Infectious Disease Clinical Research Program

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The Trauma-Related Infections Research Area is part of the Infectious Disease Clinical Research Program (IDCRP) based at the Uniformed Services University of the Health Sciences (USU), Department of Preventive Medicine and Biostatistics. There are three primary research protocols: 1) Trauma Infectious Disease Outcomes Study (TIDOS); 2) Trauma-Associated Osteomyelitis; and 3) Invasive Fungal Wound Infection (IFI) Molecular Diagnostics.

TIDOS is the centerpiece protocol of the Trauma-Related Infections Research Area and involves investigators from a variety of disciplines, including infectious disease, trauma surgery, orthopedics, surgical pathology, epidemiology, statistics, microbiology, and molecular biology. Both TIDOS and Trauma-Associated Osteomyelitis are made possible through the cooperative research of investigators and personnel across multiple clinical sites. In addition, TIDOS involves collaborations with the U.S. Army Institute of Surgical Research, Walter Reed Army Institute of Research, Naval Medical Research Center, and the United Kingdom Wound Infection Surveillance Programme. The IFI Molecular Diagnostics protocol also includes collaborations with the DoD Joint Pathology Center and the University of Texas Health Science Center at San Antonio.

TIDOS was developed with the following objectives:

- Establish a cohort of DoD beneficiaries and active-duty personnel with trauma-related injuries to determine short- and long-term outcomes and potential risk factors associated with infections.
- Describe the infectious disease epidemiology of trauma-related injuries or other nosocomial infections in the cohort population.
- Establish a database and bacterial / fungal isolate repository to support future approved sub-studies focused on informing clinical management, disease prevention, or clinical trial design.
- Inform DoD efforts to develop real-time tools for combat-related health event/outcome analysis secondary to trauma-related infections during wartime.

TIDOS is supported by U.S. Navy Bureau of Medicine and Surgery (BUMED) Wounded, Ill, and Injured Program (WII), the National Institute of Allergy and Infectious Diseases (NIAID), the DoD Global Emerging Infections Surveillance and Response System (GEIS), the Military Infectious Diseases Research Program (MIDRP) through the Defense Health Program, and U.S. Army Defense Medical Research and Development Program (DMRDP) funding. Trauma-Associated Osteomyelitis has been supported by BUMED WII and NIAID. The IFI Molecular Diagnostics protocol is supported by DMRDP. The IDCRP was formed through an Interagency agreement between NIAID and USU and is supported by the Henry M. Jackson Foundation pursuant to a cooperative agreement.

The views expressed are those of the authors and do not reflect the official views of USU, Henry M. Jackson Foundation, National Institutes of Health or the Department of Health and Human Services, DoD or the Departments of the Army, Navy or Air Force.
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For the Trauma-Related Infections Research Area, 2017 was another successful year filled with major achievements. One highlight of the past year was the completion of multiple large-scale three-year analyses using the Trauma Infectious Disease Outcomes Study (TIDOS) to comprehensively examine combat-related extremity wound infection data. As part of the analysis, we developed new definitions and methodology related to the classification of polytrauma. The analyses included an assessment of epidemiology, infection risk factors, wound microbiology, and antibiotic treatment practice patterns. The findings of the three-year analyses will be extended in forthcoming analyses using the five-year data and will ultimately support the development of clinical practice guideline recommendations. Multiple analyses under the TIDOS Multidrug-Resistant and Virulent Organisms (MDR/VO) Trauma Infections Initiative were completed this past year, with additional analyses underway or being planned. A proposal to continue the MDR/VO Initiative analyses was also approved by the Military Infectious Disease Research Program. This collaborative effort continues to provide data that will further understanding of the interaction of wound microbiology and clinical outcomes.

An additional accomplishment of 2017 was the refinement of the Invasive Fungal Wound Infection (IFI) Case Registry using revised IFI classification and definitions related to timing of laboratory fungal evidence. Using the updated IFI Case Registry, a comprehensive review of IFI epidemiology was completed. Furthermore, a major success of the past year was the completion of the retrospective analysis of archived tissue specimens to assess a PCR-based assay for the IFI Molecular Diagnostics study. Findings from the analysis were presented to an expert panel with the discussion centering on the incorporation of molecular diagnostics into Joint Trauma System clinical practice guidelines for use within U.S. military hospitals.

