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Early Complications and Outcomes in Combat Injury Related Invasive Fungal Wound Infections: A Case-Control Analysis

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Abstract

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Conflict of Interest

The authors have no conflicts of interest to declare.

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Level of Evidence: Prognostic Level III. See Instructions for Authors for a complete description of levels of evidence.

Objective—Clinicians have anecdotally noted that combat-related invasive fungal wound infections (IFIs) lead to residual limb shortening, additional days and operative procedures prior to initial wound closure, and high early complication rates. We evaluated the validity of these observations and identified risk factors that may impact time to initial wound closure.

Design—Retrospective review and case-control analysis.

Setting—Military hospitals.

Patients/Participants—United States military personnel injured during combat operations (2009–2011). The IFI cases were identified based upon the presence of recurrent, necrotic extremity wounds with mold growth in culture and/or histopathologic fungal evidence. Non-IFI controls were matched on injury pattern and severity. In a supplemental matching analysis, non-IFI controls were also matched by blood volume transfused within 24 hours of injury.

Intervention—None.

Main Outcome Measurements—Amputation revision rate and loss of functional levels.

Results—Seventy-one IFI cases (112 fungal-infected extremity wounds) were identified and matched to 160 control patients (315 non-IFI extremity wounds). The IFI wounds resulted in significantly more changes in amputation level ($p<0.001$). Additionally, significantly ($p<0.001$) higher number of operative procedures and longer duration to initial wound closure was associated with IFI. A shorter duration to initial wound closure was significantly associated with wounds lacking IFIs (Hazard ratio: 1.53; 95% CI: 1.17, 2.01). The supplemental matching analysis found similar results.

Conclusions—Our analysis indicates that IFIs adversely impact wound healing and patient recovery, requiring more frequent proximal amputation revisions and leading to higher early complication rates.

Keywords

invasive fungal infection; invasive mold infection; combat-related trauma; wound closure; amputations

BACKGROUND

Although uncommon, trauma-related invasive fungal wound infections (IFIs) in previously immunocompetent individuals involving molds (e.g., *Aspergillus* spp., *Fusarium* spp., and zygomycetes) are associated with considerable mortality (i.e., as high as 38%)[1–4] and morbidity, often resulting in either permanent disability and/or extensive rehabilitation.[1–3,5–10] Among wounded military personnel, the impact of trauma-related IFI complications became increasingly relevant as advances in combat care during recent wars in Iraq and Afghanistan improved the survivability of severe trauma, including blast-related traumatic amputations.[11,12] In general, trauma-related IFIs develop following a penetrating injury contaminated with environmental debris containing molds in susceptible patients.[1–5] Since 2001, over 52,000 United States (U.S.) service members have been wounded in the recent wars[13] with a mean annual amputation rate of 3.6 per 100 trauma admissions.[12] As

mortality due to these severe injuries declined, the proportion of IFIs documented amongst U.S. combat casualties increased.[14–18]

Case investigations of IFIs among combat casualties have provided data on patient clinical characteristics and disease management strategies.[15,17,19] A recent analysis examined commonalities among combat-related IFI cases in a multivariate analysis and determined that injuries sustained due to improvised explosive devices while on foot patrol, above knee amputations, and massive transfusions (>20 units) of packed red blood cells within 24 hours post-injury were independent risk factors for development of IFI.[18] Treatment involves serial aggressive debridements, utilization of antifungal agents, and surgical amputation or revision of amputation levels when warranted.[1,5,6,15,17,20,21] Anecdotally, clinicians involved in the management of combat-related IFIs have noted that these infections generally lead to marked shortening of residual limbs, increased time and operative procedures prior to wound closure, and high rates of early complications. Nevertheless, as these factors have not yet been quantified, the impact of IFIs on those outcomes remains uncertain. To validate these theories, we analyzed surgical endpoints, including amputation levels and revision, and early complications among an IFI case series and performed a case-control analysis to evaluate risk factors related to an extended duration following injury to initial wound closure among U.S. military personnel with combat-related injuries.

