Risk Factors Associated with Invasive Fungal Infections in Combat Trauma

Carlos J. Rodriguez,¹ Amy C. Weintrob,^{1,2} Jinesh Shah,² Debra Malone,¹ James R. Dunne,³
Allison B. Weisbrod,¹ Bradley A. Lloyd,⁴ Tyler E. Warkentien,¹ Clinton K. Murray,⁵
Kenneth Wilkins,² Faraz Shaikh,² M. Leigh Carson,² Deepak Aggarwal,² David R. Tribble²
and the Infectious Disease Clinical Research Program Trauma Infectious
Disease Outcomes Study Group

Abstract

Background: In recent years, invasive fungal infections (IFI) have complicated the clinical course of patients with combat-related injuries. Commonalities in injury patterns and characteristics among patients with IFI led to the development of a Joint Trauma System (JTS) clinical practice guideline (CPG) for IFI management. We performed a case-control study to confirm and further delineate risk factors associated with IFI development in combat casualties with the objective of generating data to refine the CPG and promote timelier initiation of treatment.

Methods: Data were collected retrospectively for United States (U.S.) military personnel injured during deployment in Afghanistan from June 2009 through August 2011. Cases were identified as IFI based upon wound cultures with fungal growth and/or fungal elements seen on histology, in addition to the presence of recurrent wound necrosis. Controls were matched using date of injury (± 3 mo) and injury severity score (± 10). Risk factor parameters analyzed included injury circumstances, blood transfusion requirements, amputations after first operative intervention, and associated injuries. Data are expressed as multivariate odds ratios (OR; 95% confidence interval [CI]).

Results: Seventy-six IFI cases were identified from 1,133 U.S. military personnel wounded in Afghanistan and matched to 150 controls. Parameters associated significantly with the development of IFI multivariate analysis were blast injuries (OR: 5.7; CI: 1.1–29.6), dismounted at time of injury (OR: 8.5; CI: 1.2–59.8); above the knee amputations (OR: 4.1; CI: 1.3–12.7), and large-volume packed red blood cell (PRBC; > 20 U) transfusions within first 24 h (OR: 7.0; CI: 2.5–19.7).

Conclusions: Our analysis indicates that dismounted blast injuries, resulting in above the knee amputations, and requirement of large volume PRBC transfusions are independent predictors of IFI development. These data confirm all the preliminary risk factors, except for genitalia/perineal injuries, utilized by JTS in their IFI CPG. Model validation is necessary for further risk factor specification.

LOCALLY INVASIVE FUNGAL INFECTIONS (IFI) are an insidious complication related to trauma characterized by high morbidity and mortality rates ranging from 11 to 38% [1–8]. Recently, combat trauma-associated IFI has emerged as a serious military health concern [9–12]. Prior to 2009, the rate of IFI diagnosed among wounded United States (U.S.)

service members was negligible ($< 0.1\%$) [9]; however, by the fourth quarter of 2010, IFI rates increased substantially to 3.5% of U.S. combat casualties admitted to Landstuhl Regional Medical Center (LRMC) in Germany [10].

One of the challenges of treating IFI in both civilian and military settings is delay in diagnosis. Delays may result from

¹Walter Reed National Military Medical Center, Bethesda, Maryland.

²Infectious Disease Clinical Research Program, Uniformed Services University of the Health Sciences, Bethesda, Maryland.

³Department of Surgery, Uniformed Services University of the Health Sciences, Bethesda, Maryland.

⁴Landstuhl Regional Medical Center, Landstuhl, Germany.

⁵San Antonio Military Medical Center, Fort Sam Houston, Texas.

the lag time between the collection of specimens for culture and histopathologic analysis and receipt of results, a lack of understanding of risk factors for developing IFI, or slow recognition of an uncommon disease that can present similarly to other types of wound infections. Early diagnosis and prompt surgical and medical treatment are crucial components for favorable patient outcomes [3,6,7,10]. Although some clinicians have suggested prescribing antifungals at the first indication of a suspected IFI, others are hesitant without culture or histopathological IFI confirmation because of the potential hepatic and nephrotoxicity of the antifungal agents [13].