The Trauma-Associated Osteomyelitis Study was also successful as the final series of case-control and case-case analyses were completed. In addition, manuscripts with the findings from the tibia case-control and case-case analyses were submitted for journal consideration. Data abstraction through our Veterans Affairs collaborator is also nearing completion, which extends the follow-up period for the subjects (many beyond 10 years), allowing for examination of co-morbidities and economic impact. Analysis of these data is forthcoming in 2018.

In the upcoming year, TIDOS analyses will focus on blast-related wound infections, wound microbiology and multidrug resistance, clinical practice guideline adherence/refinement, and antibiotic stewardship. Moreover, our collaboration with the United Kingdom Wound Infection Surveillance Programme is moving forward and analyses are being developed.

The Trauma-Related Infections Research Area’s aims and objectives remain high priorities for military medicine and continue to have significant clinical relevance during inter-war periods for the purpose of improved understanding for ongoing issues among wounded personnel, and to enhance efforts with evidence-based approaches for the next conflict.

David R. Tribble, MD, DrPH
Science Director, IDCRP
Director, Trauma-Related Infections Research Area
Scientific Strategic Plan for Trauma-Related Infections

The Infectious Disease Clinical Research Program has focused efforts on the evaluation of treatment strategies for combat-related trauma infectious complications. Infections in these complex wounds remain a major challenge, requiring well-designed clinical research in the areas of prevention and management. Treatment strategies have been complicated by the emergence of multidrug-resistant bacterial organisms and aggressive new threats, such as invasive molds. Furthermore, infections of the bone or hardware-related often create challenges due to potential for chronic or recurrent infections.

During 2017, the strategic aims of the Trauma-Related Infections Research Area were revised to reflect research priorities for the Military Health System. Four research aims were identified that will advance the Research Area in the desired direction, in line with IDCRP’s overall mission, vision, and goals.

**Aim 1:** Describe the epidemiology, clinical characteristics, and outcomes among combat blast-related wounds and infections

**Aim 2:** Compare clinical outcomes and antibiotic exposure to specific microbiological factors in colonizing or infecting organisms isolated from trauma patients (Multidrug-Resistant and Virulent Organisms Trauma Infections Initiative)

**Aim 3:** Evaluate short- and long-term health impacts of combat-related infections through ongoing care in DoD and/or VA following initial discharge

**Aim 4:** Assess adherence and outcomes to Joint Trauma System Clinical Practice Guidelines and antibiotic stewardship in support of the U.S. strategy in Combating Antibiotic Resistant Bacteria

Within each of the different trauma-related study protocols, a great deal of progress has been made to complete these research aims.

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<td>Presentation and publication</td>
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Blast-Related Trauma and Wound Infections

A high frequency of blast trauma (primarily with improvised explosive devices) occurred during the wars in Iraq and Afghanistan, resulting in substantial morbidity and potential significant long-term effects, including infectious complications. As a result, blast trauma clinical research is a priority of the Military Health System. One specific injury pattern resulting from blast trauma is dismounted complex blast injuries (DCBI). These injuries are characterized by a traumatic amputation of a lower extremity (at or through the knee) and a serious injury (or amputation) to the opposite leg, along with pelvic, urogenital, and/or abdominal injury.

As part of an invasive fungal wound infection (IFI) analysis, 720 combat casualties with open extremity wounds admitted to participating U.S. hospitals (2009-2014) who had operative tissue specimens collected for histopathology and/or wound culture were identified. Among these patients, 162 (23%) met the strict criteria for a DCBI with approximately half being classified as IFI or High Suspicion for IFI based upon laboratory fungal evidence (see Page 5). In general, patients with a DCBI and an IFI or High Suspicion classification were more severely injured than DCBI patients who were classified as Low Suspicion of IFI or non-IFI. The DCBI patients with an IFI or High Suspicion classification also required more large-volume blood transfusions within 24 hours post-injury, mechanical ventilation, and colostomies (Figure).

Patients who did not have a DCBI, but were classified as an IFI or High Suspicion of IFI were also examined. It is important to note that while the patients did not meet the strict criteria of a DCBI, the majority still sustained a dismounted blast injury, resulting in high injury severity. In particular, >40% of the non-DCBI patients had a traumatic amputation at or above the knee, >50% had an amputation plus an amputation or serious injury to the opposite limb, and >80% had perineal, genitourinary, or an abdominal injury.