PATIENTS AND METHODS

Study Population

Data were collected from 1133 U.S. service members with combat-related trauma sustained in Afghanistan from June 2009 through August 2011. After resuscitative and surgical stabilization care at support facilities in the combat zone on date of injury, patients were medically evacuated to Landstuhl Regional Medical Center (LRMC; Germany), and subsequently transferred to a U.S. military treatment facility (MTF): Walter Reed Army Medical Center (Washington, DC), National Naval Medical Center (Bethesda, MD), or Brooke Army Medical Center (San Antonio, TX). These data were acquired as part of a longitudinal, observational cohort study of infectious complications following deployment-related trauma; the U.S. Department of Defense (DoD) – Department of Veterans Affairs, Trauma Infectious Disease Outcomes Study (TIDOS).[22] The study was approved by the Infectious Disease Institutional Review Board of the Uniformed Services University of the Health Sciences (Bethesda, MD).

Case-Control Classification and Matching

To be included in the IFI case group, wounded military personnel who met predefined diagnostic criteria based upon published IFI case definitions[15,23] were identified through a retrospective review of the TIDOS database. In brief, the inclusion criteria for this analysis was evidence of an extremity wound with recurrent tissue necrosis following at least two serial surgical debridements in addition to laboratory evidence of infection (i.e., fungal growth on wound cultures, histopathological fungal elements in tissue from wound site, and/or presence of viable tissue invasion with fungal hyphae). Case files from infectious disease and trauma surgery services were also examined.

Controls were identified from the population of trauma patients admitted to LRMC and subsequently treated at a participating MTF during the same period and restricted to those with extremity wounds. The control wounds were further stratified based upon occurrence of bacterial skin and soft-tissue infections (SSTIs).

The case and control groups were matched by extremity injury/amputation pattern. Specifically, the controls were matched by the occurrence of at least one above knee amputation, a below knee amputation with/without other amputations (excluding above knee), other amputations excluding above/below knee amputations, or no traumatic amputation. The groups were also matched on injury severity score (±10).[24]

Demographics, injury patterns, inpatient care, and surgical management for the study population were collected from the DoD Trauma Registry,[11] while mold and bacterial culture results, histopathology data, and data on SSTIs were obtained via the supplemental TIDOS infectious disease module. *Candida* spp. were not included in the analysis. Multidrug-resistant organisms (MDRO) were identified in accordance with definitions published by the National Healthcare Safety Network.[25]

Clinical and Microbiological Endpoints

Outcome variables included number of operative procedures prior to initial wound closure,[26] time (days) from injury to initial wound closure, additional surgical requirements following wound closure due to complications, proximal revisions in functional amputation levels, and loss of residual femur length for patients with transfemoral amputations (TFA). Wound closure was at the treating surgeon's discretion and based upon wound appearance, as well as overall clinical status of the patient. Closure methods were delayed primary closure, skin grafts (split-thickness and full-thickness), flaps (free and rotation), and commercial dermal matrix substitutes (i.e., Integra™, Integra LifeSciences Corp., Plainsboro Township, NJ). Radiographs taken of affected extremities at time of discharge or final wound closure at U.S. MTFs were compared to films from initial hospitalization at LRMC in order to measure changes in limb length. For purposes of this analysis, only TFAs were considered because long transfemoral amputations are not routinely shortened prior to closure.

Secondary Analysis with Supplemental Matching

The supplemental matching analysis added a third criterion of volume of blood products transfused within the first 24 hours. For this secondary analysis, the case and control inclusion criteria remained the same as described in the Case-Control Classification and Matching section.