When first described in combat casualties, confirmatory IFI diagnosis took 7–10 d following injury [10]. In the spring of 2011, a process improvement initiative of screening high-risk patients for IFI was initiated at LRMC. This protocol reduced time to diagnosis by 50% (3–5 days from injury). Although these results were encouraging, they failed to demonstrate a difference in clinical outcomes, such as intensive care unit length of stay, hospital length of stay, mortality, or number of operative procedures necessary to achieve wound closure [14].

In order to improve outcomes, it is apparent that prevention of IFI should become the primary focus of research. Prior evaluations have suggested that combat casualties at highest risk for IFI are those injured in southern Afghanistan while on foot patrol. Additionally, patients sustaining a traumatic amputation (often with perineal involvement), and those requiring massive packed red blood cell transfusions (>25 U) within the first 24 h have been observed with IFI development [9–12,14–16].

To validate these observations, we performed a case-control analysis to delineate risk factors for the development of IFI among combat casualties. Our overall objective was to provide the Joint Trauma System (JTS) of the U.S. Army Institute of Surgical Research, a formal system of combat-related trauma care in theater modeled on civilian trauma systems, with evidence-based guidance to identify at-risk patients as candidates for early initiation of surgical and medical therapies in lieu of waiting for IFI confirmation via culture and/or histopathological confirmation.

Patients and Methods

Patient population

Data were collected retrospectively for U.S. service members with combat-related trauma sustained in Afghanistan from June 1, 2009 through August 31, 2011. After being treated at a combat support facility (provides highest available medical care in the combat zone), patients were medically evacuated to LRMC for initial care before being transferred to one of three participating tertiary care military treatment facilities in the U.S.: Walter Reed Army Medical Center in Washington, DC; National Naval Medical Center in Bethesda, MD; and San Antonio Military Medical Center in San Antonio, TX. Patient data were collected as part of an ongoing five-year observational cohort study of short- and long-term infectious complications following deployment-related traumatic injuries during the recent military conflicts; the U.S. Department of Defense (DoD)—Department of Veterans Affairs, Trauma Infectious Disease Outcomes Study (TIDOS) [17].

Case-control identification and investigation

Information on trauma history, injury patterns, clinical characteristics on admission, and surgical management for the case and control populations was obtained from the DoD Trauma Registry (DoDTTR, formerly called the Joint Theater Trauma Registry) [18]. The TIDOS supplemental infectious disease module was utilized to gather data on fungal culture and histopathology results. In addition, all histopathology specimens were reviewed independently by two surgical pathologists.

Criteria for U.S. military personnel to be included in the study population was the occurrence of a combat-related injury resulting in open wounds between June 1, 2009 and August 31, 2011 during Operation Enduring Freedom (OEF) and subsequent transfer from LRMC to a participating U.S. military treatment facility. Inclusion of cases in the analysis was based upon an in-depth review of the TIDOS database for all wound cultures with fungal growth, pathology with fungal elements, or administration of two or more days of antifungal agents during the period of interest. Infectious disease and trauma surgery services case records were also reviewed. Cases were confirmed as IFI using modified versions of the 2008 IFI definitions and diagnostic criteria from the Mycoses Study Group [19], and required the presence of tissue invasion with fungal hyphae angioinvasion, histopathologic fungal elements, and/or fungal growth on culture with recurrent wound tissue necrosis following two or more surgical debridements [10]. *Candida* species were not included in the analysis because of uncertainty as to their role in the pathogenesis of wound infections. Controls were matched to IFI cases on date of injury (± 3 months) to control for temporal and environmental changing conditions and on injury severity scores ($ISS \pm 10$). Because of a missing ISS, one IFI case was excluded from the analysis. Risk factor variables included circumstances of injury, presenting hemodynamics, traumatic amputation levels after first operative intervention, and associated injuries. The study was approved by the Infectious Disease Institutional Review Board of the Uniformed Services University of the Health Sciences, Bethesda, MD.

