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Lessons of War: Combat-related Injury Infections during the Vietnam War and Operation Iraqi and Enduring Freedom

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Summary

In over a decade of war, numerous advancements have been made to improve overall combat-related mortality, but infectious complications remain a leading cause of both morbidity and mortality in combat-related injured personnel. Here we will attempt to compare the challenges and lessons of combat-related injuries and infections from the Vietnam War with those of OIF/OEF. Throughout the Vietnam War and OIF/OEF, there have been similar infection-related challenges faced in caring for combat-related trauma patients. Both conflicts reinforced the importance of rapid medical evacuation and definitive surgical management of war wounds. They revealed the constant evolution of infecting organisms and the challenge of increasing antimicrobial resistance. We have also seen that with decreased mortality of severely injured personnel new morbidities must be addressed. Using the foundation of fragmented research from the Vietnam War, previously successful models were assembled into joint service research institutions which have allowed these questions to be addressed. However, many questions regarding measures to reduce infectious complications in our combat-injured personnel remain unanswered. Continued research building on established knowledge is critical for continued improvements in the care of combat-related trauma patients.

Keywords

combat-related infection; Vietnam War; OIF/OEF

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Introduction

In over a decade of war, numerous advancements have been made to improve overall combat-related mortality. Battlefield case fatality rates (CFR) have declined steadily throughout the twentieth century, from 19.1% among all wounded in World War II, to 15.8% in Vietnam, and 9.4% in OIF/OEF.(1) However, infectious complications remain a leading cause of both morbidity and mortality in combat-injured personnel. While there has also been continual evolution of battlefield tactics leading to new mechanisms of injuries and infectious complications, the trends echo patterns seen previously. We continue to face wound infections, growing antimicrobial resistance, and seek "novel" solutions which on reflection have often been previously investigated. Learning to apply the lessons of prior conflicts is of paramount importance to progress. Here we will attempt to compare the challenges and lessons of combat-related injuries and infections from the Vietnam War with those of OIF/OEF.

Infection-related Mortality

The rapid evacuation in Vietnam and OIF/OEF brought many patients who would have been considered killed in action (KIA) during prior conflicts into hospitals.(2–4) These patients have often suffered catastrophic injuries which are associated with a variety of infectious complications. Because of this, there is some degree of reciprocity beteween KIA and died of wounds (DOW) rates. An increase in DOW rates has been noted in Iraq and Afghanistan compared to the Vietnam War.(1, 5) Infection-related mortality remains a major cause of death in those surviving to hospitalization. This further emphasizes the importance of infection control and treatment following combat-related injuries.

The largest series to examine causes of death including granular data from the Vietnam War covered 19 hospitals located throughout Vietnam with 132,996 admissions. Surgical admissions accounted for 46.3% of all admissions, but 93% of the 1,253 deaths. Sepsis was the third leading cause of overall mortality in surgical patients, accounting for 12% of deaths, second only to head injury and hemorrhagic shock.(6) Of hospital deaths, 20% and 60% occurred within the first 2 and 12 hours respectively.(7) Deaths within the first 24 hours were overwhelmingly related to hemorrhage (87% of deaths), followed by sepsis and respiratory failure.(6, 8) While death from sepsis can occur quickly in unique patient populations including highly immunomodulated patients, neutropenic patients, and following splenenectomy, this study does state that sepsis deaths within the first 24 hours were in non-US civilians who had delayed hospital admission.(8) There is ongoing concern that many severely injured trauma patients with super-massive transfusions may fall within this highly immunomodulated population, though prospective data are lacking.(9) After the first 24 hours, the most common cause of death was sepsis, accounting for 38% of deaths, followed by pulmonary embolism in 26%, hemorrhage in 11%, and 8% with upper gastrointestinal bleeding, respiratory failure, and fat embolism respectively. Sepsis was most commonly associated with intra-abdominal (especially colonic) and massive soft tissue injuries.(8) Of 65 autopsies for patients who died in Japan performed at the 406th medical laboratory, the most frequent cause of death was burns in 36%, followed by missile wound with sepsis in 19%, and brain trauma in 10%. While burns comprised a disproportionate

