Early Infections Complicating the Care of Combat Casualties from Iraq and Afghanistan

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Abstract

Background: During the conflicts in Iraq and Afghanistan, more than 52,000 U.S. military members were wounded in action. The battlefield mortality rate was lower than in past conflicts, however, those surviving often had complex soft tissue and bone injuries requiring multiple surgeries. This report describes the rates, types, and risks of infections complicating the care of combat casualties.

Patients and Methods: Infection and microbiology data obtained from the Trauma Infectious Disease Outcomes Study (TIDOS), a prospective observational study of infections complicating deployment-related injuries, were used to determine the proportion of infection, types, and associated organisms. Injury and surgical information were collected from the Department of Defense Trauma Registry. Multivariable Cox proportional hazards and logistic regression models were used to evaluate potential factors associated with infection.

Results: From 2009–2012, 1,807 combat casualties were evacuated to U.S. TIDOS-participating hospitals. Among the 1,807 patients, the proportion of overall infections from time of injury through initial U.S. hospitalization was 34% with half being skin, soft tissue, or bone infections. Infected wounds most commonly grew *Enterococcus faecium*, *Pseudomonas aeruginosa*, *Acinetobacter* spp. or *Escherichia coli*. In the multivariable model, amputation, blood transfusions, intensive care unit admission, injury severity scores, mechanical ventilation, and mechanism of injury were associated with risk of infection.

Conclusions: One-third of combat casualties from Iraq and Afghanistan develop infections during their initial hospitalization. Amputations, blood transfusions, and overall injury severity are associated with risk of infection, whereas more easily modifiable factors such as early operative intervention or antibiotic administration are not.

Keywords: combat trauma; military health; trauma-related infections; wound infections

INFECTIONS are a known complication of battlefield injuries that can lead to substantial morbidity and mortality [1–3]. During World War I, there was a 5% incidence of gas gangrene with a 28% mortality rate. With the advent of antibiotic agents and decreasing time from injury to definitive surgical care, incidence and mortality decreased to 0.3%–1.5% and 15% in World War II, respectively [4,5]. Although management of combat casualties continued to advance during the Vietnam War, sepsis was still the third leading cause of death [6].

More than 52,000 U.S. military personnel were wounded in action in Iraq (Operation Iraqi Freedom [OIF]) and Afghanistan (Operation Enduring Freedom [OEF]) [7]. Deployment of forward surgical assets, utilization of tourniquets, rapid evacuation, and use of improved body armor resulted in a greater percentage of combat casualties surviving their initial injuries compared with past conflicts [8–10]. Reduced mortality rate, however, is coupled with major challenges in subsequent care because of massive

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blood loss, soft tissue and bone injuries, and extensive wound contamination requiring frequent surgeries.

Previous studies have examined the rate and types of infections complicating combat injuries during OIF/OEF. In 2003, 211 combat casualties cared for on the U.S. Naval Ship *Comfort* were evaluated for evidence of infection and the resulting rate was 27% with the majority being wound infections (84%) followed by blood stream infections (38%). *Acinetobacter* spp. were the most commonly grown isolate associated with infection followed by *Escherichia coli* and *Pseudomonas* spp. Infection risk factors included wound type, mechanism of injury, injury severity score, delay in time from injury to ship arrival, and having an external fixator device [11]. In a limited trauma registry analysis of 720 combat casualties with traumatic amputations (99% the result of improvised explosive devices [IEDs]), 17% developed wound infections and the proportion of infections increased with the number of amputations (15%–18% with single and double amputations to 25%–67% with triple and quadruple amputations). Moreover, 11% of the infections were associated with *Acinetobacter* spp. [12]. Another investigation documented a significant increase in rates of *Acinetobacter* infections after the start of OIF compared to historical trends [13].

Although these studies provide some information on the types of infections observed in patients injured during OIF/OEF, they were single site or limited trauma registry studies conducted over short periods of time without following patients through different levels of care. The Trauma Infectious Diseases Outcomes Study (TIDOS) was initiated in 2009 to prospectively collect standardized infection data from point of injury in Iraq or Afghanistan through Landstuhl Regional Medical Center (LRMC), a U.S.-run medical center in Germany where all combat casualties transit through for stabilization before returning to the United States, and during initial hospitalization at TIDOS-participating U.S. hospitals. This report describes the proportion of patients with infections, types of infections, associated organisms, and risk factors for infection in combat casualties followed in TIDOS from 2009–2012.

Patients and Methods

TIDOS study design

The Trauma Infectious Diseases Outcomes Study is an observational study of short- and long-term infectious disease complications of deployment-related traumatic injuries [14]. In addition, TIDOS serves as the infectious disease (ID) module of the Department of Defense Trauma Registry (DoDTR) [15]. Eligibility criteria include: age 18 years or older with injury during deployment to Iraq or Afghanistan requiring evacuation to LRMC for care. Trauma Infectious Diseases Outcomes Study-participating hospitals in the United States include: San Antonio Military Medical Center (San Antonio, TX); Walter Reed Army Medical Center (Washington, D.C.); and National Naval Medical Center (Bethesda, MD). The latter two merged in 2011, creating Walter Reed National Military Medical Center (Bethesda, MD). Standardized information collected from injury through hospitalization at U.S. facilities includes: laboratory values; vital signs; evidence of infection; microbiology; antibiotic administration; and operating room visits. Patient trauma history, injury severity score (ISS; e.g., anatomic classifications of injury severity [16]), and surgical history were obtained from

the DoDTR. For this study, all patients with combat-related injuries admitted to LRMC between June 1, 2009, which was the start of TIDOS, and May 31, 2012 were included.

