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Combat-Related Invasive Fungal Wound Infections

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Abstract

Combat-related invasive fungal (mold) wound infections (IFIs) have emerged as an important and morbid complication following explosive blast injuries among military personnel. Similar to trauma-associated IFI cases among civilian populations, as in agricultural accidents and natural disasters, these infections occur in the setting of penetrating wounds contaminated by environmental debris. Specific risk factors for combat-related IFI include dismounted (patrolling on foot) blast injuries occurring mostly in southern Afghanistan, resulting in above knee amputations requiring resuscitation with large-volume blood transfusions. Diagnosis of IFI is based upon early identification of a recurrently necrotic wound following serial debridement and tissue-based histopathology examination with special stains to detect invasive disease. Fungal culture of affected tissue also provides supportive information. Aggressive surgical debridement of affected tissue is the primary therapy. Empiric antifungal therapy should be considered when there is a strong suspicion for IFI. Both liposomal amphotericin B and voriconazole should be considered initially for treatment since many of the cases involve not only *Mucorales* species but also *Aspergillus* or *Fusarium* spp., with narrowing of regimen based upon clinical mycology findings.

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Conflict of Interest DR Tribble and CJ Rodriguez both declare no conflicts of interest.

Compliance with Ethics Guidelines

Human and Animal Rights and Informed Consent All studies by the authors involving animal and/or human subjects were performed after approval by the appropriate institutional review boards. When required, written informed consent was obtained from all participants.

Keywords

Invasive fungal infections; Combat-related trauma; Invasive mold infections; Wound infections; Invasive mucormycosis

Introduction

Individuals with traumatic injury sustained on the battlefield are known to be at high risk for infectious complications [1–4]. The nature and severity of injuries inflicted in combat settings (e.g., blast injuries) occur as a result of a number of factors, such as breach of physical host defenses, hypoxic tissue damage/necrosis, and implantation of foreign bodies [5]. A majority of reports from combat settings during the past decade have focused on infectious outcomes of combat-related traumatic injuries with bacterial pathogens [1, 4, 6–12]. Invasive fungal combat-related wound infections (IFIs) have emerged as an important cause of morbidity and mortality among military personnel who sustain excessive trauma, most typically due to blast injuries from improvised explosive devices (IEDs) while the individual is on foot rather than in a vehicle (termed dismounted). This review provides information on the epidemiology, circumstances leading to IFI risk, clinical mycology and diagnostics, illness course and clinical management, and areas for future investigation.

Dismounted Complex Blast Injuries and Early Surgical Care

In order to assess patient IFI risk, as well as surgical care, it is necessary to understand aspects of blast injury mechanics and the resultant complex wounds. Due to changes in geographic constraints on the ground from those of Iraq, coalition service members serving in Afghanistan conducted more frequent dismounted patrols. When conducting these patrols in southern Afghanistan, they found themselves in areas with a high risk for ground-emplaced IEDs.

When a soldier on foot patrol activates an IED, the detonation creates a devastating bodily injury from a combination of forces including overpressure injury of hollow/air-filled structures, bone fracture, heat, and throwing victim and debris [13]. Advances in prehospital care with control of catastrophic hemorrhage by application of combat tourniquets [14] and improvements in combat trauma surgical techniques have led to increased survival from dismounted blast injuries. Between 2001 and 2011, the mean rate of major limb injuries during wartime resulting in amputation was 3.6 per 100 combat support hospital admissions with a significant increase in the rate of amputations from 3.5 in 2010 to 14 in 2011 [15]. Through survivor analysis, an injury pattern emerged involving traumatic amputation of at least one leg, severe injury to another extremity, and injury to the pelvic, abdominal, or urogenital region and has been named “dismounted complex blast injuries” [16–18].