majority of deaths in this series than others (approximately 3% in larger studies), the granularity of data are insightful for underlying infectious complications as burn deaths were often related to either sepsis or hypovolemic shock.(8, 10) Nineteen of 65 patients within this autopsy series had positive cardiac blood cultures on autopsy which were primarily gram-negative pathogens including *Pseudomonas* and *Klebsiella* spp.(10, 11) Again, intestinal injuries, intra-abdominal abscess, and pneumonia were common in sepsis deaths.(11) In a more recent study of 210 U.S. marine combat-related fatalities from Vietnam, those most commonly viewed as potentially preventable today were associated with hemorrhage, severe burns, pulmonary edema, and sepsis. Antibiotics were among the medical technologies most commonly viewed as potentially lifesaving.(7)

Of all deaths, the proportion KIA fell from 88% in Vietnam and World War II to 77% in OIF/OEF. (1) Thirty-five percent of these fatalities died immediately. An additional 52% died before arriving at a military treatment facility (MTF) and only 14% died after reaching an MTF.(3) From 2002–2011, of 57,149 military personnel admitted to an MTF for combat-related injuries, 4.5% died of wounds. As in Vietnam, most died within the first 24 hours and hemorrhage was the most common cause of preventable death.(3, 4, 12, 13) Sepsis accounted for between 2–9% of preventable deaths.(4, 12) At this point, there have yet to be large studies of overall infection related mortality within OIF/OEF so this is difficult to compare directly with Vietnam. In the invasive fungal infection (IFI) population from OEF, the overall crude mortality rate was 7.8%.(14) In another study of trauma casualties evacuated from OIF to the U.S. Navy hospital ship, USNS Comfort, the overall death rate was 1.4%. While civilian casualties made up a large percentage of this cohort, those who met criteria for infection had a mortality rate of 3.6% versus 0.7% in those without infection.(15) An autopsy study examining causes of death within the US Army Institute of Surgical Research (USAISR) Burn Center at Brooke Army Medical Center (BAMC) revealed that the most common cause of death in patients burned as a result of military operations was infection. Those burned during military operations had burns of higher TBSA (median 65% versus 38%), higher ISS, more frequent inhalational injury, longer time from injury to admission, and were more likely to die of infectious complications (notably fungus, *Pseudomonas*, and *Klebsiella*) compared to their civilian counterparts.(16)

Evacuation

Increased time between injury and hospital admission is associated with increased mortality and infection rates.(2, 15) Animal studies, civilian trauma, and limited war data also indicate that increased time between injury and antimicrobial administration and surgical intervention are associated with increased infection rates(17, 18). As helicopter evacuation increased during Vietnam and became routine during OIF/OEF, evacuation times decreased.(12, 19, 20) In one study during the Vietnam War, 31% and 86% of all casualties were admitted within 1 and 4 hours respectively.(2) In comparison, as OIF/OEF progressed, average time from injury to MTF admission decreased to 45 minutes.(13) In another study, 31 of 49 casualties arrived within 20–40 minutes of injury.(21) Many wounded in Vietnam were brought directly to Army hospitals where definitive treatment including delayed primary closure by one surgical team was performed.(2) Casualties typically arrived in Japan 4–6 days following injury and in the continental United States (CONUS) within 21–

30 days.(2, 22, 23) In comparison, typical lengths of stays for injured U.S. personnel in OIF/OEF were only 2.5 days in theater and CONUS arrival within 3 days of injury.(24, 25) For a cohort of 2,899 critically–injured military personnel requiring Critical Care Air Transport Teams (CCATT) evacuation, median time from injury to arrival in Germany was 38 hours.(26)

Wound Infection Rates

With improved survival from severe injuries, emphasis has shifted to management of associated complications, including wound infections which remained a major cause of morbidity in both Vietnam and OIF/OEF.(27)