Statistical analysis

Demographic and clinical characteristics of cases and controls were examined in baseline tables. Risk factors for the development of IFI were determined using conditional logistic regression. Odds ratios (OR) and 95% confidence intervals (CI) were calculated to express significant factors. Backward conditional logistic regression was used to determine which of the potential risk factors was associated significantly with IFI status (i.e., packed red blood cells [PRBC], shock index, and base deficit) for inclusion in the multivariate analysis. A correlation analysis was also conducted to evaluate the relationship between the three potential risk factors. For the final multivariate model, multiple imputation using predictive mean matching (continuous variables) and logistic regression (binary variables) estimated the effect of each risk factor in order to utilize all available information when incomplete observations occurred [20,21]. Multivariate OR and 95% CI for the multivariate model were derived from computations of each of the five imputed datasets. P-value of 0.05 was used as a significant cutoff value. Statistical analysis

was performed using SAS® version 9.3 (SAS, Cary, NC) and R® version 2.13.2 (R Project for Statistical Computing, Vienna, Austria).

Results

Patient demographics and injury characteristics

Examination of data from 1,133 combat casualties eligible for the study population identified 77 (6.8%) IFI cases and 150 matched controls; however, as mentioned previously, one IFI case was excluded from the analysis because of a missing ISS. All cases and controls were male with a median age of 23 (Table 1). Among the 76 IFI cases evaluated in the analysis, 99% sustained blast injuries and 93% were injured while on dismounted patrol. Likewise, controls reported a predominance of blast injuries (87%) while dismounted (75%), but to a lesser extent for both characteristics ($p < 0.001$). Since utilized as matching criteria, injury severity for both IFI cases and controls was similar with a median LRMC admission ISS of 21.

The IFI cases had a significantly higher number of lower extremity amputations (79% versus 46%; $p < 0.001$; Table 2), a greater proportion of above-the-knee amputations (AKAs), pelvis and/or hip injuries, genitalia and/or groin injuries, and requirement for colostomy ($p \leq 0.05$) compared with the controls. Additionally, IFI cases were significantly more hypotensive and acidotic ($p < 0.05$) at presentation to the first medical treatment facility. Lastly, within the first 24 h of injury, IFI cases required a significantly larger volume of PRBC transfusions, median of 29 U, compared with 11 U among the controls ($p < 0.001$).

Univariate risk factor analysis

Injury circumstances, amputation levels, associated injuries, 24-h blood transfusion requirements, initial base deficits, and initial shock indices (heart rate/systolic blood pressure) were examined in a univariate analysis (Table 3). Data for some of the parameters were missing (i.e., 3% of IFI cases and 4% of controls did not have mounted status data [binary variable] and 22% of controls did not have PRBC data [continuous variable]) and were imputed. Associated

injuries were included in the analysis as a binary variable evaluating the risk of IFI based on the presence or absence of perineal, genitourinary, and/or more severe pelvic/abdominal injuries.

Mechanism of injury and foot patrol status were statistically associated with the development of IFI in the univariate analysis ($p < 0.05$). Injury patterns (AKAs and associated injuries) were also significantly associated with the development of IFI among combat wounded ($p < 0.0001$). In addition, a significant association was determined for patients requiring massive (10–20 U) and super-massive (> 20 U) PRBC transfusions within the first 24 h ($p = 0.001$ and $p < 0.0001$, respectively). Furthermore, a base deficit ≥ 10 mcg/L, and shock index ≥ 1.5 in theater were associated significantly with the development of IFI ($p < 0.0001$).