At the point of injury, wounded personnel receive care from field medics with goals to stop catastrophic hemorrhage, mitigate the effects of hypovolemia and hypothermia, and achieve reasonable pain control [18]. Patients are evacuated as soon as tactically feasible with the goal of reaching surgical care within an hour of injury. The devastating wounds sustained from dismounted IED blasts are impregnated with organic and metallic debris and require

meticulous debridement at the first opportunity. Oftentimes, patients are in the operating room for 3–4 h at their first operative debridement, focusing on removing all foreign material. The wounds are washed copiously with gravity-delivered saline. Due to a bacterial rebound phenomena associated with high-pressure pulsatile lavage, this practice has been stopped [19, 20]. As postinjury functional outcomes are dependent upon residual limb length, it is important to preserve as much soft tissue as possible to permit reconstruction. Therefore, unless there are other mitigating circumstances, guillotine amputations are discouraged [21]. All wounds in the US medevac chain typically undergo three washouts/debridements in the first 72 h after injury.

Patients typically arrive back to the USA on postinjury days 3–5 and are taken to the operating room within 12 h of arrival for wound assessment and continued debridement. It should be noted that through established practice patterns, patients are taken urgently to the operating room upon arrival to the USA should wound sepsis develop during transit. At postinjury days 3–5, uncomplicated blast wounds should begin to show initial stages of healing: presence of granulation tissue and wound volume contraction. Once these findings are evident, the wound bed is clean, and indications that systemic inflammatory response syndrome has resolved in the presence of a suitably sized pocket of soft tissue, delayed primary closure is performed [21].

IFI Epidemiology

Among immunocompetent individuals, trauma-related IFI results following a penetrating wound (e.g., agricultural injury, motor vehicle injury, and injuries sustained during natural disasters) that has been inoculated with fungal spores [22–31]. Substantial morbidity (e.g., limb amputation) and mortality (as high as 38 %) associated with IFI are attributed to angioinvasion and dissemination, for which systemic anti-fungal therapy and extensive surgical debridement are often required for control [23, 27, 32–34]. Much less is known about the epidemiology and clinical characteristics of IFI among combat casualties, as compared to bacterial infections (Table 1). The initial report from Brooke Army Medical Center (San Antonio, TX) in 2009 described a fatal case of invasive mucormycosis, due to *Actinomucor elegans*, in a service member injured by an IED in Iraq [35]. A retrospective case series conducted at Walter Reed Army Medical Center (Washington, DC) identified six cases of IFI over a 6-year period (2002–2008) among military personnel returning from the Iraq theater [36]. Although 50 % of the cases required amputation or revision of a previous amputation, there were no deaths. Furthermore, a report by British military physicians in 2011 described the occurrence of fungal soft tissue infections in heavily contaminated combat-related wounds among military service members injured in Afghanistan [5]. In that report, extensive blast injury, massive blood transfusions, and injuries occurring in the “green zone” of Helmand Province were common features.

Similar to the British experience, an outbreak of IFI was observed among US military personnel with combat-related injuries sustained in Afghanistan (Table 1). In response, an investigation was initiated that examined data collected from 1,133 US military personnel injured in Afghanistan between June 2009 and August 2011. The result was one of the largest reported series of trauma-related IFIs (i.e., 77 case patients resulting in an incidence

rate of 6.8 %). Evaluation of the data found IFI rates ranging from 0.2 to 11.7 % among ward and intensive care unit admissions following medical evacuation to the military hospital in Germany, respectively [37•].

Case Definition

The starting point in case identification is recognition of a suspicious wound. Due to the angioinvasive nature of these pathogenic molds, microvascular thrombosis occurs, leading to necrosis of the adjacent tissues and invasive disease. The majority of cases reported in the literature are described as necrotic [27, 31, 38], as was observed in the US military cases. An example of a wound immediately following injury and through the progression of IFI development is presented in Fig. 1.