Infections were classified using a combination of clinical findings, laboratory and other test results, and applying a priori standardized definitions from the National Healthcare Safety Network [17], as described previously [14]. In addition, a physician's diagnosis plus directed antibiotic therapy (5 days or more for skin and soft tissue infections [SSTIs] and 21 days or more for osteomyelitis unless surgical cure performed with amputation) without an alternative diagnosis was also considered an infection. Microbiologic evaluation was performed at the discretion of the clinical team and was not dictated by TIDOS. Antibiotic susceptibility was determined by each institution's clinical microbiology laboratory. Organisms were classified as multi-drug–resistant (MDR) if they were resistant to 3 or more classes of antibiotic agents (aminoglycosides, β-lactams, carbapenems, and fluoroquinolones) or if they expressed extended-spectrum β-lactamases or carbapenemases. Methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant *Enterococcus* were also considered MDR.

Statistical analysis

Differences between subjects transferred to TIDOS-participating and non-participating U.S. sites were compared using χ^2 testing for categorical indicators and two sample t-test (or non-parametric testing) for continuous characteristics to examine demographic, traumatic injury, early clinical- and hospitalization-related characteristics. Among patients transferred to participating U.S. sites, patients who experienced any infection were compared with those without infection. Demographics, injury cause and type, early clinical- and hospitalization-related characteristics were considered as potential risk factors and examined through the univariable and multivariable regression models. Covariates with $p \le 0.2$ from the univariable model were considered in the initial full multivariable models. Time-to-event modeling using Cox proportional hazards models were used to examine the relation of potential risk factors from the time of injury to first infection. Covariates that might be confounding were examined for interactions (e.g., amputation, shock index, first 24-hour blood transfusion, and ISS).

Logistic regression analyses were performed by defining the infection as a binary outcome variable (1 or more infection versus no infection) and examining only risk factors present prior to transferring to U.S. hospitals. Stepwise, backward, and forward model selections were conducted to choose the final multivariable model. All variables in the final model meet the criteria of being significant at $p < 0.05$.

Results

Study population

During the study period, 3,304 patients were admitted to LRMC with combat-related injuries. Of those patients, 55% transferred to TIDOS-participating U.S. hospitals, 41% went to other hospitals in the United States, 4% returned to duty, and 1% died at LRMC. Overall, the combat casualties were mostly young, male, enlisted members injured in Afghanistan with two-thirds being in the Army (Table 1). More than half of those admitted to LRMC were injured from IEDs and

TABLE 1. CHARACTERISTICS OF WOUNDED MILITARY PERSONNEL ADMITTED TO LANDSTUHL REGIONAL MEDICAL CENTER BETWEEN JUNE 2009 AND MAY 2012 BY DISPOSITION[a]

	Total (n=3,304)	Return to duty (n=121)	Died at LRMC (n=34)	Transferred to TIDOS-participating sites (n=1,807)	Transferred to non-participating sites (n=1,342)	p[b]
Operational theater, No. (%)						0.009
Operation Iraqi Freedom (OIF)	200 (6.1)	6 (5.0)	2 (5.9)	93 (5.1)	99 (7.4)	
Operation Enduring Freedom (OEF)	3,027 (91.6)	113 (93.4)	32 (94.1)	1,677 (92.9)	1,205 (89.8)	
Non-OIF/OEF deployment[c]	76 (2.3)	2 (1.7)	0	36 (2.0)	38 (2.8)	
Missing	1	0	0	1	0	
Male	3,253 (98.5)	115 (95.0)	34 (100)	1,784 (98.7)	1,320 (98.4)	0.392
Median age at time of injury (IQR)	24.4 (21.9–28.3)	26.3 (22.7–32.0)	23.5 (21.9–28.7)	24.2 (21.8–28.1)	24.6 (22.0–28.1)	0.377
Branch of service, No. (%)						<0.0001
Army	2,167 (66.7)	98 (84.5)	22 (66.7)	1,100 (61.8)	947 (71.7)	
Marine	897 (27.6)	11 (9.5)	11 (33.3)	566 (31.8)	309 (23.4)	
Air Force	74 (2.3)	3 (2.6)	0	45 (2.5)	26 (2.0)	
Navy	92 (2.8)	1 (0.9)	0	57 (3.2)	34 (2.6)	
Other	18 (0.6)	3 (2.6)	0	11 (0.6)	4 (0.3)	
Missing	53	5	1	27	20	
Military Rank, No. (%)						0.007
Enlisted	2,994 (93.1)	97 (82.9)	33 (100)	1,615 (92.5)	1,249 (94.7)	
Warrant/Officer	201 (6.3)	13 (11.1)	0	121 (6.9)	67 (5.1)	
Civilian	20 (0.6)	7 (6.0)	0	10 (0.6)	3 (0.2)	
Missing	89	4	1	61	23	
Mechanism of injury, No. (%)						<0.0001
Blast alone	2,307 (69.8)	82 (67.8)	21 (61.8)	1,379 (76.3)	825 (61.5)	
IED	1,803 (54.6)	62 (51.2)	17 (50.0)	1,116 (61.8)	608 (45.3)	
Non-IED blast[d]	504 (15.3)	20 (16.5)	4 (11.8)	263 (14.6)	217 (16.2)	
Non-blast	997 (30.2)	39 (32.2)	13 (38.2)	428 (23.7)	517 (38.5)	
Traumatic Amputations, No. (%)[e]						<0.0001
Any distal amputation	189 (5.7)	1 (0.8)	1 (2.9)	167 (9.3)	20 (1.5)	
Any proximal amputation	267 (8.1)	0	9 (26.5)	243 (13.5)	15 (1.1)	
No amputation or digit only amputation	2,845 (86.2)	119 (99.2)	24 (70.6)	1,395 (77.3)	1,307 (97.4)	
Missing	3	1	0	2	0	
Fractures, No. (%)[f]						<0.0001
Closed	1,032 (31.2)	49 (40.5)	10 (29.4)	534 (29.6)	439 (32.7)	
Open only/both open and closed	1,241 (37.6)	16 (13.2)	19 (55.9)	787 (43.6)	419 (31.2)	
Abbreviated Injury Scale Upper Extremity Maximum severity, No. (%)[g]						<0.0001
None	1,508 (45.6)	70 (57.9)	20 (58.8)	739 (40.9)	679 (50.6)	
1	923 (27.9)	37 (30.6)	6 (17.6)	518 (28.7)	362 (27.0)	
2	585 (17.7)	10 (8.3)	3 (8.8)	352 (19.5)	220 (16.4)	
3	225 (6.8)	4 (3.3)	2 (5.9)	144 (8.0)	75 (5.6)	
4	59 (1.8)	0	3 (8.8)	51 (2.8)	5 (0.4)	
5	4 (0.1)	0	0	3 (0.2)	1 (0.1)	