Of 17,726 patients admitted to Army hospitals in Vietnam, 4% developed wound infections while hospitalized within Vietnam. Seventy percent of patients received antibiotics with penicillin used in 92% of cases.(2) In Japan's Seventh Field Hospital lower extremity wounds were especially problematic with infectious complications in 27% of lower compared to 10% of upper extremity wounds. The anterior tibial region was particularly difficult because of the extensive nature of the wounds, precarious blood supply, and remaining edematous and macerated skin.(22) Of 84 patients with open tibial fractures between 1965 and 1968 at Brooke General Hospital, 4% of the 23 patients with high velocity gunshot wounds and 10% of 61 lower velocity metal fragment wounds were subsequently diagnosed with osteomyelitis with the most frequent associated organisms being *S. aureus* and *Pseudomonas*.(23) Of 61 civilian-incurred and 228 combat-related tibial shaft fractures that were cared for at Fitzsimons Army Medical Center in Denver, CO between 1968–1972, a 4% infection rate was noted after open penetrating injuries.(28)

It is difficult to compare wound infection rates in Vietnam to those in OIF/OEF as most data from Vietnam primarily include only those infections diagnosed in-theater and does not provide the granularity, multivariate analysis, or longterm follow-up reported during OIF/OEF. In comparison, most infections during OIF/OEF were diagnosed in CONUS.(2, 29) The Trauma Infectious Disease Outcome Study (TIDOS) is an ongoing 5-year prospective observational cohort study of infectious complications associated with traumatic injury sustained during deployment with follow-up extending from DoD through VA care. Initial analysis revealed that soft tissue infection and osteomyelitis diagnoses increased from 1% and 0.4% in Germany to 18% and 9% in CONUS respectively.(30) Risk factors noted for infectious complications after combat-related injuries included surgery prior to CONUS admission, higher ISS, blast injuries, abdominal soft-tissue wounds, more than three injury locations, or loss of limb.(15, 29, 31) As in Vietnam, lower extremity, especially open tibial wounds remained particularly problematic.(32–34) Of 192 OIF/OEF military personnel with 213 type III open tibial shaft fractures, 27% developed deep infections and 22% of extremities affected required amputation at an average of 24 months follow-up. Gustilo and Anderson type III B and C fractures, deep infection, and osteomyelitis were associated with amputation.(33) The statistics from Vietnam are not comparable as they include all open tibial fractures regardless of severity and lack clear definitions of osteomyelitis.(23, 28) Meanwhile, OIF/OEF studies concentrated on the most severe, Orthopedic Trauma Association type C fractures, especially Gustilo and Anderson type III, which have been

associated with increased rates of infections.(33–35) While these injuries were typically managed with hard casting in Vietnam, during OIF/OEF 60% of those with a diagnosis of osteomyelitis had indwelling hardware.(23, 32) Studies from the British military did not indicate increased rates of osteomyelitis in those with intramedullary nail placement compared to casting.(36) However, American studies have shown that while the initial diagnosis of osteomyelitis was more commonly associated with external fixation, recurrent osteomyelitis was more common with internal fixation.(23, 32, 36) There was also a trend towards more amputations during initial episodes of osteomyelitis (27%) compared to those of recurrences (17%).(32) Soldiers suffering from type III open tibial fractures who subsequently developed any type of infection had lower rates of return to duty and higher disability scores than those without infection. Within this cohort, infection contributed to the indication for amputation in 10 of the 11 amputated limbs.(37) Ultimately, the question of the best fixation strategy for combat-related tibial fractures remains a source of ongoing debate.(17)

New Pathogens Associated with Various Mechanisms of Injury

With the transition from aerial bombs, armor, and littoral and sea-engagements seen in World War II to small unit fire, explosive devices, and maneuvering common in Vietnam, new wound patterns and complications were noted.(3) The injuries associated with improvised explosive devices (IED) used in OIF/OEF have been associated with more severe tissue damage and perineal injuries which present a challenge to balance risk of infection with preservation of function when performing the required aggressive debridements.(38, 39)

A retrospective review of 210 Vietnam casualties suffered by U.S. Marines revealed that 10 were related to “booby traps.”(7) The most frequently cited were punji sticks. These were sharpened bamboo sticks hidden with foliage.(19, 40) The puncture could result in a stick fragment retained in the wound tract.(40) The resulting wounds were associated with increased infection rates (10% compared to 4% overall wound infections) and hospital length of stays. These increased complications were thought to be related to a deceptively deep wound compared to the “innocuous appearance” and the fact that they were rumored to have been dipped in fecal matter prior to placement.(2)

