



US DEPARTMENT OF DEFENSE

## BLAST INJURY RESEARCH PROGRAM COORDINATING OFFICE

### Anti-infective Studies

#### Blast-related Polytraumatic Extremity Wounds and Infectious Outcomes: Trauma Infectious Disease Outcomes Study and Trauma-associated Osteomyelitis

Trauma Infectious Disease Outcomes Study (TIDOS) of the Infectious Disease Clinical Research Program located within the Department of Preventive Medicine and Biostatistics, Uniformed Services University of the Health Sciences (USUHS; Bethesda, Maryland) has an ongoing large-scale epidemiological evaluation of the characteristics of battlefield wounds and subsequent infections. Over a period of three years (2009-2012), 1858 combat casualties were admitted to Landstuhl Regional Medical Center and transferred to a participating hospital in the U.S., of which 1409 (76 percent) had at least one open extremity wound with 323 (23 percent) developing a combat-related extremity wound infection (CEWI). Approximately 80 percent of these combat casualties sustained blast-related trauma. Due to the complexity of the polytrauma, TIDOS researchers developed a refined methodology for classifying polytraumatic extremity wounds, as well as for matching infections to wounds. Classifying the 1,409 patients by their most severe injuries (Table 1), 437 had amputations (57 percent with  $\geq 1$  CEWI), 511 patients with open fractures and no amputations (17 percent with  $\geq 1$  CEWI) and 461 patients had open extremity wounds other than fractures or amputations (4 percent with  $\geq 1$  CEWI). A manuscript detailing the CEWI methodology and classification is nearing finalization.

Among the 323 patients with a CEWI, organisms were recovered from 250 patients with 335 confirmed unique infections, of which 131 and 204 were monomicrobial and polymicrobial, respectively (Table 2). Cultures collected from monomicrobial infections were predominantly Gram-negative bacteria (57 percent), followed by Gram-positive bacteria (23 percent), mold/yeast (15 percent), and anaerobes (five percent). Cultures collected from polymicrobial infections were 61 percent bacterial alone; however, 30 percent recovered bacteria plus mold, five percent bacteria plus mold and yeast, and one percent had only mold. A manuscript with findings from the CEWI analysis is nearing finalization.

Using a subset population of 669 subjects with traumatic amputations or open fractures as their most severe injury, sustaining an amputation, being injured via an improvised explosive device, first documented shock index  $\geq 0.80$ , receipt of  $\geq 10$  units of blood within 24 hours of injury, and having  $>4$  injury sites were identified as independent risk factors for CEWI development. Having a confirmed non-extremity infection  $\leq 4$  days prior to CEWI diagnosis was associated with a lower likelihood of CEWI risk. Findings from the CEWI risk factors analysis were presented at the 2017 Military Health System Research Symposium (MHSRS) and a manuscript is in preparation (*Tribble 2017a*).

Lastly, antibiotic prescribing patterns among subjects with a CEWI are also being assessed. It was determined that patients with only a CEWI received  $\leq 2$  antibiotics, while those with both a CEWI and a non-extremity infection had  $\geq 3$  antibiotics.





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**TABLE 1:** Characteristics of Subjects with at Least one Open Extremity Wound, by Most Severe Wound Group (Table used with permission from the authors)

Characteristics	≥ 1 Amputation (N=437)	≥ 1 Open Fracture (N=511)	Other Wounds (N=461)
Age, median (IQR)	23.5 (21.6-27.2)	24.3 (21.8-28.3)	24.2 (21.9-28.3)
Male	416 (98.8)	494 (99.0)	444. (99.1)
Blast Injury	430 (98.4)	373 (73.0)	341 (74.0)
Injury Severity Score, median (IQR)	30 (21-38)	17 (10-27)	13 (6-27)
First 24 hour blood transfusion, median units, (IQR)	16 (8-26)	4 (2-10)	4 (2-8)
Total hospitalization, median days (IQR)	43 (27-60)	25 (16-43)	14 (9-24)
≥1 CEWI	248 (56.7)	89 (17.4)	17 (3.7)

**TABLE 2:** Confirmed Monomicrobial and Polymicrobial Extremity Wound Infections (Table used with permission from the authors)

	Monomicrobial Infections Number of Cultures (%)	Polymicrobial Infections Number of Cultures (%)
<b>Total Unique Infections</b>	<b>131</b>	<b>204</b>
Gram-negative Bacteria	75 (57.3)	175 (85.8)
Gram-positive Bacteria	30 (22.9)	146 (71.6)
Mold or Yeast	20 (15.3)	80 (39.2)
Anaerobes	6 (4.6)	35 (17.2)