Statistical Analysis

Conditional logistic regression was utilized to compare variables between the cases and controls in order to account for the matching. Frailty Model[27] was used to analyze the association between potential risk factors and initial time to wound closure for univariate analysis. In addition, a correlation analysis was conducted to evaluate the relationship between potential risk factors. Variables found potentially significant ($p \leq 0.2$) in the

univariate model were examined in a multivariate analysis using the best-fitting parsimonious model. The final multivariate model contained only significant terms ($p<0.05$).

For both univariate and multivariate models, the potential risk factor was used as the reference variable (e.g., fungal infection); therefore, a hazard ratio greater than one for the comparison variable (e.g., no fungal infection) indicated an association with a reduced time following injury to initial wound closure. Significant factors were expressed as hazard ratios and 95% confidence intervals. Statistical significance was defined as $p<0.05$.

RESULTS

Patient Characteristics

Seventy-one IFI cases (112 IFI wounds) were included in the analysis and matched to 160 controls (315 non-IFI extremity wounds). The mechanism of injury was blast for 100% of the IFI cases and controls with the majority of personnel injured while on foot patrol (Table 1). Amputations of lower extremities and open fractures were predominant for both IFI cases (80% and 70%, respectively) and controls (81% and 62%, respectively). While injury severity was comparable between the groups, the number of patients receiving massive transfusions of packed red blood cells (>20 units) within 24 hours post-injury was significantly greater for IFI cases (66%) compared to controls (27%; $p<0.001$; Table 2). Moreover, IFI cases had a significantly larger proportion of patients with a shock index ≥1.5 (35% versus 14%; $p=0.006$). Ultimately, four (6%) IFI case and two (1%) control patients died.

Extremity Wound Characteristics

On a per extremity wound basis (112 IFI and 315 non-IFI control wounds), the proportion of SSTIs associated with either bacteria or yeast was significantly higher among case wounds (55%) compared to controls (16%; $p<0.001$; Supplemental Table 1). In addition, SSTIs among the IFI wounds were more frequently associated with MDROs (27% versus 7%; $p<0.001$). The most common MDROs were *Enterococcus facecium*, *Escherichia coli*, and *Acinetobacter spp*. (Supplemental Table 2). The IFI cases also had an increased number of wounds with more than one SSTI prior to initial wound closure (7% versus 2%; $p=0.006$).

Clinical and Orthopedic Outcomes

A statistically higher proportion of IFI wounds required proximal revision of a functional amputation level(s) ($p<0.001$). Specifically, an increased number of TFA with fungal infections were revised to hemipelvectomies or hip disarticulations ($p=0.006$). Furthermore, on a per extremity wound basis, there was a significant increase in the median number of operative procedures (9 and 6, respectively; $p<0.001$) and days to initial wound closure (16 and 9, respectively; $p<0.001$) between the IFI cases and controls (Table 3). The type of wound closures utilized was also statistically different between IFI case and control wounds ($p=0.011$) with delayed primary closure as the predominant method (53% and 63%, respectively) followed by a combination of skin grafts and dermal matrix products (34% and 18%, respectively). Complications requiring repeat surgery after wound closure and during initial hospitalization occurred in 50% of IFI wounds and 20% of control wounds and

primarily involved either superficial (16% and 5%, respectively) or deep infections (12% and 6%, respectively).

Case-Control Risk Analysis

Risk factors were assessed in a univariate analysis for their potential impact on time from injury to initial wound closure. Wounds without infections (IFI or SSTI) were associated with reduced time to initial wound closure (Table 4). Among wounds with diagnosed SSTIs, there was an improved time to wound closure when the infecting organism was not multidrug-resistant. In addition, both <20 units of blood product transfusions within 24 hours of injury and admittance to the ward rather than the intensive care unit at LRMC were statistically associated with a shorter duration from injury to initial wound closure.

