered studies may otherwise quickly exceed available financial resources and time constraints. Furthermore, accurate estimates of incidence and distribution can clarify the effect of environmental, geographical, and climactic patterns on post-traumatic IFI.

Beyond more appropriate case capture, diagnosis and treatment of post-traumatic IFI may benefit from improved prediction of IFI development, discovery and incorporation of more rapid diagnostic methods, and head-to-head comparisons of interventions. Although several risk factors have already been identified in the military literature, predisposing characteristics in civilians have only been suggested by small case-control studies (Neblett Fanfair et al., 2012). Future researchers seeking to expand this topic can use risk prediction methods to corroborate these findings in larger cohorts as well as develop and incorporate novel methods of early IFI detection such as serological biomarkers. Technological advancements in molecular assay methods can also be applied to the goal of early post-traumatic IFI diagnosis (Millon et al., 2016; Mery et al., 2016). The accuracy and utility of these assays should be assessed in relation to the current standards of diagnosis by culture and histopathological analysis. Finally, our current treatment strategies are without a strong evidence base. Animal and human comparative trials are needed, not only to compare commonly used therapies, but also to explore the effectiveness of adjunctive treatments (e.g. hyperbaric oxygen), prophylactic methods, and empiric therapy in high-risk patients (Spellberg et al., 2005; Trzaska et al., 2015).

Conclusion

Invasive fungal infections are a rare but potentially devastating infection complicating traumatic wounds. Patients typically present with necrosis and are diagnosed based on high clinical suspicion and laboratory analysis of tissue. The presence of post-traumatic IFI may lead to higher rates of mortality and worse clinical outcomes. Treatment usually consists of early surgical debridement and systemic antifungal therapy. Future research should focus on further illumination of risk factors, improved diagnostic methods, and optimal treatment regimens. Additionally, comparative and higher-quality evidence is needed to confirm the findings from observational studies.

Conflicts of Interest Statement

The authors have no conflicts of interest to declare.

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Ethics Approval

This study did not require ethics approval.

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