Correlation analysis

Although the base deficit and shock index were associated with the development of IFI in the univariate model, these parameters were removed from the intermediate multivariate models during a backward stepwise model selection process, as part of the conditional logistic regression analysis, because of their being highly associated with the strongest predictor of IFI, PRBC transfusion requirements within the first 24 h (Pearson correlation coefficient: 0.44 for shock index and 0.45 for base deficit; $p < 0.0001$). Therefore, base deficit and shock index were not included in the final multivariate analysis.

Multivariate risk factor analysis

The multivariate analysis expanded upon the results of the univariate model and controlled for mounted status (mounted versus dismounted at time of injury), type of injury (blast versus non-blast), LRMC admission ISS (included in multivariate analysis to provide greater control of injury severity-based matching), PRBC transfusion (> 20 U versus < 20 U) within first 24 h, amputation categories (AKA versus no AKA), and associated injuries (genitalia and more severe injuries versus none). Results of the multivariate analysis are reported in Table 3. Mechanism of injury, foot patrol status, AKAs, and PRBC

TABLE 1. DEMOGRAPHIC CHARACTERISTICS AND INJURY CIRCUMSTANCES OF COMBAT-INJURED U.S. SERVICE MEMBERS (2009–2011)

Characteristics	IFI cases (N = 76)	Controls (N = 150)	P-value
<i>Demographics, No. (%)</i>			
Age, median (IQR)	23.1 (21.7, 26.3)	23.0 (21.4, 26.2)	0.73
Male	76 (100)	150 (100)	-
Enlisted ^a	72 (100)	137 (93.2)	0.03
Marine	58 (76.3)	69 (46.0)	< 0.001
Army	13 (17.1)	73 (48.7)	
Navy	1 (1.3)	4 (2.7)	
<i>Injury Circumstances, No. (%)</i>			
Blast injury	75 (98.7)	130 (86.7)	< 0.001
Dismounted ^b	69 (93.2)	108 (75.0)	< 0.001
LRMC ISS, median (IQR)	21 (17, 26)	21 (17, 24)	0.15
Medical facilities in theater of operation (> 2), No. (%)	9 (12.0)	14 (9.0)	0.56
Days from injury to arrival at LRMC, median (IQR)	2 (2, 3)	2 (2, 3)	0.75

IFI = invasive fungal infection; IQR = interquartile range; ISS = injury severity score; LRMC = Landstuhl Regional Medical Center.

^a Data for this parameter are missing for some patients (cases $n = 4$; controls $n = 3$).

^b Data for this parameter are missing for some patients (cases $n = 2$; controls $n = 6$).

TABLE 2. PATTERNS OF INJURIES, CLINICAL CHARACTERISTICS IN THEATER AND BLOOD TRANSFUSION REQUIREMENTS (1st 24 HOURS) AMONG COMBAT-INJURED U.S. SERVICE MEMBERS (2009–2011)

Characteristics	IFI cases (N = 76)	Controls (N = 150)	p value
<i>Amputations, No. (%)</i>			
Lower extremity ^a	60 (78.9)	69 (46.0)	<0.001
Above the knee	48 (63.2)	32 (21.3)	<0.001
Through the knee	20 (26.3)	23 (15.3)	0.05
Below the knee	17 (22.4)	25 (16.7)	0.30
Upper extremity	11 (14.5)	7 (4.7)	0.01
Both upper and lower extremity	10 (13.2)	6 (4.0)	0.01
<i>Associated Injuries, No. (%)^b</i>			
Genitalia/Groin	56 (73.7)	51 (34.0)	<0.001
Rectal/bladder and genitalia	4 (5.3)	1 (0.7)	0.05
Colostomy ^c	28 (36.8)	14 (9.3)	<0.001
Penetrating abdomen	11 (14.5)	19 (12.7)	0.71
Pelvis/hip (skeletal)	27 (35.5)	35 (23.3)	0.05
<i>Clinical Characteristics In Theater, median (IQR)</i>			
Heart Rate	124.5 (103.3, 139.8)	110.0 (91.5, 129.5)	0.002
Systolic blood pressure	99.0 (79.5, 122.5)	123.0 (109.0, 142.3)	<0.001
Blood gas – base deficit ^d	9.0 (12.5, 4.0)	3.0 (6.0, 0)	<0.001
Blood gas – pH	7.24 (7.12, 7.30)	7.31 (7.24, 7.39)	<0.001
Shock Index (≥ 1.5), No. (%) ^{d,e}	24 (34.3)	10 (7.8)	<0.001
<i>Blood Transfusion Requirements, median units (IQR)</i>			
Packed red blood cells ^d	29 (16, 39)	11 (4, 19)	<0.001
Fresh frozen plasma	27 (16, 37)	11 (4, 18)	<0.001