(continued)

TABLE 1. (CONTINUED)

	Total (n=3,304)	Return to duty (n=121)	Died at LRMC (n=34)	Transferred to TIDOS-participating sites (n=1,807)	Transferred to non-participating sites (n=1,342)	p[b]
Abbreviated Injury Scale Lower Extremity Maximum Severity, No. (%)[g]						<0.0001
None	970 (29.4)	43 (35.5)	15 (44.1)	456 (25.2)	456 (34.0)	
1	747 (22.6)	43 (35.5)	4 (11.8)	327 (18.1)	373 (27.8)	
2	595 (18.0)	23 (19.0)	2 (5.9)	271 (15.0)	299 (22.3)	
3	447 (13.5)	11 (9.1)	1 (2.9)	279 (15.4)	156 (11.6)	
4	263 (8.0)	1 (0.8)	1 (2.9)	219 (12.1)	42 (3.1)	
5	282 (8.5)	0	11 (32.4)	255 (14.1)	16 (1.2)	
Injury Severity Score, No. (%)[h]						<0.0001
0–9 (mild)	1,718 (52.1)	89 (74.2)	0	635 (35.2)	994 (74.1)	
10–15 (moderate)	690 (20.9)	22 (18.3)	2 (5.9)	426 (23.6)	240 (17.9)	
16–24 (severe)	565 (17.1)	6 (5.0)	5 (14.7)	477 (26.4)	77 (5.7)	
≥ 25 (life-threatening)	329 (10.0)	3 (2.5)	27 (79.4)	268 (14.8)	31 (2.3)	
Missing	2	1	0	1	0	
Shock index,[i] median (IQR)	0.7 (0.5–0.8)	0.6 (0.5–0.7)	0.8 (0.7–1.0)	0.7 (0.6–0.8)	0.6 (0.5–0.7)	<0.0001
Blood product transfusions within first 24 hours, No. (%)[j]						<0.0001
Zero or missing units	2,229 (67.5)	116 (95.9)	8 (23.5)	923 (51.1)	1,182 (88.1)	
1–9 units	613 (18.6)	4 (3.3)	8 (23.5)	473 (26.2)	128 (9.5)	
10–20 units	252 (7.6)	1 (0.8)	7 (20.6)	228 (12.6)	16 (1.2)	
> 20 units	210 (6.4)	0	11 (32.4)	183 (10.1)	16 (1.2)	
LRMC admission unit, No. (%)						<0.0001
Intensive care unit	1,117 (33.9)	8 (6.8)	33 (97.1)	954 (52.9)	122 (9.1)	
Ward	2,176 (66.1)	110 (93.2)	1 (2.9)	849 (47.1)	1,216 (90.9)	
Missing	11	3	0	4	4	
Mechanical ventilation at LRMC, No. (%)[k]	741 (22.4)	2 (1.7)	34 (100)	651 (36.0)	54 (4.0)	<0.0001

[a] Data are missing for some variables. Percentages are calculated excluding the missing data from the denominator.
[b] p value compares data from the TIDOS-participating sites to the non-participating sites. Missing values are not included in p value calculation.
[c] Non-OIF/OEF deployment includes Operation New Dawn, which began in Iraq on September 1, 2010 and continued until the end of military operations in Iraq on December 15, 2011.
[d] Non-blast mechanisms include burns, gunshot wounds, motor vehicle crashes, and falls.
[e] Amputation data collected from LRMC. Distal amputations include below the knee or below the elbow. Proximal amputations include through the knee, above the knee, or above the elbow. Digit only amputations are excluded from the distal and proximal categories.
[f] Digit-only fractures are not included. Fracture data obtained from LRMC.
[g] The Abbreviated Injury Scale is an anatomically based severity scoring system that classifies traumatic injuries by body region using an ascending scale of injury severity (0=none; 5=critical injury) [16].
[h] The Injury Severity Score is an overall measure calculated for each patient based on the top three maximum Abbreviated Injury Scale anatomic region values [44].
[i] Shock index is defined as the heart rate divided by systolic blood pressure. It was documented at the initial support hospital following injury.
[j] Blood transfusion data are missing for 2,116 patients. Missing blood transfusion data are not randomly distributed. Patients with missing blood data are characterized by lower injury severity scores and shock indices. In addition, the majority of patients with missing blood data did not sustain a traumatic amputation and were not admitted to the LRMC intensive care unit.
[k] Mechanical ventilation data missing three patients who transferred to a TIDOS-participating site and one at a non-participating site

IED=improvised explosive device; IQR=interquartile range; LRMC=Landstuhl Regional Medical Center; TIDOS=Trauma Infectious Disease Outcomes Study.