With the increased sophistication of enemy tactics in OIF/OEF, wounds followed injuries associated with more explosive power, deadlier fragmentation, and a larger fire ball.(12) The injuries suffered while on dismounted foot patrols during the OEF counterinsurgency phase were associated with multiple traumatic amputations and frequent exsanguination from truncal or junctional hemorrhage.(3) With advances in tactical combat casualty care (TCCC), the increased survival of patients with these complex injuries led to new infectious complications, namely IFI.(41) In comparison to the arid conditions of Iraq, southern Afghanistan, with large agricultural areas and lush vegetation, allowed blast injuries to be inoculated with heavy concentrations of environmental molds.(41, 42) Risk factors for IFI included lower extremity amputations, perineal or pelvic injury, and receipt of massive blood transfusions following blast injuries while on foot patrol in southern Afghanistan, especially Helmand and Kandahar provinces.(42) There are concerns about the iron burden

associated with these massive transfusions, as well as the role acidosis associated with these severe injuries may play in augmenting risk for *Mucorales* infections.(41) However, the duration of acidosis and systemic versus local tissue acidosis have proved difficult to evaluate in combat-related evacuees. While IFI was often polymicrobial, monomicrobial infections were typically *Aspergillus* spp. or from the *Mucorales* group.(14, 41, 42) After the identification of the IFI outbreak and characterization of risk factors, a local clinical practice guideline (CPG) was introduced at LRMC in early 2011 to screen for IFI in high-risk patients. After CPG initiation, there were statistically significant decreases in time to diagnosis of IFI and time to initiation of antifungals, increase in antifungal initiation at LRMC, as well as decreased likelihood that cases were associated with angioinvasion on histopathology. There was also a non-significant reduction in mortality from 11.4% to 6.7%.(43)

Bacteriology of War Wounds

As the most common cause of death outside the first 24 hours in Vietnam was secondary to sepsis, understanding the bacteriology of war wounds was of vital importance.(7, 8) With changing environmental factors, antimicrobial selection pressures, and surgical methods, continued reassessment of the bacteriology of war wounds has been necessary.

In a seminal study by Tong et. al, the initial bacteriology of war wounds was evaluated in 30 U.S. marines hospitalized in the Naval Support Activity Hospital in DaNang, Vietnam (Table 1). Of extremity wounds with positive cultures, approximately half of the 63 isolates were gram-positive on admission culture. However, by day 5 gram-positive organisms accounted for only 23 of 146 isolates.(44) Gram-negative organisms became the predominant isolates from wound cultures as time from injury and length of hospitalization increased.(11, 22, 45) *P. aeruginosa*, which accounted for only 3 isolates on day 1, accounted for the majority of gram-negative isolates by day 5. Other notable gram-negatives isolated later in the hospitalization included the *Enterobacter* group, *Proteus* group, *E. coli*, and *Mimae-Herellea-Bacterium-Alcaligenes* group [often quoted as *Acinetobacter baumanii complex* (ABC), but without clear evidence to support this reclassification].(44, 46) Fungal cultures are not described, but *Candida* spp. are mentioned as a rare finding.(10) While gram-positive skin flora represent the majority of initial wound isolates over the course of the year, during summer months there was a marked increase in isolation of enteric gram-negatives. This was felt to be related to environmental changes, warmer weather, and antimicrobial selection.(11, 45, 47, 48) Gram-negative sepsis was a recurrent issue, with the most frequent blood culture isolates being *Enterobacter*, *Mimae* groups, *Klebsiella*, *Pseudomonas*, *E. coli*, and *Proteus*.(8, 44) Bacteria isolated from blood cultures often, though not always, matched those from wounds.(11, 44) With the broad use of antimicrobials and aggressive wound debridement, notably absent were clinically significant *Clostridial* infections despite their continued isolation from soil samples.(19, 22, 49, 50)