IFI=invasive fungal infection; IQR=interquartile range.

^a Due to bilateral amputations, this total does not reflect sum of above-knee, below-knee, and through-knee amputations.

^b Associated injuries are not mutually exclusive.

^c Colostomy occurred either in theater or at LPMC.

^d Data for this parameter are missing for some patients (Base deficit: cases n=10, controls n=28; Shock Index: cases n=6, controls n=22; Packed red blood cells: cases n=1, controls n=33).

^e Shock Index: heart rate/systolic blood pressure.

^f One unit of packed red blood cells or fresh frozen plasma is approximately 250–300 mL.

transfusions requirements were independently associated with the development of IFI. However, no significant statistical association for associated injuries was observed.

Discussion

Identification of risk factors associated with the development of combat-related IFI are necessary to support clinicians in making earlier diagnoses, which is a crucial component of

disease management. Our analysis compared data from 76 IFI cases and 150 matched controls identified from a population of 1,133 combat casualties (June 2009 through August 2011). The results of the multivariate analysis indicate that military personnel at greatest risk for developing IFI are those who were on dismounted patrol when injured by a blast that resulted in at least one AKA and super massive (>20 units) PRBC resuscitation requirements in the first 24 h after injury. These results corroborate common characteristics

TABLE 3. ODDS RATIO ANALYSIS FOR POTENTIAL RISK FACTORS OF DEVELOPING AN INVASIVE FUNGAL INFECTION AMONG COMBAT-WOUNDED (2009–2011)

Potential risk factor	Univariate odds ratio (95% CI)	Multivariate odds ratio (95% CI) ^a
<i>Injury circumstance</i>		
Blast	11.6 (1.8 - 493.2)	5.7 (1.1 - 29.6)
Dismounted	5.3 (1.7 - 21.6)	8.5 (1.2 - 59.8)
Above the knee amputation	10.0 (4.2 - 29.1)	4.1 (1.3 - 12.7)
Associated injuries ^b	4.4 (2.2 - 9.4)	2.3 (0.8 - 6.3)
PRBC transfusions (> 20 U in first 24 h)	47.1 (9.8 - 479.3)	7.0 (2.5 - 19.7)
<i>Clinical characteristics in theater^c</i>		
Base deficit (≥ 10)	8.7 (3.0 - 31.8)	-
Shock index (> 1) ^d	4.5 (2.2 - 10.4)	-

CI=confidence interval; PRBC=packed red blood cells.

^a Controls are matched to cases by injury date (± 3 months) and injury severity score (ISS; ± 10). ISS was included in multivariate analysis to provide greater control of injury severity-based matching.

^b Includes perineal, genitourinary, and/or more severe pelvic/abdominal injuries.

^c Due to high correlation with PRBC, base deficit and shock index were not included in the multivariate analysis.

^d Shock Index: heart rate/systolic blood pressure.

observed in earlier case investigations of combat casualties who ultimately developed IFI [9–12,14–16].