For the US military outbreak investigation, case definitions from the 2008 Mycoses Study Group, developed for disease in immunocompromised individuals, were modified for a trauma patient population [37•, 39]. Diagnostic criteria were as follows: (1) presence of traumatic wound(s), (2) recurrent tissue necrosis on 2 consecutive debridements, and (3) IFI laboratory evidence. Cases were classified by supporting histopathological laboratory evidence as either proven IFI (fungal hyphae angioinvasion of viable tissue), probable IFI (viable tissue invasion, but no angioinvasion), or possible IFI (mold grown in culture, but either histology not performed or no fungal elements seen).

Risk Factors

Following a tornado in Joplin, MO, 13 individuals developed a trauma-related IFI. A case-control analysis identified penetrating trauma (odds ratio [OR] 8.8; 95 % confidence interval [CI] 1.1–69.2) and multiple wounds (OR 2.0; 95 % CI 1.2–3.2) as risk factors [33]. Among combat trauma-related patients, independent predictors of IFI risk included blast injuries (OR 4.1; 95 % CI 1.1–29.6) while dismounted (OR 8.5; 95 % CI 1.2–59.8), above knee traumatic amputations (OR 4.1; 95 % CI 1.3–12.7), and resuscitation requirements ≥ 20 units of packed red blood cell in the first 24 h following injury (OR 7.0; 95 % CI 2.5–19.7) [40••].

The vast majority of US and UK personnel received their initial care at a combat support hospital in the Helmand or Kandahar provinces of southern Afghanistan in the “green zone,” where the vegetation is not as sparse as elsewhere in the country [5]. It is unknown whether this observation simply reflects the increase total number of casualties from these southern provinces, or whether the different environment in this geographic region actually plays a role in IFI. Currently, an analysis is in the process to evaluate geographic factor association with risk of wound contamination with molds and subsequent association with IFI.

In general, patients with mucormycosis and other invasive mold infections have underlying medical (i.e., immunosuppressive) conditions, including hematopoietic stem cell or solid organ transplantation, hematologic malignancy, diabetes mellitus, and prolonged steroid administration [41]. Conversely, patients with cutaneous infections tend to have intact immune systems [23, 32]. The US military personnel with IFI sustained extensive combat-related polytrauma and received a median of 30 units of packed red blood cells within 24 h of injury, well in excess of the 10 units defined as “massive transfusion” (Table 2). In addition to relative immunosuppression from extensive trauma, there is evidence that receipt

of massive blood transfusions can have immunosuppressive effects [42]. An additional consideration is the iron burden that is received with blood transfusions. There is a clear association between invasive mucormycosis and iron overload states, such as hemochromatosis, and the use of the iron chelator, desferoxamine, which allows iron to become more readily available to the molds as a nutrition source [43–45].

Clinical Presentation and Diagnosis

The majority of combat trauma IFI presents within 1 week from time of injury with an increasing systemic inflammatory response with high fever and leukocytosis accompanied by evidence of muscle necrosis in previously clean wound beds postdebridement. Laboratory diagnosis of IFI is based upon histopathology examination and/or positive culture [23] in the presence of a wound found to have recurrent necrosis. Since fungal cultures require several days to grow and may be insensitive [46], obtaining a surgical sample for histopathology evaluation is essential for prompt and accurate diagnosis. The surgical sample should be taken at the border of necrotic and viable tissue. Standard staining with hematoxylin and eosin can be insensitive for detection of fungal elements, so special staining should be used, such as Gomori methenamine silver and periodic acid Schiff [34]. Among the US military case series, 70 % were diagnosed based upon histopathology. Angioinvasion, the basis for meeting proven criteria, was seen in 35 %. Selected examples of positive histopathology findings on IFI wounds are included in Fig. 2. Although fungal morphology (i.e., discriminating septate and aseptate molds) is sometimes possible to determine, the common occurrence of multiple fungal morphologies and necrosis may make such determinations difficult. Tissue should also be sent for fungal culture and reviewed for growth daily for 5 days then weekly for 4 weeks.