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approximately 14% suffered at least one traumatic amputation and 69% at least one bone fracture. The ISS indicated that 17% and 10% of patients sustained severe and life-threatening injuries, respectively. In the first 24 hours post-injury, 14% received at least 10 units of red blood cells.

Patients transferred to a TIDOS-participating hospital had a higher proportion of injuries because of IED blasts in Afghanistan, any amputation, an ISS greater than 10, and a greater number of blood transfusions in the first 24 hours in those who went on to non-TIDOS–participating hospitals (Table 1).

Proportion of infections, types, and associated organisms

The median number of days between injury and arrival at LRMC was 2.0 (interquartile range [IQR]: 2.0–3.0) and the duration of hospitalization at LRMC was 2.0 (IQR: 1.0–3.0) days. The overall infection rate at LRMC for all patients with combat-related injuries was 6.4% (Fig. 1). Among the 1,807 patients who transferred to TIDOS-participating U.S. sites, 9.9% at LRMC were diagnosed with any infection. The median duration of hospitalization at TIDOS-participating U.S. sites was 18.0 (IQR: 9.0–36.0) days and the overall infection rate was 30.7%. At both LRMC and the TIDOS-participating U.S. sites, infections were more common in patients with amputations as well as those admitted to the intensive care unit (ICU). Including infections at both LRMC and the U.S., 34% of patients who went to a TIDOS-participating U.S. site had at least one infection. Of those patients with infections, more than half had more than one infection (24% had two infections, 14% had three infections, and 19% had four or more infections). The infection incidence density rate (first infection/100-person days, 95% confidence interval) was 1.9 (1.7–2.0).

Among the patients transferred to TIDOS-participating U.S. sites, there were a total of 1,514 infections in theater, LRMC, and the United States, of which 45% were SSTIs, 15% pneumonia, 15% blood stream infections, and 8% osteomyelitis (Fig. 2A). Central nervous system infections and

sepsis not linked to another infection type were uncommon. On a patient level, of the 1,807 patients, 20% developed a SSTI during their initial hospitalization, 12% developed pneumonia, 10% a blood stream infection, and 6% osteomyelitis (Fig. 2B). Time to first infection varied by infection type (Fig. 2A). Table 2 presents the microbiologic profile associated with SSTI, osteomyelitis, and blood stream infections and the percentage of organisms that were MDR. Although the majority of the *Acinetobacter* spp. and *Escherichia coli* isolates were MDR, the opposite was true of *Pseudomonas aeruginosa* and *Enterococcus faecium*.

Infection risk factors

The Cox model was used to examine unadjusted and adjusted association of time to infection with potential risk factors among patients with combat injuries who were transferred to TIDOS-participating U.S. sites (Table 3). In the multivariable model, amputation (both distal and proximal), blood transfusions in the first 24 hours post-injury, LRMC ICU admission, severe or life-threatening ISS, and mechanical ventilation were associated with increased risk of infection (Table 3). In addition, non-IED blasts were associated with lower infection risk compared with those with non-blast injuries. The risk factor analysis was repeated using logistic regression to evaluate for risk factors associated with any infection and the results were similar (data not shown).

Discussion

The Trauma Infectious Diseases Outcomes Study is the first study to evaluate comprehensively combat trauma infection rates, types, and risks by collecting standardized data from across multiple levels of care from the combat theater to the United States. One-third of combat casualties treated at TIDOS-participating U.S. sites develop infections during their initial hospitalization with more than half being SSTI or bone infections. Among those with amputations, two-thirds develop infections. The most common organisms cultured from infected wounds include *Enterococcus faecium*, *Pseudomonas aeruginosa*, MDR *Acinetobacter* spp.,
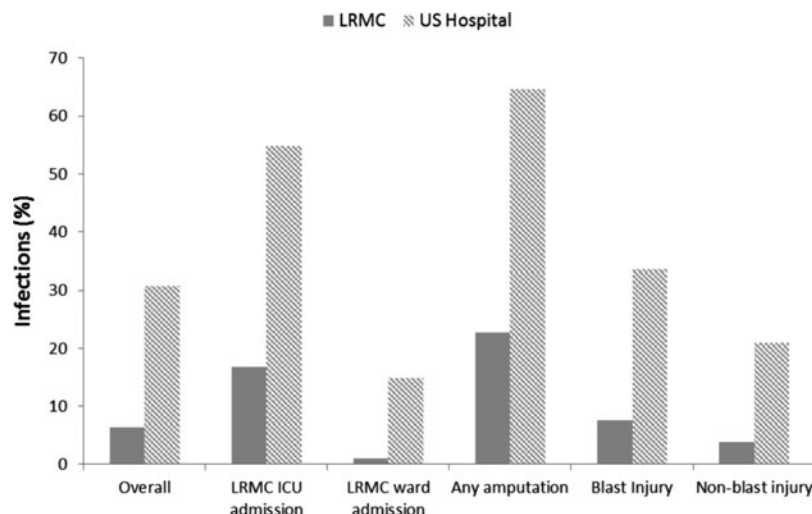