Trauma-associated IFI cases within civilian populations are associated primarily with traffic or agricultural accidents and natural disasters [2,3,6–8] and are characterized generally by penetrating wounds contaminated with environmental debris. An analysis of 75 patients diagnosed with IFI following a traumatic injury sustained during a traffic accident, agricultural accident, or natural disaster, reported that 100% of the cases occurred in a soil environment. In addition, 41% of the patients had either multiple injuries or injuries involving extremities [7]. However, the penetrating trauma does not need to be severe. In some cases, IFI complications have resulted from needle sticks, insect bites, and scratches [2,3].

Aside from our case-control analysis, there has only been one other study that examined IFI risk factors associated with trauma. In May 2011, more than 1,000 people were injured by a tornado in Joplin, Missouri, of which 13 were diagnosed with IFI. All of the IFI patients sustained injuries in the zone that suffered the most severe damage during the tornado. The median number of wounds among the 13 patients was 5 (range: 1–7) with 69% and 38% experiencing blunt and penetrating, respectively (patients often sustained injuries through both mechanisms). A case-control analysis matched the 13 patients to 35 controls and determined that the primary risk factors were penetrating trauma (OR: 8.8; CI: 1.1–69.2) and occurrence of multiple wounds (OR: 2.0; CI: 1.2–2.0). Lacerations and fractures were not associated with the development of IFI [6]. The patients in the Joplin case series were not categorized by an injury severity scoring system to permit direct comparison to our analysis. However, the independent risk factors documented support that patients with more severe injuries (e.g., polytrauma and traumatic amputations) are at greatest risk for developing IFI complications, which is comparable with our series.

Improvements in combat casualty care have resulted in greater survival rates, especially in the severely injured patients [17,18,22,23]. In this analysis, injury patterns sustained from blast trauma were extensive. Patients presented in profound hemorrhagic shock with a median heart rate of 124 beats/min, systolic blood pressure of 99, base deficit of 9, and pH of 7.24. Additionally, initial resuscitation requirements were significant with patients receiving a median of 29 U of PRBCs and 27 U of fresh frozen plasma. These super-massive transfusions may result in the patient experiencing a temporary state of immunosuppression [24–27] increasing susceptibility to IFI after traumatic inoculation of fungal elements [3,7,28]. The blood product transfusions may have also resulted in a state of iron overload, which is suggested in the scientific literature as a risk factor for mucormycosis because of the association between serum iron availability and Mucorales growth and virulence [29,30].

Another likely explanation for the increase in combat-related IFI involves the change in geography. Civilian case reports, including the analysis of Joplin tornado IFI patients, indicate that IFI in immune competent patients occurs from inoculation of contaminated soil into traumatic wounds [6,7,28]. During the recent military conflicts, personnel have shifted geographically from the arid climate of Iraq to the agricultural provinces of Helmand and Kandahar in southern Afghanistan where soil has a high concentration of decaying

vegetation and mold. A similar distribution of IFI cases are being observed among British military personnel evacuated medically from southern Afghanistan [12].

The results of our multivariate model have been presented to the JTS for incorporation into the existing IFI clinical practice guidelines (CPG) and will require validation as the CPG is refined. Limitations of the analysis include the missing data, of which some are not randomly distributed. Additionally, injury severity matching was limited by the availability of control patients, thereby, lessening statistical power to detect less robust differences in the multivariate analysis.

Ongoing clinical research on IFI includes a case-control study to evaluate IFI-related impact on clinical and orthopedic outcomes. Our overall objective is to promote early identification and diagnosis and develop refined preventive and early treatment strategies to inhibit tissue invasion among high-risk patients.

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Address correspondence to:

Dr. David R. Tribble
*Infectious Disease Clinical Research Program
 Preventive Medicine and Biometrics Department
 Uniformed Services University of the Health Sciences
 4301 Jones Bridge Rd.
 Bethesda, MD 20814-5119*

E-mail: David.Tribble@usuhs.edu