Clinical Mycology

The IFI cases associated with traumatic injury often present with soil-contaminated wounds [22, 30, 35, 47, 48]. While most of the reports in the literature involve disruption of an extensive amount of the cutaneous surface [22, 24, 49], occasionally invasive disease is reported after only a minor insult [50]. Among the US military case series, wound cultures grew only Mucorales in 35 % [5, 35]. These fungi are commonly found in the environment, particularly in soil with decaying vegetation [34]. In addition to Mucorales, other environmental molds such as *Aspergillus* spp., *Fusarium* spp., and *Scedosporium* spp. have been reported to cause wound infections [27, 31, 51]. To our knowledge, there is no literature documenting which environmental molds populate the soil in Afghanistan. The closest geographic review is a study from Turkey wherein a total of 110 species from 32 genera of fungi were found [52].

Although most case series involving mucormycosis report *Rhizopus* spp. as the most common pathogen, in our series, *Mucor* spp. (62 %) was the most frequent with *Rhizopus* spp. only accounting for 4 %. *Saksenaea vasiformis* (14 %) and *Apophysomyces elegans* (5 %) were also commonly reported, and the higher percentage of these rarer molds may be due to culturing technique or geographic variations, but it also supports the observation that these organisms tend to occur as invasive cutaneous infections in otherwise immune-

competent hosts, rather than in those with more traditional risk factors, such as diabetes [34, 49, 50, 53]. While the majority of patients with proven IFI (angioinvasion) with positive cultures grew a Mucorales, several only grew other molds, such as *Aspergillus* spp., so these non-Mucorales filamentous fungi should be considered as potential causes of wound IFI as well. It is also noteworthy that the majority of IFI wounds were also colonized or infected with a bacterial organism or yeast.

IFI Patient Management

Given the rapid systemic progression and contiguous spread of IFI [54], aggressive surgical debridement and systemic antifungal therapy are immediately started once the infection is clinically suspected, even before histopathological proof is obtained [37•, 55, 56••].

Surgical Care

Surgical debridement of necrotic material is paramount, as the thrombosed blood vessels from the IFI result in poor tissue penetration of systemic antifungal agents [41]. Frequent debridement is necessary (potentially daily, depending on the amount of necrotic tissue present at each operation). In the US military cases meeting the definition of proven IFI, a median of 17 debridements was required. In addition to serial surgical debridements, amputations or revision of traumatic amputations may be necessary to manage the infection. This may result in a change in the amputation level of a below knee to above knee or a higher level of amputation (i.e., hemipelvectomy or hip disarticulation). In the US military cases, 19 % required high-level amputations.

Antifungal Management

Empiric systemic antifungal therapy should also be considered when there is a strong suspicion for IFI. Both liposomal amphotericin B (LFAB) and voriconazole should be considered initially for treatment since many of the cases involve not only species in the Mucorales order but also *Aspergillus* or *Fusarium* species. There is no clear role identified in the literature for dual or triple systemic antifungal therapy, nor are there controlled trials demonstrating evidence of overall or specific agent efficacy. Therapy should be tailored to the agent or agents deemed most effective based upon laboratory results. As there is no evidence on duration of therapy and systemic antifungal therapy is not without risk, empiric therapy should be stopped as soon as possible if the suspicion of IFI is no longer being considered.

The majority of data on antifungal therapy for mucormycosis focuses on the polyenes, amphotericin B deoxycholate, and LFAB [41]. An amphotericin B product should be started as empiric therapy when diagnosis of trauma-related IFI is suspected, and LFAB is preferred due to lower potential for nephrotoxicity. Although one small retrospective study in diabetic patients with rhinocerebral mucormycosis showed better outcomes with the combination of caspofungin and amphotericin B compared to amphotericin B monotherapy [57], there have not been any prospective data to confirm this finding. While mortality rates are generally quite high [58], these patient populations typically have hematologic malignancies or other underlying immune suppression, and there are no data stating to what extent antifungal

agents improve outcomes in patients with traumatic wound infections outside of few case reports.