A multivariate analysis was used to evaluate for independent risk factors associated with shorter time to wound closure (Table 4). Two of the variables related to SSTIs (i.e., linkage to bacterial organisms and to MDROs) were found to be highly correlated (chi-square $p<0.001$). The variable, SSTIs linked to MDROs resulted in a better goodness-of-fit and, therefore, remained in the final multivariate model. A reduced duration to initial wound closure was independently associated with noninfected wounds (IFI or SSTI), non-MDROs linked to SSTIs, <20 units of blood products transfused within 24 hours, and admission to the ward at LRMC instead of the intensive care unit.

Supplemental Matching Analysis

The case-control analysis described above was matched to control for injury severity; however, blood transfusion requirement (a surrogate for injury severity) was retained as significant variable in the multivariate analysis. Therefore, a third matching criterion of blood volume was added in a supplementary analysis comprised of 59 IFI cases (89 IFI wounds) and 78 controls (152 non-IFI extremity wounds; Supplemental Table 3). Extremity wound characteristics and microbiology were comparable to the above case-control analysis. The results of the multivariate analysis were also similar to the analysis described above, except that admitting unit at LRMC, blood product transfusion volume of 10–20 units, and above knee amputations were not associated with a reduced time to wound closure. Due to the similarities of the results, the matching in the case-control analysis appears to be sufficient.

DISCUSSION

Infectious complications, such as IFIs, represent a major challenge in the management of severe, combat-related extremity injuries or similar devastating civilian trauma. Substantial residual limb shortening and functional level loss have been frequently observed by clinicians due to serial, aggressive debridements required to obtain persistently viable wound margins. In an effort to provide quantification of these anecdotal data, we evaluated orthopedic outcomes among a cohort of combat casualties diagnosed with IFIs and analyzed risk factors for an impact on the duration from injury to initial wound closure in a case-control analysis. Prior studies have briefly discussed debridements and surgical amputation procedures related to IFI complications[15–17]; however, to the best of our knowledge, this is

the first analysis to provide data on a per wound level related to outcomes (e.g., amputation functional level losses) and time to wound closure. The results of our evaluation confirm that IFI complications among wounded military personnel adversely impact wound management and patient prognosis. Overall, our analysis provides the largest case-control series related to orthopedic outcomes among severely injured patients with IFIs.

Statistical differences related to clinical and orthopedic outcomes between IFI case and non-IFI control wounds confirm the adverse impact that fungal infections have on wound management. Specifically, the number of days and operative procedures required to wound closure were significantly different. In addition, results of the risk factor analysis indicate that patients who develop an IFI are 2.4 times more likely to experience a longer duration to wound closure. Furthermore, IFI cases more frequently experienced amputation revisions with over a third requiring revision to a more proximal amputation level. A likely explanation for the necessity of multiple aggressive surgical procedures is that they are required to address the recurring and progressive necrosis associated with IFI. The low rate of free and rotational flaps to help preserve functional levels in both groups is notable, which can be attributed to the continued concern for infection and limited indications for free tissue transfer following amputations, as well as the multiple extremity involvement in these patients limiting acceptable donor sites.

Following wound closure, IFI extremities had a high early complication rate, with 38% requiring a return to the operating room prior to initial discharge for reasons of drainage or infections alone, and 50% requiring return for all indications. These early complications are undoubtedly related to the complexity of IFI wounds as more than half also developed a bacterial SSTI with the infecting organism frequently identified as multidrug-resistant. Furthermore, SSTIs not only complicated IFI case wounds, but were also independent risk factors impacting time to wound closure. The occurrence of bacterial co-infections is not unexpected as injuries sustained by military personnel in our analysis were primarily via a blast mechanism while on foot patrol. This injury mechanism/circumstance frequently results in large penetrating wounds that are not only contaminated with environmental debris potentially containing multiple molds, but may also be exposed to bacterial organisms, including MDROs, through healthcare-associated acquisition. Wound complexity has also been reported among civilian trauma-related IFI cases. In particular, concurrent bacterial growth of incident IFI wounds was observed among 77% of the IFI patients following the Joplin tornado disaster.[1]