FIG. 1. Proportion of infections by facility (i.e., Landstuhl Regional Medical Center [LRMC] or a participating hospital in the United States) at the time of diagnosis. ICU = intensive care unit.
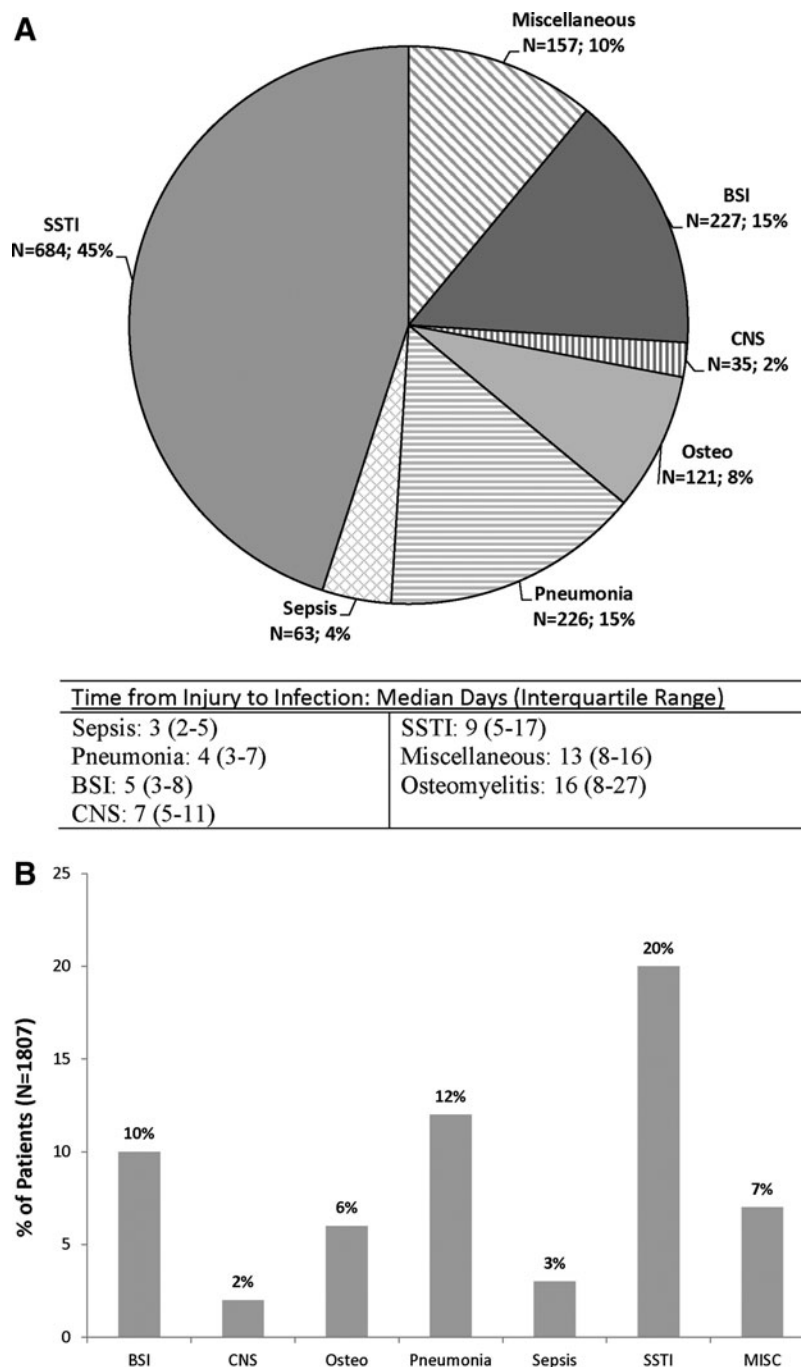
A

Miscellaneous
N=157; 10%

BSI
N=227; 15%

CNS
N=35; 2%

Osteo
N=121; 8%

Pneumonia
N=226; 15%

Sepsis
N=63; 4%

SSTI
N=684; 45%

Time from Injury to Infection: Median Days (Interquartile Range)	
Sepsis: 3 (2-5)	SSTI: 9 (5-17)
Pneumonia: 4 (3-7)	Miscellaneous: 13 (8-16)
BSI: 5 (3-8)	Osteomyelitis: 16 (8-27)
CNS: 7 (5-11)	

B

% of Patients (N=1807)

BSI 10%; CNS 2%; Osteo 6%; Pneumonia 12%; Sepsis 3%; SSTI 20%; MISC 7%

FIG. 2. Distribution of types of infections from the inpatient period at participating sites in the United States. (**A**) Data are on a per infection basis. Miscellaneous infections are urinary tract infections (5.7%), intra-abdominal infections (2.3%), *Clostridium difficile* (1.0%), sinusitis (0.6%), bronchitis (0.3%), eye infections (0.1%), and otitis (0.1%). Percentages are calculated based upon the total number of infections during the inpatient period (n = 1,514). (**B**) Data are on a per subject basis. Percentages are calculated based upon the total number of patients admitted to participating sites in the United Sates (n = 1,807). BSI = blood stream infection; CNS = central nervous system; MISC = miscellaneous; Osteo = osteomyelitis; SSTI = skin and soft-tissue infection.

and ESBL-producing *Escherichia coli*. Risk factors for developing infection include having a traumatic amputation, receiving blood transfusions within 24 hours of injury (particularly if more than 10 units), ICU admission, early mechanical ventilation, and having a moderate to severe ISS. Less risk of infection was associated with the non-IED injury mechanism relative to other blast trauma.