A similar study to that performed by Tong et. al evaluating the bacteriology of acute war wounds in Vietnam was completed at the 31st Combat Support Hospital in Baghdad, Iraq (Table 1). In comparison to the even mix of gram-positive and gram-negative bacteria isolated from initial war wounds in Vietnam, in a cohort of 49 casualties with 61 wounds,

gram-positive organisms accounted for 93% of isolates. Similar to the findings in Vietnam the initial colonizing gram-negative isolates were typically low-virulence environmental organisms.(21, 51) Of concern was the finding that 2 of 4 *S. aureus* isolates were methicillin-resistant (MRSA). Importantly, positive wound cultures were noted in 5 of 8 wounds with only antimicrobial administration prior to admission, compared to 0 of 6 wounds with field irrigation only, and 1 of 6 with both field irrigation and antimicrobial administration.(21) As time from injury increased, antimicrobial exposures accumulated, and patients were evacuated along echelons of care, there was a transition from predominantly gram-positive and saprophytic gram-negative colonization of war wounds to nosocomial, and increasingly resistant gram-negative organisms, especially ABC, *Klebsiella* spp, *P. aeruginosa*, and *E coli*.(15, 33–35, 51–57) Similar findings were noted in a study of combat-related trauma patients with thermal injuries examining all bacterial isolates from respiratory, wound, blood, and urine cultures at the USAISR Burn Center ICU, BAMC. This study revealed a transition from isolation of *S. aureus* and ABC on arrival (following evacuation through LRMC and arriving an average of 4 days post-injury) to predominantly *P. aeruginosa* and *K. pneumoniae* after the first 15 days of hospitalization.(58) Despite increasing gram-negative colonization and infections during prolonged hospitalizations, late infectious complications and colonization of U.S. service members with combat-related traumatic injuries are predominantly secondary to gram-positive organisms, notably *S. aureus*.(32, 33, 35, 52)

Topical Antimicrobial Agents and Wound Management

During the Vietnam War, animal and human studies with topical antimicrobials yielded valuable information on bacteriology of war wounds and localized soil, as well as antimicrobial resistance patterns. Prior animal studies had shown that topical antimicrobial application was associated with decreased growth of *C. perfringens* in wounds and prolongation of life.(59) In other animal studies simulating crush wounds with contamination using soil recovered from various areas around Vietnam, the mortality rate decreased from 93% without treatment to 51% in those administered systemic oxytetracycline. However, the lowest mortality rate was noted in those treated with topical neomycin-bacitracin-polymyxin B, topical penicillin, or oxytetracycline spray.(60) Studies completed in human wounds in-theater also showed decreased infection rates and bacterial colony counts with topical therapies. In a foreshadowing of future antimicrobial resistance, none of the tested topical regimens were effective against *Pseudomonas*.(49, 61, 62) Despite encouraging animal and human studies, topical antimicrobial agents never gained wide acceptance in traumatic injuries. In contrast, the use of topical antimicrobials in burn patients was widely adopted during the Vietnam War. Prior studies by the Surgical Research Unit (SRU) had shown a decrease in burn wound sepsis from 59% to 10% and overall mortality from 38% to 20% with the use of topical mafenide acetate.(63) With centralization of burn patient care in Japan at the 106th General Hospital, protocols evolved to include topical therapy with mafenide acetate. The authors attributed the elimination of burn sepsis in their patients with 20–59% total body surface area burns (TBSA) to this transition. Mortality rates in similar cohorts from 1927 as well as the SRU prior to their transition to mafenide acetate were between 30–43% compared to 11% at the 106th General Hospital

after the addition of mafenide acetate to their protocols.(64) Later logistic regression analysis showed that topical antimicrobial therapy was of greatest benefit for patients age 20–50 and with burns of 30–79% TBSA.(65)

Additional approaches to minimize wound complications continued to be evaluated in OIF/OEF. Promising results have been noted with the incorporation of wound vacuum-assisted closure as well as use of antibiotic-impregnated beads in complex wounds.(20, 66–69) With the outbreak of IFI in U.S. service members suffering dismounted IED blasts in southern Afghanistan and concerns of adequate debridements of these complex injuries, there was a renewed interest in topical antimicrobial therapy. To address this, a study of topical agents against molds isolated from patients with IFI was completed. This revealed that Dakins solution exhibited the most favorable balance of efficacy and toxicity.(39) The efficacy of Dakins solution in vivo, with its rapid loss of activity, leading to requirements for frequent application when applied topically, is yet to be determined.(70) Topical antimicrobial agents, with their high local concentrations, have been evaluated in attempts to combat the increasing antimicrobial resistance in bacteria recovered from burn patients. However, without standardized breakpoints, recommendations remain unchanged for use of silver products and mafenide acetate for gram-negative organisms and mupiricin for MRSA.(71)

Antimicrobial Resistance

Antimicrobial therapy is often used as a complementary strategy to surgical debridement and irrigation for war wound infections. As antimicrobial agents are introduced, new resistance is noted. War wound bacteriology has not been immune to this evolutionary relationship.