In June 2017, the DoD Blast Injury Research Program released the report on the proceedings and recommendations from the 2016 International State-of-the-Science (SOS) Meeting on ‘Minimizing the Impact of Wounds Infections Following Blast-Related Injuries’. Six recommendations were detailed in the report and many involve elements that are captured under the scope of the TIDOS aims and objectives. In particular, the SOS Meeting report highlighted the importance of sustained wound infection surveillance, furthering the understanding of blast-related wound infections, and measuring compliance with Joint Trauma System guideline recommendations. It is also notable that TIDOS is directly named in Recommendation #6. These recommendations and findings were presented by COL Kirby Gross at the 126th Annual AMSUS Meeting on Force Health Protection: From Battlefront to Homefront.

The next steps involves the examination of best practices in relation to antibiotic treatment of blast trauma wound infections and assessment of infection risk factors and clinical outcomes.

Executive Summary
Recommendation 6:
Preserve, sustain, and improve the DoD Trauma Registry and related programs (e.g., Trauma Infectious Disease Outcome Study and the Military Orthopedic Trauma Registry) to improve care and advance military relevant research relating to wound infections after blast-related injury.

2016 International SOS Meeting report
https://blastinjuryresearch.amedd.army.mil/
Extremity injuries among combat casualties are frequently complicated by infections, resulting in extended hospitalizations, significant morbidity, and mortality. As a result, Drs. David Tribble and Laveta Stewart (IDCRP/USU) led an investigation assessing combat-related extremity wound infection (CEWI) risk factors. To be included in the study population, patients were required to have ≥1 combat-related open extremity wound, be admitted to Landstuhl Regional Medical Center within 6 days post-injury, and be transferred to a participating hospital in the United States within 7 days post-injury. The resulting study population of 1409 patients was classified based upon their most severe injury (i.e., amputation, open fracture without amputation, or other open soft-tissue injury without an open fracture or amputation). The highest proportion of infections were among patients with amputations (47% compared to 14% and 3% with open fracture and other open soft-tissue injuries, respectively).

Factors associated with risk of CEWIs within 30 days post-injury among patients with traumatic amputations and open fractures were assessed in a Cox proportional hazard model. Sustaining an amputation was found to have a 85% increased risk of developing a CEWI. Receipt of blood within 24 hours post-injury, being injured via an improvised explosive device (IED) blast mechanism, having a first documented shock index ≥0.80, and having >4 injured sites were also associated with risk of developing a CEWI (Figure). Being diagnosed with a non-extremity wound infection ≤4 days prior to a CEWI diagnosis was associated with a reduced likelihood of a CEWI.

Although the independent risk factors for CEWI development identified in this preliminary model are primarily related to injury severity (e.g., amputations, injury mechanism, polytrauma, and blood volume), the association of a lower likelihood of CEWI development with occurrence of a non-extremity wound infection indicates that there may be potentially modifiable factors with early surgical wound management and antimicrobial exposure that warrant further investigation. In particular, the impact of timing and type of surgical procedures, antimicrobial regimens, and duration of antimicrobial use have on CEWI risk will be assessed in follow-on analyses.

The findings from the CEWI risk factor analysis were presented at the 2017 Military Health System Research Symposium (Photo) and a manuscript was submitted for journal consideration. Furthermore, manuscripts detailing our refined polytraumatic extremity wound classification methodology and presenting the findings of the CEWI wound microbiology analysis are nearing finalization. Analyses utilizing the 5-year TIDOS dataset are planned.
Invasive Fungal Wound Infection Molecular Diagnostics

Invasive fungal wound infections (IFIs) are a complication of severe trauma characterized by high morbidity. Dr. Anuradha Ganesan (IDCRP/USU; Walter Reed National Military Medical Center) led the effort to systematically review the TIDOS database and refine the IFI classification scheme based on timing of laboratory fungal evidence (histopathology and/or fungal culture). The hallmark of an IFI remains a suspicious wound with a necrotic infection, suggestive of invasive fungi. Using the refined classification, IFIs further require that laboratory fungal evidence be collected at the time of (or after) wound necrosis. If a patient had laboratory evidence of a fungal infection, but did not meet IFI criteria, they were further assessed and classified as either High Suspicion or Low Suspicion of IFI. High Suspicion required a patient to have an infection event and receipt of antifungal therapy for ≥10 days. If a patient received <10 days antifungal therapy, they were classified as High Suspicion if they had an amputation within 10 days of injury or died. Patients with fungal laboratory evidence who did not meet the criteria of an IFI or High Suspicion were classified as Low Suspicion. Information on the refined IFI classification system was presented by Dr. Ganesan at 2017 Military Health System Research Symposium and 2017 IDSA ID Week (Photo 1).