Voriconazole is not active against mucormycosis, but is the primary therapy for invasive aspergillosis [59, 60] and has efficacy against certain molds, such as *Aspergillus terreus* and *Scedosporium prolificans*, which are resistant to amphotericin B [60]. In the US military cases, a large percentage of wounds presented with multiple mold species, both Mucorales and either *Aspergillus* spp. or *Fusarium* spp., and a few with angioinvasive disease from only *Aspergillus* spp. Given the critical status of the majority of the affected patients and concerns with inadequate drug absorption, it is necessary to initially administer the antifungal therapy through an intravenous route. Voriconazole requires intravenous coadministration with the solubilizing excipient sulfobutyl ether β -cyclodextrin, which can accumulate in patients with impaired renal function (creatinine clearance <50 mL/min), leading to a package warning due to observed adverse effects in an animal model [61]. An observational study in oncology patients with invasive fungal disease who received between three and seven consecutive days of intravenous voriconazole showed that the antifungal agent did not cause a decline in renal function [62]. No new onset antifungal agent toxicity was documented on review of US military records; however, renal insufficiency at the time of IFI diagnosis was commonly observed among the proven IFI cases highlighting the need to limit empiric therapy to patients with a strong suspicion for IFI and prompt discontinuation of antifungal therapy if histopathology returns negative and IFI is no longer being considered.

Posaconazole has been shown to have a 60–70 % partial response rate as a salvage regimen for mucormycosis [63, 64], but it is not recommended as primary monotherapy due to decreased efficacy in murine model head-to-head trials versus amphotericin [41]. Data from the UK describe the use of LFAB and posaconazole for prophylactic use and empiric therapy in high-risk injuries [63]. Posaconazole is only available orally, and since many of these patients are critically ill and it takes several days to achieve effective serum levels, we recommend posaconazole as salvage therapy or oral consolidation therapy after a course of intravenous LFAB, rather than as part of an initial regimen.

Due to concern that tissue levels of systemically administered antifungal agents are low in the presence of ongoing necrosis, local therapies can also be considered. Adjunctively, topical therapy with antimicrobial beads [56•], including the use of amphotericin B [65], may be used; however, no evidence from controlled trials is available. Nystatin topical powder has been used in burn patients with angioinvasive fungal wound infections [66], but its use with a wound vacuum of polytrauma patients, such as those in our report, would be problematic and has not been documented. Wound-based antifungal therapy can be used at the surgeon's discretion, but any topical antifungal use is likely compromised by poor tissue penetration. Therefore, local therapy with a disinfectant that has antifungal properties is preferred. Sodium hypochlorite (Dakin's solution) has been known to have disinfectant properties since the turn of the twentieth century and was used frequently as a topical agent for combat wound infections in the pre-antibiotic era [67]. One case series of wounded military personnel with IFI describes the use of 0.025 % Dakin's solution with negative

pressure wound therapy, in addition to surgical debridements and appropriate antifungal therapy. All three case patients in the study were successfully managed [68].

Outcomes and Timeline

Overall, a crude mortality rate of 8 % has been observed although half of these deaths were not attributable to the IFI diagnosis (Table 2) [37•]. The median duration from time of injury to admission at the US hospital in Germany was 2 days with approximately a 3-day stay there before transfer to the USA (hospitalization of approximately 1–2 months). Diagnosis of IFI most commonly occurred after admission to a US clinical facility; the median (interquartile) duration from the time of injury to first diagnosis of IFI, first positive mold culture, and first histopathology examination was 6 (3, 10), 6 (3, 10), and 5 (3, 9) days, respectively.

The effect of IFIs on orthopedic outcomes and wound closure was recently investigated in a case-control analysis. The results demonstrated that fungal-infected wounds required a greater number of operative procedures, had a longer duration from injury to initial wound closure, an increased amount of residual limb shortening, and a greater proportion of changes in amputation level (Lewandowski et al., manuscript in preparation). As previously stated, 19 % of the IFI cases received a high-level amputation.