As combat care continues to evolve, previously fatal injuries have become progressively more survivable through new resuscitation techniques and improved support facilities within combat zones.[11,23,28,29] These advances have been repeatedly demonstrated during the recent conflicts as mortality decreased with increasingly grievous injuries.[11,12] Correspondingly, many severely-injured personnel received massive transfusions (>20 units) of blood products within 24 hours of injury. Multiple analyses have shown that large-volume transfusions may lead to transient immunosuppression and, therefore, increase the likelihood of an otherwise immunocompetent patient to develop unexpected complications, including IFIs.[3,5,30–34] This immunosuppression leads to conversion of a prior Cierny-Mader Type A host to become a Type B host,[35] allowing for opportunistic infections. In

fact, massive blood product transfusions were determined to be an independent risk factor for developing an IFI following combat trauma in a recent case-control analysis.[18] These data further corroborate the results of our multivariate analysis, which associates large-volume blood product transfusions with delayed initial wound closure.

Ultimately, four (6%) IFI and two (1%) control patients died. While the crude mortality rate for the IFI cases was not statistically different from the control patients, it was dramatically lower than rates reported in association with trauma-related IFI in the civilian literature, which range from 11% to 38%.[1–4,6] This is likely the result of our previously healthy patient population, early initiation of antifungal treatment, topical wound therapy between surgical procedures, and radical surgical debridements per established hospital protocols and Joint Trauma System clinical practice guidelines, which dictate collection of biopsies for histopathology and fungal culture from patients deemed high-risk for IFI on the basis of injury mechanism and severity, in addition to clinical suspicion based on gross wound appearance.[17]

Despite our attempts to be diligent in case-control matching, the retrospective nature of this study is a limitation as it does not allow for conclusions to be drawn from the surgical and medical interventions utilized. This is in part due to the inability to control for all factors when comparing the two groups such as terrain or climate at time of injury, treating surgeon or final treatment facility. The results of the multivariate model will also require external validation. Nevertheless, the sample size for both the IFI case and control cohorts exceeds that of the few similar studies regarding orthopedic or wound outcomes, and we believe that our analysis and findings are valid for the population studied.

Overall, these data support prior observations that fungal infections do have an adverse impact on wound healing and patient recovery, and are the first to conclusively demonstrate that IFIs are associated with a greater need for proximal revision of amputation length or levels versus similar patients without an IFI. Furthermore, the results demonstrate that the complex nature of fungal-infected wounds (e.g., concurrent bacterial growth) also negatively affects time to wound closure. In general, there continues to be concern about the application of military combat experience data to civilian medical treatment; however, in the light of experiences following the Joplin tornado[1,36] and recent domestic terrorism in Boston (M. Kocher, personal communication), we feel that these data are more relevant than ever for improvement of both civilian and military healthcare. Further analyses should concentrate on surveillance of IFI trends and development of improved therapeutic methods. Based on our experience, we recommend a low threshold for early fungal cultures and histologic evaluation in patients with massive transfusions and contaminated multi-system or junctional injuries, early administration of both systemic and local antifungals, aggressive surgical debridements every 24–48 hours until wound and patient stabilization, and the use of topical treatments (e.g., dilute sodium hypochlorite and negative pressure wound therapy) between surgical treatments.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Demographic Characteristics and Injury Circumstances of Combat-Injured United States Service Members (2009–2011)

Characteristics	IFI Case Patients (N = 71)	Non-IFI Control Patients (N = 160)
Demographics, No. (%)		
Age, median (IQR)	23.1 (21.7, 26.2)	23.0 (21.5, 25.7)
Male	71 (100)	158 (99)
Enlisted	69 (97)	143 (89)
Marine	57 (80)	92 (57)
Army	11 (16)	59 (37)
Injury Circumstances, No. (%)		
Blast Injury	71 (100)	160 (100)
Dismounted (foot patrol)	65 (92)	126 (79)
LRMC ISS, median (IQR)	21 (18, 26)	21 (17, 24)
ISS ≥ 26, No. (%)	22 (31)	28 (17)