It is well recognized that early diagnosis followed by aggressive debridement and directed antifungal chemotherapy is crucial to improve the prognosis of patients with IFIs. As the result of an award from the Defense Medical Research and Development Program, Dr. Ganesan led a retrospective analysis to evaluate the use of a PCR-based molecular assay to aid in the rapid identification of filamentous fungal DNA using archived formalin-fixed paraffin-embedded (FFPE) pathology specimens identified at the level of the surgical wound. The study population included 64 subjects with positive histopathology (angioinvasion or nonvascular tissue invasion) and 102 control subjects who had specimens from extremity wounds collected for histopathology without any evidence of a fungal or bacterial infection. Overall, specimens from 95 injury sites from histopathology positive subjects and 118 injury sites from control subjects were examined.

The FFPE specimens were analyzed by our collaborator (Dr. Brian Wickes) at the University of Texas Health Sciences Center at San Antonio, Texas using a panfungal PCR-based assay. Approximately 15% of specimens were also shipped to our collaborator (Dr. Ralf Bialek) in Germany (LADR GmbH, Medizinisches Versorgungszentrum Dr. Kramer & Kollegen) who utilized a semi-nested PCR-based assay.

When compared against findings from concomitant fungal wound cultures collected with 24 hours of histopathology specimen collection, the panfungal PCR-based assay had a higher detection of pathogenic fungi from the order Mucorales (48% vs 33%), which was the predominant fungal agent identified. In addition, when occurrence of invasive disease was considered, a higher proportion of order Mucorales fungi was identified from sites with angioinvasion compared to the sites with nonvascular tissue invasion (75% vs 21%, respectively; Figure). Saksenaea spp. accounted for the majority of order Mucorales fungi from both sites with angioinvasion and nonvascular tissue invasion.

Figure: Distribution of fungi identified with PCR-based assay from sites with angioinvasion and nonvascular tissue invasion. Saksenaea spp. are a subset of the order Mucorales data.
Overall, the panfungal PCR-based assay had high specificity (99%), but lower sensitivity (63%). The assay failed to detect fungal DNA in a portion of specimens from sites with positive histopathology (false negatives), which may be a result of DNA degradation from the formalin fixation. After restricting to sites with angioinvasion, the sensitivity of the assay increased to 83% and the number of false-negatives decreased, indicating the potential utility of the assay in subjects with invasive disease. When the findings from the panfungal assay were compared to the semi-nested assay, there were differing results; however, concordance improved in sites with fungi from the order Mucorales. Use of the semi-nested PCR-based assay also resulted in a lower proportion of false-negatives.

Following completion of the analysis, a technical report was prepared with the findings and presented to experts in the field of infectious disease, clinical mycology, pathology, and surgery at an IFI Diagnosis Technical Meeting held on 1 November 2017 (Table; Photos 2).

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<tr>
<th>Expert Panel Member</th>
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<th>Affiliation</th>
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<tr>
<td>Dr. John Bennett</td>
<td>Infectious disease and medical mycology</td>
<td>National Institute for Allergy and Infectious Diseases</td>
</tr>
<tr>
<td>Dr. Stephen Dumler</td>
<td>Pathology</td>
<td>Uniformed Services University</td>
</tr>
<tr>
<td>COL Michael Kozar</td>
<td>Microbiology</td>
<td>Military Infectious Disease Research Program</td>
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<tr>
<td>Col Bradley Lloyd</td>
<td>Infectious disease</td>
<td>Wright Patterson Medical Center</td>
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<tr>
<td>COL Clinton Murray</td>
<td>Infectious disease</td>
<td>1st Area Medical Laboratory, Aberdeen</td>
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<tr>
<td>Dr. Thomas Patterson</td>
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<td>University of Texas Health Sciences Center San Antonio</td>
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<td>CAPT Carlos Rodriguez</td>
<td>Surgery (trauma)</td>
<td>Walter Reed National Military Medical Center</td>
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<td>COL Stacy Shackelford</td>
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<td>DoD Joint Trauma System</td>
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<tr>
<td>CAPT Timothy Whitman</td>
<td>Infectious disease</td>
<td>Walter Reed National Military Medical Center</td>
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Based on the discussion of the findings with the expert panel, it was recommended that the PCR-based assay be used as a complement to histopathology and cultures. It was also recommended that additional analysis be conducted with a wider range of IFI specimens, including fresh tissue specimens, if possible. Further examination of differences between the panfungal and semi-nested assays, including the probes utilized in the assays, is also warranted. An executive summary of the findings and recommendations will be presented in a brief to the Joint Trauma System (JTS). A manuscript is also in preparation.