During the Vietnam War, a study revealed that of 30 U.S. marines, 12 were septicemic, and 3 ultimately died. All blood isolates were resistant to penicillin and streptomycin, the two most frequently employed antibiotics.(19, 44, 62) Half of the organisms isolated at the 249th General Hospital in Japan were resistant to streptomycin.(11) A study of antimicrobial susceptibility of the four predominant organisms from cultures in Saigon, Vietnam, revealed that penicillin susceptibility was so poor the author remarked that “if routine antibiotics are to be used, penicillin is not the drug of choice.”(47) Outcomes from gram-negative infections remained poor, even with widespread use of carbenicillin and gentamycin.(6)

Infections related to resistant gram-negative organisms and MRSA continued to plague the military during OIF/OEF.(30, 34,51,54, 55, 72, 73) During OIF, an outbreak of ABC infections noted in U.S. military service members resulted in providers using increasingly broad spectrum antimicrobials, primarily imipenem, at the point of injury and continued through level II and III hospitalizations.(personal communication, Clinton K. Murray (CKM), (20, 74, 75)) Ultimately, outbreak investigations determined the source to be nosocomial transmission from a reservoir of host nation patients with prolonged hospitalizations, higher rates of pre-existing colonization with MDR gram-negative pathogens, and environmental contamination.(56, 76–78) One study evaluating the effectiveness of aggressive infection control protocols and antimicrobial stewardship revealed its feasibility in the combat zone. Rates of ventilator associated pneumonia at an

Air Force Theater Hospital in Iraq significantly decreased from 60.6/1,000 ventilator days at baseline in May 2006, to 11.1/1,000 ventilator days within 3 months. Overall ABC susceptibilities to the most commonly employed antimicrobials significantly increased from 46% to 64% for meropenem and 41% to 68% for amikacin.(79) Subsequent studies revealed that after intensive environmental cleaning and infection control protocols, previously contaminated sites showed no evidence of MDR isolation.(77) The decrease in ABC colonization rates temporally correlated with initiation of CPGs for antimicrobial use and infection control. An increase in rates of other MDR gram-negative bacterial colonization, primarily with ESBL-producing *Enterobacteriaceae* was noted.(80) Rates of MDR gram-negative colonization, increased from 7% at LRMC to 12% at participating CONUS institutions,(55) without evidence of clonality in these isolates.(54) Instead, this likely reflected an increase in pre-injury ESBL-producing *E. coli* colonization as well as antimicrobial selection pressure that accumulated along the evacuation chain.(30, 54, 81) In order to combat these increasing rates of resistance, a CPG was released in 2008 emphasizing the avoidance of unnecessarily broad-spectrum antimicrobials (especially imipenem) which resulted in an improved compliance rate in antimicrobial prescribing, especially in relation to penetrating abdominal wounds (increased from 10% to 68%) and closed injuries (from 52% to 80%). However, this may have been related to improved categorization of wounds.(75) An ongoing preliminary analysis indicates continued improvement in adherence to the CPG recommendations and seeks to further clarify related clinical outcomes (personal communication, CKM).