It is difficult to compare the rate of infection during OIF/OEF with that of other conflicts because past conflicts have not had similar registries that were able to follow patients from the battlefield through initial hospitalization in the United States. For example, a study evaluating 17,726 casualties from the Vietnam War found an overall infection rate of 3.9% [2]. This study, however, only evaluated patients

TABLE 2. MICROBIOLOGIC PROFILE OF COMMON TRAUMA-RELATED INFECTIONS[a]

Organism	Percentage of total organisms per infection syndrome	Percentage classified as multidrug-resistant
Blood stream infection organisms (n=313)		
Gram-positive bacteria	47.6	6.7
Coagulase-negative *Staphylococcus*	33.2	0
Enterococcus faecium	6.1	26.3
Gram-negative bacteria	41.5	42.3
Acinetobacter calcoaceticus baumannii complex	9.0	92.9
Escherichia coli	7.0	90.9
Pseudomonas aeruginosa	6.7	4.8
Anaerobes	3.2	0
Osteomyelitis organisms (n=263)		
Gram-positive bacteria	23.2	21.3
Enterococcus faecium	8.0	23.8
Coagulase-negative *Staphylococcus*	5.7	0
Gram-negative bacteria	46.8	47.2
Acinetobacter calcoaceticus baumannii complex	11.0	86.2
Pseudomonas aeruginosa	10.3	18.5
Escherichia coli	8.8	78.3
Enterobacter cloacae	6.1	12.5
Anaerobes	12.5	0
Skin and soft-tissue infection organisms (n=1,341)		
Gram-positive bacteria	26.9	13.9
Enterococcus faecium	9.9	17.3
Gram-negative bacteria	46.5	41.8
Pseudomonas aeruginosa	9.6	10.2
Escherichia coli	9.6	73.4
Acinetobacter calcoaceticus baumannii complex	8.7	94.8
Enterobacter cloacae	6.3	1.2
Anaerobes	7.6	0

[a]Includes organisms contributing ≥5% to the microbiologic profile; organisms were detected in cultures but may not be the etiologic agent for the infection.

during their hospitalization in Vietnam (mean duration: 9 days) with more than one-third evacuated from Vietnam in less than 5 days and almost three-quarters in less than 15 days. In our analysis, SSTIs and osteomyelitis accounted for more than half of the infections and these did not occur until a median of 9–16 days post-injury. Therefore, the infection rate reported in the Vietnam study is not comparable to the one in our study. The 34% infection rate observed in the current analysis, however, is higher than the 8%–9% infection rate associated with non-combat trauma [18–20] and the 4% reported overall U.S. hospital-acquired infection rate [21].

An earlier analysis of TIDOS data that included only three months of data collection (June 2009 to August 2009) found an infection rate of 27% among those transferred from LRMC to U.S. TIDOS-participating sites [14], which is similar to the rate observed in the current three-year analysis. This is in contrast to an analysis that used the DoDTR to investigate infection rates in deployment-injured patients from March 2003 to April 2009 and found an overall infection rate of 5.5% [22]. The latter evaluation pre-dated the TIDOS ID module of the DoDTR in which there were limited infection-related outcomes data captured. Given the risk factors associated with infection, the combat-related injuries are likely to have higher rates of infection.

Organisms cultured from infected sites in patients injured in OIF/OEF are similar to ones observed in patients injured in

Vietnam. A study of 30 U.S. Marines injured in Vietnam found that on admission wounds initially grew gram-positive skin flora along with *Enterobacter*, *Escherichia coli*, *Klebsiella pneumoniae*, and members of what was called the Mimaea-*Herellea-Bacterium-Alcaligenes* group (may have included *Acinetobacter* spp.) [23]. By the fifth hospital day, wound bacteriology changed with increased isolation of *Pseudomonas aeruginosa* and *Proteus*. All of the gram-negative bacteria were resistant to penicillin, the antibiotic agent given to the combat casualties. The wounds in that study were not necessarily infected, but rather sampled to understand the bacteriology of war wounds over time [23]. Likewise, a study of 100 Vietnam casualties found that the most common bacterial species isolated from war wounds requiring amputation included *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Proteus,* and *Klebsiella* [24].

Although the types of organisms are similar to those that have been observed in the past, the antibiotic resistance patterns are different and are becoming more resistant over time [25,26]. Approximately 95% of the *Acinetobacter* spp. isolated from wounds was MDR and 75% of the *Escherichia coli* isolates produced ESBLs. Several previous studies have investigated the potential sources of these MDR bacteria. Studies of healthy service members in the United States have not demonstrated significant colonization with MDR *Acinetobacter* prior to deployment [27,28], however, one study showed an 11% prevalence of MDR *Escherichia*

TABLE 3. ANALYSIS OF RISK FACTORS FOR THE DEVELOPMENT OF INFECTIONS AMONG MILITARY PERSONNEL WITH COMBAT-RELATED INJURIES