IFI – Invasive Fungal Infection; IQR – Interquartile Range; ISS – Injury Severity Score; LRMC – Landstuhl Regional Medical Center

Table 2

Patterns of Injuries, Trauma Characteristics, and Outcomes among Combat-Injured United States Service Members (2009–2011)

Characteristics	IFI Case Patients (N = 71)	Non-IFI Control Patients (N = 160)	p-value[1]
Amputations, No. (%)			
Lower Extremity[2]	57 (80)	129 (81)	–
Above the knee	51 (72)	95 (59)	–
Below the knee	6 (8)	34 (22)	–
Upper Extremity	11 (15)	10 (6)	0.044
Both Upper and Lower Extremity	10 (14)	7 (4)	0.044
Fractures[3], No. (%)			0.776
None	14 (20)	42 (26)	
Closed only	7 (10)	19 (12)	
Open only or both open and closed	50 (70)	99 (62)	
Shock Index, No. (%)			0.006
0 ≤ HR/SBP < 1	18 (25)	65 (41)	
1 ≤ HR/SBP < 1.5	28 (40)	72 (45)	
HR/SBP ≥ 1.5	25 (35)	22 (14)	
Blood Transfusion Requirements[4], No. (%)			<0.001
None / Missing Data	0	12 (7)	
<10 units	3 (4)	46 (29)	
10 – 20 units	21 (30)	59 (37)	
>20 units	47 (66)	43 (27)	
Admission Unit – LRMC, No. (%)			0.059
Intensive care unit (ICU)	69 (97)	136 (85)	
Ward	2 (3)	24 (15)	
Admission Unit – U.S. MTFs, No. (%)			0.015
Intensive care unit	65 (92)	120 (75)	
Ward	6 (8)	40 (25)	
Hospitalization, median days (IQR)			
LRMC ICU length of stay	2 (1, 3)	2 (1, 3)	0.027
LRMC hospitalization	3 (3, 4)	3 (2, 4)	0.323
U.S. MTF hospitalization	53 (38, 75)	39 (26, 54)	0.020
Total hospitalization	56 (41, 78)	44 (30, 58)	0.019
Deaths, No. (%)	4 (6)	2 (1)	0.135

HR – heart rate; IFI – Invasive Fungal Infection; IQR – Interquartile Range; LRMC – Landstuhl Regional Medical Center; MTFs – Military Treatment Facilities; SBP – systolic blood pressure

[1] P-value is calculated using conditional logistic regression to account for matching

[2] Due to linear dependency between the variables, no p-value was calculated

[3] Fractures, excluding digits, are limited to those identified at LRMC

[4] Blood product transfusions within the first 24 hours following injury

Table 3

Orthopedic Outcomes among Combat-Injured United States Service Members (2009–2011)[1]

Characteristics	IFI Case Wounds (N=112)	Non-IFI Control Wounds (N=315)	p-value[2]
LRMC and U.S. MTF OR visits[3]			<0.001
Visits prior to initial wound closure, median (IQR)	9 (6, 13)	6 (5, 7)	
At least 1 visit prior to initial wound closure, No. (%)	102 (91)	304 (96)	
Type of Initial Wound Closure[4]*, No. (%)*			0.011
STSG + FTSG + Integra	38 (34)	58 (18)	
DPC	60 (53)	198 (63)	
Rotational flap	4 (4)	6 (2)	
Free flap	5 (4)	8 (3)	
Time from injury to wound closure, median days (IQR)[5]	16 (11, 23)	9 (7, 13)	<0.001
Number of U.S. MTF OR visits, median (IQR)	6 (4, 9)	3 (2, 4)	<0.001
Loss of femur length, mean cm	5.55	3.07	0.109
Change of amputation level[6], No. (%)	38 (34)	40 (13)	<0.001
Revision from TFA at LRMC to high-level amputation at U.S. MTF[7], No. (%)	9 (15)	4 (3)	0.006
Complications Requiring Return to OR, No. (%)			
Drainage	12 (11)	9 (3)	0.996
Superficial wound infection	18 (16)	17 (5)	0.227
Deep wound infection	13 (12)	20 (6)	0.285
Bony prominence	1 (1)	1 (0.3)	NA
Skin graft[8]	3 (3)	6 (2)	0.229
Tight closure and other breakdown	4 (4)	9 (3)	0.284
Heterotopic ossification	5 (4)	2 (1)	0.995