Blood Product Usage and Complications

Mass casualties remain a challenge to the forward operating hospital.(82, 83) Management transitioned from streamlining supportive care with minimal documentation of complications in Vietnam to attempting to quantify and minimize possible transfusion-transmitted infections (TTI) and the immunomodulatory effect of transfusions in OIF/OEF. During the Vietnam War, more than 100,000 Group O uncross-matched, universal donor transfusions were given without guarantees of safety and no formal investigations of complications.(82) Concerns regarding local blood acquisition were triggered by knowledge that two of the leading causes of fever in Vietnam (second to fever of unknown origin) were malaria and hepatitis.(83, 84)

Following the Vietnam War, there was a growing awareness of other possible complications of transfusions including immunomodulatory effects. A prospective study of 210 critically injured patients admitted to the USNS Comfort during OIF revealed that infection rates and ICU length of stay were significantly higher in those with blood transfusions. There was a linear correlation between the incidence of infection and amount of blood transfused.(85) To address concerns, including those regarding TTI, a CPG was developed to delineate the use of fresh whole blood (FWB).(86, 87) Initial testing in the field for the walking donor program used non-FDA approved kits which upon validation revealed sensitivity for HBV of 16% and HCV of 28%. (personal communication, CKM) Despite this, there have been no TTI reported for HIV or HBV, only one HCV TTI (incidence of 2.1/1,000 persons), and one TTI-related HTLV-I in post-transfusion screening.(88, 89) After release of the FWB CPG, there was a decrease in the incidence of hypothermia on presentation (which has been

associated with greater operative blood loss, higher rates of postoperative wound infections, and longer hospital stays). There was also a decrease in mortality noted with increased adherence to component therapy.(90) However, these improvements were also likely related to additional multidisciplinary improvements along the eschelon of care including prehospital care and other trauma systems approaches.(90, 91)

Research in the Trauma Zone

Research has been recognized as vital to addressing questions that are unique to the combat-injured patient. In-theater research during prior conflicts has led to attempts to form large, standardized databases that allow more systematic evaluation of these questions.

During the Vietnam War, research efforts were fragmented. In-theater clinical studies were limited to the Trauma Study Section of the US Army Medical Research Team and Walter Reed Army Institute of Research (WRAIR).(92) This began in 1966, but long-term follow-up of subjects was not possible.(10) Notably, the largest study of wound analysis from Vietnam makes special note that the records upon which it was based were “frequenctly completed under stress, by command, without enthusiasm, by physicians who considered it another thankless task, and therefore the accuracy of some of the data may be questionable.” Nonetheless, this was the best available data at the time.(2) Process improvement efforts at the time resulted in unpredictable feedback of variable applicability to in-theater conditions.(92)

The efforts of the Vietnam War developed into centralized, systematic databases that have enabled integrated joint service research during OIF/OEF.(92, 93) The Department of Defense Trauma Registry (DoDTR) is the largest and most comprehensive database of wartime wounded patients ever assembled, enabling the evaluation of over 57,000 soldiers with trauma-related injuries between 2002 and 2011.(13, 29,31, 92, 93) Research has attempted to address infectious complications of war wounds. This has included several studies focusing on interventions at the point of injury.(32, 52, 94) A study of the 75th Ranger Regiment prehospital trauma registry between 2003 and 2010, revealed that only 28% of 405 total casualties received prehospital antimicrobials.(52) To address the need for standardization, a CPG emphasizing standardization of post-injury antimicrobials, the importance of debridement and irrigation of war wounds, and surgical management was released.(17, 20) This CPG, and many others covering topics unique to combat casualties have led to more uniform practice in the combat zone and are frequently reassessed.(95) Process improvement includes real-time feedback via the Joint Trauma System with weekly worldwide trauma center video teleconferences.(68, 92) These process improvement projects, along with the knowledge gained through them have been associated with improved outcomes for the combat wounded.(91) The Multidrug-resistant Organism Repository and Surveillance Network (MRSN) from WRAIR has facilitated investigations of MDR outbreaks, surveillance, and research. Studies of longterm infectious complications, clinical, and functional outcomes are also new concepts since the Vietnam War.(37, 96) The TIDOS project has allowed the completion of unprecedented large, longitudinal studies of antimicrobial resistance, infectious complications and outcomes, unique injury patterns including IFI risk factors, and evaluation of adherence to antimicrobial use

recommendations stretching into follow-up care within the DoD and VA health systems.(30) Further analyses of this data are currently ongoing.