Risk factor	Total (n=1,807); No. (% of total)	Patients with ≥1 infection (n=612); No. (% of row)	Patients with no infection (n=1,195); No. (% of row)	Unadjusted hazard ratio (95% CI)	Adjusted hazard ratio (95% CI)
Operational theater					
Operation Iraqi Freedom	93 (5.1)	31 (33.3)	62 (66.7)	1.0	—
Operation Enduring Freedom	1,677 (92.9)	573 (34.2)	1,104 (65.8)	1.10 (0.77– 1.59)	—
Non-OIF/OEF deployment	36 (2.0)	8 (22.2)	28 (77.8)	0.72 (0.33– 1.58)	—
Gender					
Female	23 (1.3)	4 (17.4)	19 (82.6)	1.0	—
Male	1,784 (98.7)	608 (34.1)	1,176 (65.9)	2.15 (0.81– 5.76)	—
Branch of service					
Army	1,100 (60.9)	348 (31.6)	752 (68.4)	1.0	—
Marine	566 (31.3)	224 (39.6)	342 (60.4)	1.31 (1.10– 1.54)	—
Air Force	45 (2.5)	12 (26.7)	33 (73.3)	0.72 (0.41– 1.29)	—
Navy	57 (3.2)	17 (29.8)	40 (70.2)	1.01 (0.62– 1.65)	—
Other	39 (2.2)	11 (28.2)	28 (71.8)	0.96 (0.53– 1.75)	—
Military rank					
Enlisted	1,637 (93.0)	548 (33.5)	1,089 (66.5)	1.0	—
Warrant / Officer	123 (7.0)	45 (36.6)	78 (63.4)	0.99 (0.73– 1.34)	—
Civilian / Missing	47	19	28	NA	—
Mechanism of injury					
Non-blast	428 (23.7)	102 (23.8)	326 (76.2)	1.0	1.0
IED	1,116 (61.8)	461 (41.3)	655 (58.7)	1.80 (1.45– 2.23)	1.07 (0.84–1.35)
Non-IED blast	263 (14.6)	49 (18.6)	214 (81.4)	0.73 (0.52– 1.03)	0.69 (0.49–0.97)
Traumatic Amputations[a]					
No amputation or digits only amputation	1,395 (77.3)	332 (23.8)	1,063 (76.2)	1.0	1.0
Any distal amputation excluding digits	169 (9.4)	90 (53.3)	79 (46.7)	2.09 (1.66– 2.64)	1.46 (1.11–1.92)
Any proximal amputation excluding digits	241 (13.4)	190 (78.8)	51 (21.2)	4.67 (3.90– 5.59)	1.57 (1.23–2.01)
Any fracture, excluding digits[b]					
None	441 (24.4)	91 (20.6)	350 (79.4)	1.0	—
Closed only	435 (24.1)	121 (27.8)	314 (72.2)	1.36 (1.04– 1.79)	—
Open +/- closed	931 (51.5)	400 (43.0)	531 (57.0)	2.01 (1.60– 2.53)	—
Abbreviated Injury Scale Upper Extremity Maximum Severity[c]					
0 (none)	739 (40.9)	189 (25.6)	550 (74.4)	1.0	—
1	518 (28.7)	164 (31.7)	354 (68.3)	1.29 (1.05– 1.59)	—
2	352 (19.5)	167 (47.4)	185 (52.6)	1.97 (1.60– 2.42)	—
3	144 (8.0)	60 (41.7)	84 (58.3)	1.68 (1.26– 2.25)	—
4	51 (2.8)	30 (58.8)	21 (41.2)	2.53 (1.72– 3.72)	—
5	3 (0.2)	2 (66.7)	1 (33.3)	5.45 (1.35–21.99)	—

(continued)

TABLE 3. (CONTINUED)

Risk factor	Total (n=1,807); No. (% of total)	Patients with ≥1 infection (n=612); No. (% of row)	Patients with no infection (n=1,195); No. (% of row)	Unadjusted hazard ratio (95% CI)	Adjusted hazard ratio (95% CI)
Abbreviated Injury Scale Lower Extremity Maximum Severity[c]					
0 (none)	456 (25.2)	99 (21.7)	357 (78.3)	1.0	—
1	327 (18.1)	58 (17.7)	269 (82.3)	0.79 (0.57–1.09)	—
2	271 (15.0)	55 (20.3)	216 (79.7)	0.77 (0.56–1.08)	—
3	279 (15.4)	108 (38.7)	171 (61.3)	1.39 (1.06–1.83)	—
4	219 (12.1)	99 (45.2)	120 (54.8)	1.78 (1.35–2.36)	—
5	255 (14.1)	193 (75.7)	62 (24.3)	4.26 (3.34–5.43)	—
Injury Severity Score[d]					
0–9 (mild)	635 (35.2)	68 (10.7)	567 (89.3)	1.0	1.0
10–15 (moderate)	426 (23.6)	119 (27.9)	307 (72.1)	2.37 (1.76–3.20)	1.21 (0.88–1.67)
16–24 (severe)	477 (26.4)	241 (50.5)	236 (49.5)	5.21 (3.98–6.83)	1.46 (1.06–2.00)
≥ 25 (life-threatening)	268 (14.8)	184 (68.7)	84 (31.3)	8.37 (6.34–11.06)	1.79 (1.29–2.49)
Shock index[e]					
<0.6 (lowest quartile)	457 (25.3)	79 (17.3)	378 (82.7)	1.0	—
0.6–0.8 (IQR)	820 (45.4)	242 (29.5)	578 (70.5)	1.57 (1.22–2.03)	—
>0.8 (highest quartile)	528 (29.3)	291 (55.1)	237 (44.9)	3.22 (2.51–4.13)	—
Blood product transfusions within first 24 hours[f]					
Zero or missing units	923 (51.1)	107 (11.6)	816 (88.4)	1.0	1.0
1–9 units	473 (26.2)	190 (40.2)	283 (59.8)	3.21 (2.53–4.07)	1.80 (1.40–2.33)
10–20 units	228 (12.6)	153 (67.1)	75 (32.9)	6.36 (4.96–8.15)	2.00 (1.48–2.70)
> 20 units	183 (10.1)	162 (88.5)	21 (11.5)	13.48 (10.53–17.24)	3.19 (2.30–4.42)
LRMC admission unit					
Ward	849 (47.1)	88 (10.4)	761 (89.6)	1.0	1.0
Intensive care unit	954 (52.9)	522 (54.7)	432 (45.3)	6.47 (5.16–8.11)	1.92 (1.42–2.60)
Mechanical ventilation at LRMC	651 (36.0)	421 (64.7)	230 (35.3)	5.40 (4.55–6.41)	2.12 (1.70–2.65)
Any operating room visit in theater	1,535 (84.9)	580 (37.8)	955 (62.2)	2.96 (2.07–4.23)	—
Splenectomy performed prior to first infection	3 (0.2)	3 (100)	0	3.59 (1.15–11.16)	—
Any antibiotic use in the first 48 hours	1,466 (81.1)	559 (38.1)	907 (61.9)	2.38 (1.79–3.15)	—
Colonization with MDROs prior to first infection	344 (19.0)	149 (43.3)	195 (56.7)	1.33 (1.10–1.60)	—