Future Issues

With regard to prevention, the use of primary antifungal prophylaxis is supported by evidence-based medicine in certain high-risk immune-compromised populations [69]. Posaconazole has been shown to have survival advantage and fewer proven and probable IFIs when compared to fluconazole or itraconazole in these populations [70, 71]. Reduction in the number of IFIs with amphotericin B as primary prophylaxis in patients with prolonged neutropenia has been observed as well [72, 73]. While the role of antifungal primary prophylaxis of high-risk immunocompromised patients is well established, there are no studies evaluating their role in immune-competent patients with traumatic injuries. The authors from the UK military suggest the use of LFAB and posaconazole for early empiric therapy in those felt to be at highest risk upon initial arrival in the UK following medevac from Afghanistan [5]. Early recognition of trauma patients at high risk should prompt aggressive surgical therapy accompanied by tissue-based diagnostic studies and consideration of early use of antifungal chemotherapy in patients with suspicious wounds. If antifungal therapy is initiated, it is critical to reassess on serial debridements and repeat tissue-based laboratory testing in order to discontinue therapy if no evidence of IFI presents, in order to limit drug-related toxicity.

As previously stated, early diagnosis is critical for effective treatment, which requires aggressive surgical debridement and targeted antifungal therapy. Although the presence of invasive fungal elements on histopathology examination is the standard, additional studies to optimize prompt and sensitive diagnosis should be pursued. Further research into what role molecular techniques or mold antigen-based immunohistochemical staining may play in the diagnosis of IFIs is warranted, particularly if a more prompt and accurate diagnosis would result. Additional questions that should be applied to this population include looking at the

diagnostic utility of serum “biomarkers” like beta-glucan and galactomannan, as well as exploring the differences in wound cytokines of these patients compared to others with non-IFI traumatic injuries.

More research is also needed in the controversial area of in vitro sensitivity testing for antifungal agents and how it corresponds with clinical outcomes. Future research should focus on whether clinical outcomes are improved with the use of in vitro sensitivity testing, and if so, for which organisms is such testing beneficial. In addition, consideration of preclinical animal model studies to investigate the efficacy of preventive and/or therapeutic strategies both at the local and systemic levels may add further support to apply to clinical settings.

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Fig. 1.

Progression of an invasive fungal wound infection following blast injury. **a** Wound immediately following blast injury, demonstrating severity of contamination. **b** Following surgical debridement and high-level lower extremity amputation with necrotic fibrinous material documented on histopathology with aseptate mold angioinvasion (initial presentation). **c** Wound appearance after serial debridements, hemipelvectomy, and antifungal therapy (8 days after photo was taken of wound in **b**). Wounds in **b** and **c** are from the same patient. The photos were provided by CAPT (sel) Carlos Rodriguez (Trauma Surgery) and CDR Mark Fleming (Orthopedics, National Naval Medical Center). A portion of this figure has been reprinted from Warkentien et al. [56••] by permission of Oxford University Press

Fig. 2.

Wound tissue histopathology. **a** Hematoxylin and eosin staining of necrotic tissue showing mold with broad aseptate hyphae at low power (×200). **b** Hematoxylin and eosin staining of necrotic tissue showing mold with broad aseptate hyphae at high power (×400). **c** Gomori methenamine silver staining (×100) showing angioinvasive mold with septate hyphae. The photos were provided by MAJ Justin Wells (Pathology, Walter Reed National Military Medical Center)