In 2017, a proposal was accepted by the Military Infectious Disease Research Program to conduct analyses with the goal of refining the JTS Clinical Practice Guideline related to management of IFIs in war wounds. The findings from the molecular diagnostics analysis will be used to support refinement of the JTS recommendations. Analyses utilizing the refined IFI classification and updated IFI Case Registry related to outcomes to support refinement of the recommendations are planned.

Photos 2: IFI Technical Meeting; Meeting attendees (left); Drs. Bialek and Wickes (middle), Dr. Ganesan (right)
Trauma-Associated Osteomyelitis

Osteomyelitis is a serious complication of open fractures, which negatively impacts the outcome of the patient by resulting in further surgical procedures and subsequent morbidity. Thus, characteristics of patients with osteomyelitis and risk factors for developing the disease have been examined in patients with open fractures of the tibia, femur and long bones of the arm.

In August, Dr. David Tribble (IDCRP/USU) presented findings from the tibia case-control analysis assessing osteomyelitis risk factors at the 2017 Military Health System Research Symposium. Findings from the tibia case-case comparison analysis related to osteomyelitis recurrence were presented by MAJ Joseph Petfield (Landstuhl Regional Medical Center) at the Royal British Legion Centre for Blast Injury Studies (CBIS) Annual Networking and Research Update Event (Photo), as well as by MAJ Daniel Stinner (Brooke Army Medical Center) at the 59th Annual Meeting of the Society of Military Orthopaedic Surgeons. Furthermore, an abstract with findings from the femur case-case osteomyelitis recurrence analysis was accepted as an oral presentation at the 38th Annual Surgical Infections Society meeting. Manuscripts with the tibia case-control and case-case findings were also submitted for journal consideration and a manuscript with the findings of the femur case-control analysis is nearing finalization.

Through a bidirectional data use agreement with the St. Louis VA Health Care System, data abstraction has been completed for over 550 patients who entered VA care. In the upcoming year, these data will be examined to evaluate the long-term impact of open long bone fractures and osteomyelitis. Co-morbidities and healthcare economics will also be assessed in the forthcoming analyses.

DoD VA Outcomes

Although ~5% of combat casualties wounded in Iraq or Afghanistan sustained genitourinary trauma, long-term infectious complications of these injuries are not well-described. Therefore, in collaboration with Dr. Jay McDonald (St. Louis VA Health Care System) and Dr. Stephen Liang (Washington University School of Medicine in St. Louis), urinary tract infections among these casualties who entered VA care were assessed. Among 530 TIDOS enrollees who entered VA care, 89 (17%) sustained genitourinary trauma, of which 93% resulted from blast injuries. Approximately 21% of the patients with genitourinary trauma were diagnosed with a urinary tract infection with 25% of the infections occurred during the initial hospitalization, 25% during DoD follow-up, and 50% after entering VA care. Non-infectious consequences of genitourinary trauma were also examined and 36% of patients experienced sexual dysfunction, 19% chronic/intermittent urinary catheterization, 14% urinary retention / incontinence, and 8% had urethral stricture.

Predictors of urinary tract infections following genitourinary trauma included a pelvic soft-tissue infection during the initial trauma hospitalization and occurrence of urinary retention and/or incontinence. Overall, the data show that while urinary tract infections are common during the initial trauma hospitalization, they may also develop long after the injury during VA care. These data were presented at the 2017 IDSA ID week (Photo) and a manuscript is in preparation.
In a multivariate logistic regression model, MDRGN colonization prior to infection diagnosis was the strongest predictor for a MDRGN infection. The combined regimen of 1st generation cephalosporins plus fluoroquinolones, as well as vancomycin plus a carbapenem were also independent risk factors for the development of a MDRGN infection. Further assessment of the antibiotic practice patterns is presently underway. These findings were presented by LCDR Campbell at the 2017 IDSA ID Week (Photo).