Infectious outcomes with regards to post-trauma antibiotic prophylaxis were assessed in subjects with open fractures over a five-year period (2009-2014). The patients received either DoD-directed narrow-spectrum antibiotics or expanded Gram-negative coverage (i.e., narrow-spectrum antibiotic plus a fluoroquinolone and/or aminoglycoside). Approximately 81 percent of the subjects were injured via a blast mechanism. The findings demonstrated that although there was a reduction in skin and soft-tissue infections with expanded Gram-negative coverage, there was no difference in the proportion of osteomyelitis between the groups. In addition, subjects who received expanded Gram-negative coverage had a higher proportion of recovery of resistant organisms. These findings support the current post-combat trauma antibiotic prophylaxis guidelines for open fractures (Lloyd, Murray, Shaikh, et al. 2017).

Invasive fungal wound infections (IFIs) are another area for TIDOS blast-related research. Over the past year, the TIDOS database was comprehensively searched for subjects with a suspected IFI. Between June 2009 and December 2014, 246 combat casualties had laboratory evidence of a fungal infection





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with 94 meeting the strict criteria of an IFI (recurrent wound necrosis and laboratory fungal evidence at the time of or after observed necrosis). For subjects who did not meet the strict IFI criteria, new classifications were developed related to level of suspicion (High Suspicion and Low Suspicion). Among the 246 subjects, 98 percent sustained blast-related injuries with the majority being dismounted. A total of 77 (61 percent of 126 with mounted status available) of the IFI or High Suspicion subjects met the strict criteria to be classified as a dismounted complex blast injury (DCBI). The remaining 73 subjects who did not meet the DCBI criteria were still blast injured (97 percent) and often dismounted (88 percent of subjects with available data), but frequently lacked the required injury pattern criteria (amputation at or above knee, severe injury to opposite extremity, and perineal, genitourinary, or abdominal injury). Despite not meeting the DCBI criteria, most subjects were classified with critical injury severity (Injury Severity Score  $\geq 26$ ). These findings were included in an IFI Molecular Diagnostic Technical Report that was presented to a panel of subject matter experts on infectious disease, molecular diagnostics, pathology, and surgery on 1 November 2017. Specific recommendations to advance diagnostic approach for at-risk blast trauma patients are being finalized and will be provided to the Joint Trauma System (JTS) and Military Infectious Disease Research Program for guidance, implementation, and prioritization of future research needs.

Under a separate protocol (Trauma-Associated Osteomyelitis), patients who sustained an open fracture (tibia, femur, and arm long bones) between March 2003 and December 2009 were assessed with regards to risk of osteomyelitis. A high proportion of patients included in these analyses sustained blast trauma (>64 percent). Among subjects with open tibia fractures, sustaining a blast injury, increasing fracture severity to include transtibial amputations as the highest level, muscle damage and dead muscle/loss of function, and foreign body at fracture site were independent risk factors for development of osteomyelitis. Being injured between 2003 and 2006 was also identified as a risk factor and is likely the result of changing practice patterns in that timeframe (e.g., decrease use of high pressure irrigation, increased use of negative pressure wound therapy, and reduced crystalloid use). These findings were presented at the 2017 MHSRS and a manuscript has been submitted for journal consideration (*Tribble 2017b*). Manuscripts related to antibiotic practice patterns, impact of combat theater on infection rates, microbiology, antifungal activity of Manuka honey, and biofilm were also published during the past year (*Campbell et al. 2017, Cardile et al. 2017, Lloyd, Murray, Bradley, et al. 2017, Mende et al. 2017, Mende et al. 2016, Tribble et al. 2016, Yabes et al. 2017*).

TIDOS investigators participated on the Expert Panel at the 2016 International State-of-the-Science Meeting on “Minimizing the Impact of Wound Infections Following Blast-Related Injuries” in Arlington, Virginia on 29 November – 1 December, 2016 organized by the DoD Blast Injury Research Program Coordinating Office. The overall goal of the meeting was to assess the current state of the science on strategies to diagnose, prevent, and treat infections following combat-related blast injury. In addition, findings from TIDOS blast-related analyses on extremity wound infections and IFIs were presented at the meeting. The meeting proceedings were published; one of the expert panel recommendations (#6) included a direct reference to the TIDOS project. It stated “Preserve, sustain, and improve the DoD





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Trauma Registry and related programs (e.g., TIDOS and the Military Orthopedic Trauma Registry) to improve care and advance military relevant research relating to wound infections after blast-related injury.”

Understanding the pathogens that infect traumatic wound sites is critically important to the formation of effective clinical practice guidance. Findings from these studies will support further refinement of current DoD JTS clinical practice guidance on risk stratification and clinical management related to extremity wound infections and invasive fungal wound infection prevention and management.

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