Conclusion

The historically low CFR noted during OIF/OEF is undoubtedly related to building on experiences from prior conflicts. The Vietnam War and OIF/OEF reinforced the importance of rapid medical evacuation and definitive surgical management of war wounds. They revealed the constant evolution of infecting organisms and the fact that wars are not immune to the ever-present threat of increasing antimicrobial resistance. We have also seen that with decreased mortality of severely injured personnel new complications must be addressed.

Despite the continued decrease in CFR, the cyclical themes cannot be overlooked. These range from wound infections to infection-related mortality as a leading cause of delayed death in combat-related injured patients. Better, faster diagnostics are desperately needed. Examples include molecular platforms for rapid diagnosis and improved methods to differentiate colonizing and infecting organisms.(97) While we await these diagnostic breakthroughs, there will be continued need for empiric treatment based on clinical judgements often made in the absence of serial evaluations during medical evacuations traversing the globe within a week.

Using the foundation of fragmented research from the Vietnam War, previously successful templates were assembled into joint service research institutions which have allowed questions unique to the combat-injured casualty to be addressed. However, coordinating research continues to be a struggle within the war zone. As such, much data analyzed within this paper is based on retrospective studies with all of the associated flaws. Yet efforts are ongoing to increase the ability to prospectively examine questions of critical importance to our combat-wounded personnel. The translation to improvement in care of combat casualties from systems like the DoDTR, USAISR, MRSN, and TIDOS cannot be overemphasized. It is imperative that we continue to pursue aggressive, collaborative research.

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Table 1

A summary of select studies of aerobic bacteria isolated from wound cultures prior to or shortly after initial debridement of war wounds during the Vietnam War and OIF/OEF

	Wound culture results prior to surgical intervention				**Wound culture results on follow-up evaluation**						
	Vietnam	**Vietnam**	**OIF**	**OEF***	**Vietnam**	**Vietnam**	**Vietnam**	**Vietnam**	**OIF/OEF****	**OIF/OEF*****	**OEF***
Reference	(44)	(47)	(21)	(51)	(44)	(44)	(22)	(10)	(33)	(57)	(51)
Dates of Study	1968–1969	May–June 1967	2004	2013–2014	1968–1969	1968–1969	n/a	1968	2003–2007	2007–2008	2013–2014
Number of patients	30	110	49	10	30	30	115	n/a	192	34	10
Number of wounds evaluated	63	112	61	13	63	63	n/a	n/a	145	91	11
Number of bacteria isolated	186	122	37	27	124	146	n/a	1484	133	33	13
Timing of culture	Admission	Admission or in OR	Within ER	Day of injury	3 days following injury	5 days following injury	1–2 days after transfer to Japan	While hospitalized in Japan	Within 72 hours of level V admission	Within 72 hours of level V admission	Day 3–12 post-injury
Gram-Positive (%)	48	35	93	44	37	16	39	38	19	15	54
Staphylococcus aureus (%)	4	70	11	0	13	22	n/a	89	8	0	0
Coagulase-negative *Staphylococcus* spp. (%)	52	14	86	8	37	35	n/a	11	28	0	0
Enterococcus spp. (%)	6	16	0	42	0	0	n/a	n/a	56	60	57
Gram-Negative (%)	52	65	7	56	63	84	61	57	81	85	46
Pseudomonas aeruginosa (%)	3	n/a	0	0	21	34	n/a	43	12	0	17
A. baumannii complex (%)	-	-	0	0	-	-	n/a	-	53	71	0
Mimeae-Herellea-Bacterium-Alcaligenes group (%)	30	-	-	-	18	13	n/a	-	-	-	-
Escheriae coli (%)	17	14	33	0	18	10	n/a	32	6	4	34
Proteus spp. (%)	2	18	0	0	6	14	n/a	10	0	0	0
Enterobacter spp. (%)	25	42	0	7	19	21	n/a	14	16	7	17
Klebsiella spp. (%)	13	1	0	0	6	3	n/a	2	12	0	0
Serratia marcescens (%)	10	1	0	0	6	5	n/a	n/a	0	0	0

ER: Emergency room, OR: operating room, n/a: not available, level V: tertiary care hospital within the continental United States

* Cultures from mangled lower extremity injuries only

** Cultures from open tibial fractures only

*** Cultures from biopsy of open wounds being treated with vacuum-assisted wound closure devices