In a multivariate logistic regression model, MDRGN colonization prior to infection diagnosis was the strongest predictor for a MDRGN infection. The combined regimen of 1st generation cephalosporins plus fluoroquinolones, as well as vancomycin plus a carbapenem were also independent risk factors for the development of a MDRGN infection. Further assessment of the antibiotic practice patterns is presently underway. These findings were presented by LCDR Campbell at the 2017 IDSA ID Week (Photo).

In separate analysis led by Col Bradley Lloyd (Wright Patterson Medical Center), infectious outcomes were assessed among 287 combat casualties with open extremity soft-tissue injuries based on receipt of DoD-directed narrow-spectrum antibiotic regimens (i.e., IV cefazolin, clindamycin, or amoxicillin-clavulanate) or expanded Gram-negative (EGN) coverage (i.e., a narrow-spectrum antibiotic plus a fluoroquinolone and/or aminoglycoside). Approximately 74% of the patients received a narrow-spectrum antibiotic regimen, while 26% received EGN coverage. There was no statistically significant difference in the proportion of extremity wound infections between the patients who received narrow-spectrum and EGN antibiotics (3% and zero, respectively; Figure). Nevertheless, there was a higher proportion of resistant Gram-negative organisms recovered from any site from the EGN coverage group (36% versus 19%).

These and the findings from Col Lloyd’s assessment of infectious outcomes among patients with open fractures (Lloyd et al., 2017) support current DoD guidelines regarding use of narrow-spectrum antibiotics. A manuscript with the open soft-tissue findings has been accepted for publication in Military Medicine.

During 2017, a proposal was accepted by the Military Infectious Disease Research Program to conduct analyses with the goal of expanding the Joint Trauma System Clinical Practice Guideline on combat-related trauma infection prevention to include management, as well as continue to assess adherence to guideline recommendations.

Figure: Outcomes by Antibiotic Regimen
Microbiological Infections

The TIDOS Multidrug-Resistant and Virulent Organisms (MDR/VO) Trauma Infections Initiative, led by Dr. Katrin Mende (IDCRP/USU; Brooke Army Medical Center), continues to be an important collaboration with DoD laboratories (Walter Reed Army Institute of Research [WRAIR], Naval Medical Research Center [NMRC], and U.S. Army Institute of Surgical Research [USAISR]) to further the understanding of combat trauma-related wound infection microbiome, assess the impact of multidrug resistance on clinical outcomes, and develop a novel antimicrobial countermeasure evaluation pipeline within the DoD laboratories. Over the past year, multiple analyses have been completed (and published) with additional analyses being planned or are underway. At the 2017 Military Health System Research Symposium (MHSRS), Dr. Mende presented an update on the MDR/VO analyses (Photos 1).

Through collaboration with WRAIR Wound Infections Department, the genetic diversity of 407 Enterococcus spp. isolates collected from open extremity wounds was examined. The majority of the isolates were identified as E. faeicum (80%), while 14% were E. faecalis. Approximately 13% of the isolates were MDR. In vitro antagonism studies assessing Enterococcus spp. isolates with ESKAPE pathogens and biofilm cells are underway in collaboration with NMRC Wound Infections Department.

As part of the collaboration with USAISR, biofilm formation of 376 Enterococcus spp. isolates was assessed. The biofilm response was generally weak with 1.9% in unsupplemented media and 8.8% in the presence of human plasma (Table). Biofilm response was also variable across the Enterococcus strains with E. faecalis showing the greatest response (30% biofilm with human plasma).

Findings from the Enterococcus spp. and biofilm analyses were presented at the 2017 MHSRS by MAJ Samandra Demons (WRAIR) and Dr. Lee Mangum (USAISR), respectively (Photos 1).

In 2017, additional funding was awarded by the Military Infectious Disease Research Program to continue and expand the MDR/VO Trauma Infections Initiative. In particular, new collaborative analyses with WRAIR and NMRC being planned will focus on the interaction of coagulase-negative staphylococci and ESKAPE pathogens (Enterococcus faeicum, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa, and Enterobacter spp.) with other common genera of bacterial wound pathogens. Other analyses in development will evaluate the impact of bacterial (MDR and non-MDR) and fungal organisms in monomicrobial and polymicrobial combat trauma-related extremity wound infections on clinical outcomes.