Table 1

Literature review of combat-related invasive fungal wound infection data

Reference	Number of cases	Principal finding
Tully et al. [35]	1 case	First case of invasive mucormycosis secondary to <i>Actinomyces elegans</i> infection. Mucormycosis should be considered in cases with recurrent, necrotic wounds when other risk factors (e.g., open traumatic wound with resulting immune suppression) are also present as it is likely fatal until treated early and appropriately
Calvano et al. [74]	1 case	Rare infection with a plant fungal pathogen (<i>Pythium aphanidermatum</i>)
Evrivades et al. [5]	Unspecified	Risk factors suggested for the development of fungal wound infections were as follows: (1) injured in southern Afghanistan; (2) dismantled blast injury; (3) extensive wounds/amputations contaminated with environmental debris; and (4) required massive blood product transfusions (>8 units) within 24 h of injury
Hospenthal et al. [75]	1 case	First report of newly described species, <i>Saksenaia erythrospora</i> , as a cause of a fatal human infection
Radowsky et al. [54]	1 case	Early diagnosis and testing for invasive fungal infections is critical for effective management
Paolino et al. [36•]	6 cases	Invasive fungal infections are a rare complication of combat wounds but are associated with significant morbidity and may be increasing in frequency
Warkentien et al. [56••]	37 cases	Case investigation of emerging combat trauma-related invasive fungal infections, which lead to significant morbidity. Early identification, aggressive surgical debridement, and antifungal therapy are critical for effective management
Barsoumian et al. [76]	No cases	Dakin's solution exhibits better dose-dependent toxicity and efficacy compared to mafenide acetate and amphotericin B with regard to topical application
Fares et al. 2013 [77]	9 cases	Blast wounds were contaminated with fungi and heat and moisture resulting from heavy, dirty clothing creating ideal habitat for fungal growth and proliferation
Lewandowski et al. [68]	3 cases	The use of Dakin's solution, along with surgical management and antifungal therapy, was successful at treating angioinvasive fungal infections
Lloyd et al. [55]	74 cases	Implementation of a local clinical practice guideline resulted in earlier diagnosis and initiation of treatment for invasive fungal infections. Nonetheless, no difference in clinical outcome was observed
Rodriguez et al. [40••]	76 cases	Case-control analysis determined that blast injuries sustained while dismantled, resulting in above knee amputations and requiring large-volume blood product transfusions (>20 units) within 24 h of injury, are independent risk factors for the development of invasive fungal infections
Lundy et al. [78]	2 cases	Provides first description of management of complex pelvic/perineal soft tissue injuries complicated with invasive fungal infection through the use of proctectomy
Weintrob et al. [37•]	77 cases	Trauma-related invasive fungal infection classification scheme an effective tool for clinical and epidemiological surveillance/ research
Mitchell et al. [79]	11 cases	Aggressive surgical treatment is necessary to manage invasive mucormycosis. Implementation of a standard protocol or surveillance cultures should be considered
Rodriguez et al. [80]	77 cases	In the absence of recurrently necrotic wounds, mold growth on wound cultures among patients with blast trauma does not require systemic antifungal therapy

Table 2

Demographics, injury circumstances, clinical parameters, management, and outcomes of combat-injured US service members (2009–2011) by invasive fungal infection (IFI) case classification