[a]Traumatic amputations recorded at Landstuhl Regional Medical Center. Distal amputations include below the knee or below the elbow. Proximal amputations include through the knee, above the knee, or above the elbow.
[b]Fracture data collected from all levels of care.
[c]The Abbreviated Injury Scale is an anatomically based severity scoring system that classifies traumatic injuries by body region using an ascending scale of injury severity (0=none; 5=critical injury) [16].
[d]The Injury Severity Score is an overall measure calculated for each patient based on the top three maximum Abbreviated Injury Scale anatomic region values [44].
[e]Shock index is defined as the heart rate divided by systolic blood pressure. It was documented at the initial support hospital following injury.
[f]Blood transfusion data are not randomly distributed. Patients with missing blood data did not sustain a traumatic amputation and were not admitted to the LRMC intensive care unit. Missing blood transfusion data are missing for 2,116 patients. In addition, the majority of patients with missing blood data are characterized by lower injury severity scores and shock indices.
CI=confidence interval; IQR=interquartile range; LRMC=Landstuhl Regional Medical Center; MDRO=multidrug-resistant organism.

coli colonization in healthy U.S. service members who were in Afghanistan [29]. Also, MDR organisms have not been prevalent in cultures from soil in deployed locations [30] and war wounds have not been found to be colonized with MDR organisms at the time of injury [31]. There is evidence of nosocomial spread of *Acinetobacter* spp. [13], but less so for *Escherichia coli* [32] in deployed subjects and another potential source includes acquired resistance of endogenous flora because of antibiotic pressure. Over a three-year period (2009–2012), 14% of 2079 military trauma patients admitted to participating hospitals in the United States were colonized on hospital admission with MDR gram-negative bacilli with *Escherichia coli* being the most frequent MDR (or ESBL-producing) organism identified [33].

Although the *Acinetobacter* and *Escherichia coli* isolates associated with infection were usually MDR, the *Pseudomonas* and *Enterococcus* isolated from infected sites remained largely antibiotic susceptible. This may be secondary to the antibiotics that were given for post-injury prophylaxis [34], however, further investigation should be conducted on the potential association between post-injury antibiotic exposure and multidrug resistance.

Similar to other studies [2,19,35], factors associated with infection risk in this analysis were related mostly to injury pattern or severity. Blood transfusions, especially more than 10 units in the 24 hours post-injury, had the highest infection risk. Transfusion is a marker of severity of injury, however, in addition this may also be caused by the immunomodulatory effects of blood transfusions [36]. Several studies have also shown that transfusion of red blood cells collected more than 14 days prior is associated with increased rates of infection [37,38]. Since 2008, there has been a concerted effort by the Armed Services Blood Program to reduce the age of red blood cells available for transfusion in theater [39]. From 2007 to 2011, the average age of red blood cells received in theater decreased from 13 to 7 days and the average age upon transfusion to massively transfused (more than 10 units per 24 hours) patients decreased from 33 to 23 days. Because TIDOS does not collect information on the age of red blood cells transfused, the impact of this on infection could not be examined in this study.

Unfortunately most of the factors associated with infections in this analysis are not easily modifiable. For example, neither going to the operating room in the theater of combat (indicating early operative intervention) nor receiving antibiotic agents within 48 hours post-injury were associated with infection risk. The injuries in Afghanistan have been characterized by an increase in amputation rate along with abdominal–pelvic injuries sustained by service members injured by explosive devices while conducting dismounted (foot) patrols [10]. Our data suggest that in order to decrease the rate of infections, injury prevention is needed (perhaps through more mounted missions or further improvement in body armor). Another possible modification is decreasing the number of red blood cell transfusions by using post-injury tranexamic acid, an anti-fibrinolytic agent that has been shown to decrease mortality in bleeding trauma patients [40,41], or using younger blood products or blood product alternatives. It is not clear if any of these interventions would affect infection rates, however, one retrospective analysis that compared military trauma patients who did and did not receive tranexamic acid reported no significant association between tranexamic acid and infection risk [42].

Another study examining tranexamic acid and infection risk in civilian trauma patients had similar findings [43].

Several limitations of this analysis should be noted. Patients who were evacuated from LRMC to TIDOS-participating sites in the United States were injured more severely than those who went to other hospitals in the United States, therefore, the infection rates observed in this analysis may not be generalizable to all combat casualties. Still, more than half of the injured patients at LRMC went to one of the U.S. TIDOS-participating sites; therefore, these findings are still relevant to the majority of combat casualties. The information in this report may not be generalizable to most civilian trauma given the common mechanism of injury (blasts) and the setting requiring multiple evacuations for definitive care. Another limitation is that infected sites (often wounds) may be polymicrobial or grow contaminants or colonizing organisms. We do not have any way of determining which organisms were true pathogens. Any organism growing from infected wounds was considered associated with the infection. For blood stream infections, stricter criteria were used [14]. Strengths of this analysis include the fact that we used a priori criteria to define infections, collected standardized data across multiple levels of care from injury through U.S. hospitalization, and followed all combat injured who came through LRMC during the given time period.

Although the infection rate is high (34% overall; 68% in amputees), this only considers infections that occurred during initial hospitalization. Many of these patients require rehospitalization and further surgical management of their injuries. The rate of incident infections after the initial hospitalization also needs to be determined to understand the full impact of infections complicating the care of combat casualties. Given the large number of patients with combat trauma injuries, high infection rate, and prevalence of MDR organisms, the cost of combat trauma infections to the healthcare system as well as the patient is high. Further research should focus on strategies for improving prevention and treatment of these infections.

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