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Table: Enterococcus spp. aggregate biofilm data as compared to biofilm formation by referent standard (Staphylococcus epidermidis)

Photos 1: [from left] MAJ Samandra Demons, Dr. Lee Mangum, and Dr. Katrin Mende at 2017 MHSRS
Two recent MDR/VO Trauma Infections Initiative analyses were Graduate Medical Education (GME)-supported projects. In the first analysis, *P. aeruginosa* isolates collected from wound and blood cultures from 146 combat casualties were assessed by CPT Mary Ford (Medicine Intern) and Maj Dana Blyth (mentor). Antibiotic susceptibilities of initial isolates ranged from 74% with meropenem to 92% with gentamicin (Figure). When serial isolates from 40 patients were considered, susceptibilities decreased for all assessed antibiotics (25% with meropenem to 60% with gentamicin). Patients with recovery of MDR *P. aeruginosa* isolates more frequently sustained blast injuries, had higher injury severity, required a longer duration of mechanical ventilation, and had a longer hospitalization period.

In the second GME-supported MDR/VO Trauma Infections Initiative analysis, Capt Nicholas Keaton (Internal Medicine Resident) and Maj Dana Blyth (mentor) evaluated antifungal susceptibility of 28 initial mold isolates (from 18 patients) collected from combat-related wounds. Serial isolates from five patients were also assessed. While the *Aspergillus* spp. isolates did not demonstrate significant antifungal resistance, approximately half of the order Mucorales isolates developed resistance to posaconazole and amphotericin B. Susceptibility between posaconazole and voriconazole was also comparable, indicating the potential for use of posaconazole as part of an empiric antifungal treatment regimen. The findings of these two GME-supported analyses were presented by CPT Ford and Capt Keaton at the 2017 IDSA ID Week (Photos 2). CPT Ford also presented the *P. aeruginosa* analysis at the 2017 U.S. Army/U.S. Air Force American College of Physicians Chapter Meeting.

For 2018, multiple new GME-supported microbiological analyses under the mentorship of Maj Blyth and Dr. Mende are underway. In one of the analyses, CPT John Kiley (ID Fellow) will evaluate the clinical characteristics, resistance patterns, and outcomes of *K. pneumoniae* infections in wounded military personnel. In another analysis, the antifungal activity of cerium nitrate against molds and yeasts collected from combat casualties will be assessed by CPT Heather Pomerantz (ID Fellow) in collaboration with investigators from USAISR. This analysis will also investigate the cytotoxicity of cerium nitrate on human cells to support potential treatment strategies. Lastly, Capt Sarah Schall (Internal Medicine Resident) will examine the incidence, epidemiology, and outcomes of *Clostridium difficile* infections among combat casualties.

**Figure:** Susceptibility of *Pseudomonas aeruginosa* initial and serial isolates to selected antibiotics

**Photos 2:** [from top] CPT Mary Ford and Capt Nicholas Keaton at 2017 IDSA ID Week
Publications in 2017


Weintrob AC, Murray CK, Xu J, Krauss M, Bradley W, Warkentien TW, Lloyd BA, Tribble DR and the IDCRP TIDOS Group. **Early Infections Complicating the Care of Combat Casualties from Iraq and Afghanistan.** *Surgical Infections.* Accepted for publication.

Book Chapter in 2017


Posters and Presentations in 2017

2017 ASM Microbe. 1-5 June 2017, New Orleans, LA


Military Health System Research Symposium, 27-30 August 2017, Kissimmee, FL.—continued

Military Health System Research Symposium, 27-30 August 2017, Kissimmee, FL.—continued


Mangum LC Garcia GR, Tribble DR, Mende K, and Akers KS. Biofilm Formation Capacity among Enterococcus species Isolates from Clinical Wound Infections of Injured US Military Personnel. [Poster #234].


U.S. Army/U.S. Air Force American College of Physicians Chapter Meeting, 7-9 September 2017, Lackland Air Force Base, JBSA Fort Sam Houston, TX.


ID Week, A Joint Meeting of IDSA, SHEA, HIVMA, and PIDS, 4-8 October 2017, San Diego, CA.


* Keaton N, Mende K, Beckius ML, Farmer A, Rizzo J, Ganesan A, Murray CK, Tribble DR, and Blyth DM. Antifungal Resistance Patterns in Molds Isolated from Wounds of Trauma OEF/OIF/OND and Burn Patients. [Poster #160].


59th Annual Meeting of the Society of Military Orthopaedic Surgeons. 11-15 December 2017, Scottsdale, AZ


* Presentation/publication from a Graduate Medical Education analysis.
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