Characteristics	Proven (N=27)	Probable (N=27)	Possible (N=23)	Total (N=77)
Demographics, no. (%)				
Age, median (IQR)	22.6 (21.6, 28.7)	22.4 (21.7, 26.6)	24.2 (21.9, 25.4)	23.1 (21.7, 26.3)
Enlisted	27 (100)	24 (88.9)	21 (91.3)	72 (93.5)
Marine	20 (74.1)	23 (85.2)	15 (65.2)	58 (75.3)
Army	6 (22.2)	2 (7.4)	5 (21.7)	13 (16.9)
Injury circumstances and trauma care, no. (%)				
Injury circumstances				
Blast injury	27 (100)	26 (96.3)	21 (91.3)	74 (96.1)
Injured on foot patrol	26 (96.3)	25 (92.6)	18 (78.3)	69 (89.6)
Traumatic amputations				
Lower extremity	21 (77.8)	15 (55.6)	14 (60.9)	50 (64.9)
Upper extremity	1 (3.7)	0	0	1 (1.3)
Both upper/lower extremities	2 (7.4)	5 (18.5)	3 (13.0)	10 (13.0)
In-theater shock indices (combat support hospital), median (IQR)				
Heart rate	134 (118, 152)	114 (97, 136)	119 (107, 132)	125 (103, 140)
Systolic blood pressure	100 (80, 120)	99 (75, 132)	97 (65, 117)	99 (80, 123)
Blood gas—base deficit	11 (14, 8)	6 (10, 3)	7 (9, 4)	9 (13, 4)
Blood gas—pH	7.2 (7.0, 7.3)	7.3 (7.2, 7.3)	7.2 (7.1, 7.3)	7.2 (7.1, 7.3)
Blood product requirements in-theater, median (IQR)				
Packed red blood cells plus whole blood	31 (26, 42)	30 (15, 44)	22 (13, 33)	30 (17, 42)
Plasma ^a	31 (26, 40)	24 (15, 42)	22 (13, 36)	29 (18, 40)
Injury severity score, median (IQR)	21 (18, 28)	22 (18, 25)	21 (15, 26)	21 (17, 26)
IFI management, no. (%)				
IFI antifungal treatment regimen				
No treatment	0	6 (22.2)	6 (26.1)	12 (15.6)
Single agent	1 (3.7)	4 (14.8)	2 (8.7)	7 (9.1)
Dual (amphotericin B + triazole)	16 (59.3)	16 (59.3)	10 (43.5)	42 (54.5)
Combination (dual + echinocandin)	10 (37.0)	1 (3.7)	4 (17.4)	15 (19.5)
Systemic antifungal agents				
Amphotericin B (liposomal)	26 (96.3)	19 (70.4)	15 (65.2)	60 (77.9)
Voriconazole	25 (92.6)	19 (70.4)	15 (65.2)	59 (76.6)
Posaconazole	12 (44.4)	2 (7.4)	3 (13.0)	17 (22.1)
Caspofungin	10 (37.0)	1 (3.7)	4 (17.4)	15 (19.5)
Micafungin	1 (3.7)	0	2 (8.7)	3 (3.9)
Antifungal duration, median days (IQR)				
Amphotericin B (liposomal)	25 (17, 42)	19 (11, 32)	17 (8, 21)	21 (12, 30)
Voriconazole	14 (5, 26)	18 (14, 28)	16 (9, 20)	17 (9, 26)
Total antifungal treatment	26 (13, 41)	18 (4, 30)	11 (6, 22)	18 (7, 29)

Characteristics	Proven (N=27)	Probable (N=27)	Possible (N=23)	Total (N=77)
Hospitalization, median (IQR)				
US MTF hospitalization (days)	59 (38, 73)	46 (30, 61)	37 (27, 53)	47 (29, 66)
Total hospitalization (days) ^b	61 (40, 76)	48 (34, 63)	40 (29, 57)	49 (32, 68)
US MTF duration in ICU (days)	14 (5, 23)	6 (3, 17)	8 (4, 11)	8 (4, 18)
Total duration in ICU (days) ^b	16 (7, 24)	9 (5, 20)	9 (6, 16)	11 (6, 20)
Overall OR visits	17 (12, 24)	14 (9, 18)	13 (8, 16)	15 (9, 18)
Overall outcome, no. (%)				
High-level amputations ^c	7 (25.9)	5 (18.5)	3 (13.0)	15 (19.5)
Deaths	4 (14.8)	1 (3.7)	1 (4.3)	6 (7.8)

Table modified from Weintrob et al. [37•]

ICU intensive care unit, IQR interquartile range, MTF military treatment facility, OR operating room

^aPlasma is fresh frozen plasma plus whole blood

^bTotal hospitalization/duration in ICU combines data from Landstuhl Regional Medical Center and US MTFs

^cHigh-level amputations are defined as total hip disarticulation or hemipelvectomy