DPC – delayed primary closure; FTSG – full-thickness skin graft; IFI – invasive fungal infection; IQR – Interquartile Range; LRMC – Landstuhl Regional Medical Center; MTF – military treatment facility; NA – not applicable; OR – operating room; STSG – split-thickness skin graft; TFA – transfemoral amputation

[1] Data are on a per wound basis

[2] P-value is calculated using conditional logistic regression to account for matching

[3] Not all wounds required operations and some patients transferred to other facilities so their total number of operating room visits is unknown; therefore, variable does not include 10 IFI case wounds and 11 non-IFI control wounds

[4] Type of closure data are missing for 5 IFI case wounds and 45 control wounds

[5] Time to wound closure data missing for two IFI cases and four controls

[6] Includes both a change from a traumatic amputation to a higher level following surgical procedures or a patient who did not sustain a traumatic amputation requiring a surgical amputation procedure

[7] Denominator is different for TFA (cases=62, controls=132); high-level amputation is defined by either a hemipelvectomy or hip disarticulation

[8] Complications from skin grafts generally resulted from the failure of portions of the graft to survive requiring a repeat of the procedure

Table 4

Analysis of Potential Factors Associated with a Shorter Time to Initial Wound Closure among Combat-Wounded (2009–2011)[1]

Potential Factors	Univariate Hazard Ratio (95% CI)	Multivariate Hazard Ratio (95% CI)
Fungal Infection		
Nonfungal wound	2.36 (1.87, 2.99)	1.53 (1.17, 2.01)
Fungal wound	Reference	Reference
Above the knee amputation[2]		
No	1.19 (0.97, 1.46)	0.66 (0.49, 0.89)
Yes	Reference	Reference
Blood product transfusions units in 1st 24 hours		
<10 units / missing data	3.16 (2.42, 4.14)	2.63 (1.81, 3.82)
10–20 units	1.70 (1.35, 2.32)	1.44 (1.10, 1.87)
>20 units	Reference	Reference
Admission unit – LRMC		
Ward	2.59 (1.87, 3.59)	1.53 (1.01, 2.31)
Intensive care unit	Reference	Reference
SSTI linked to bacterial organism[3]		
No	2.68 (2.11, 3.41)	–
Yes	Reference	–
SSTI linked to MDRO		
No SSTI	3.75 (2.69, 5.23)	2.89 (2.02, 4.11)
SSTI not linked to MDRO	1.96 (1.31, 2.94)	1.92 (1.27, 2.90)
SSTI linked to MDRO	Reference	Reference
>1 SSTI between injury and initial wound closure date		
No	2.62 (1.52, 4.52)	–
Yes	Reference	–

CI – confidence interval; LRMC – Landstuhl Regional Medical Center; MDRO – multidrug-resistant organism; SSTI – skin and soft-tissue infection

[1] Hazard ratio greater than one indicates a beneficial outcome; missing data for relevant variables were not included in the models

[2] Includes through the knee amputations

[3] The factors of SSTI linked to bacterial organisms and SSTI linked to MDROs were highly correlated (chi-square $p<0.001$). Factor of SSTI linked to MDRO was found to have a better fit in the final model