Epidemiology of Infections Associated With Combat-Related Injuries in Iraq and Afghanistan

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Enhanced medical training of front line medical personnel, personal protective equipment, and the presence of forward surgical assets have improved the survival of casualties in the current wars in Iraq and Afghanistan. As such, casualties are at higher risk of infectious complications of their injuries including sepsis, which was a noted killer of casualties in previous wars. During the current conflicts, military personnel who develop combat-related injuries are at substantial risk of developing infections with multidrug resistant bacteria. Herein, we describe the bacteriology of combat-related injuries in Operation Iraqi Freedom and Operation Enduring Freedom that develop infections with particular attention to injuries of the extremities, central nervous system, abdomen and thorax, head and neck, and burns. In addition, the likely sources of combat-related injuries with multidrug resistant bacteria infections are explored.

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By September 30, 2006, approximately 1.4 million military personnel had been deployed to Iraq and Afghanistan in support of Operation Iraqi Freedom (OIF) and Operation Enduring Freedom (OEF) (http://www1.va.gov/opa/fact/docs/amwars.pdf, accessed June 14, 2007). In total, 29,531 were wounded in action, of which 13,514 did not return to duty (http://www.defenselink.mil/news/casualty.pdf, accessed September 21, 2007). The number of casualties died of wounds has gradually declined from 8% in World War I, to 4.5% in World War II, 2.5% in Korea, 3.6% in Vietnam, 2.1% in Desert Storm, and 6.4% in Somalia.1 The total number of died of wounds has not yet been determined for OIF/OEF. Deployment of forward surgical assets, rapid evacuation to medical care, enhanced training and expertise of combat medics and corpsmen, and improved body armor has culminated in a greater number of casualties surviving initial injuries.

Extremity injuries account for the majority of wounds (~65%), followed by head and neck (~15%), thorax (~10%), and abdomen (~7%). This has remained stable throughout the last century of warfare and during OIF/OEF.2–6 Historically, burns complicate 5% to 10% of combat casualties; this has been true in OIF/OEF.7,8 Although there are differences between combat theaters and over time as individual theaters mature, wounding is most frequently caused by explosive devices.4,9,10 Gunshots, grenades (including rocket-propelled), and mortars are also responsible for a number of injuries. Patients typically suffer multiple injuries, involving, on average, 1.6 different body parts.4 Explosive devices typically result in a greater number of injury sites and greater severity of injuries.

Despite our extensive knowledge of wounding patterns, we have not adequately characterized the trends of infectious complications and associated outcomes of personnel injured in OIF/OEF. During the Vietnam War, sepsis was the third leading cause of death for combat casualties in theater.11 Among the casualties of the Vietnam War, 2% to 4% developed wound infections during hospitalization in that country. Data regarding infections that developed after transportation out of theater are more difficult to describe.12 Factors influencing the development of wound infections in a combat theater include wound type and severity, the presence of embedded foreign material or fragments (such as soldier’s clothing, dirt, and debris), evacuation time from point of injury to medical care, initiation of antimicrobial agents, adequacy of initial wound debridement, immediate wound care, definitive surgical care, rehabilitative care, prior antimicrobial pressure, and the presence of nosocomial pathogens, (especially multidrug resistant pathogens) at treatment facilities. The appropriate management of injury and subsequent infection should be influenced by the mechanism and type of injury, whether caused by low- or high-velocity weaponry, mines, mortars, or explosive devices. Some systems, such as mines and other explosive devices, can increase the risk of infection caused by contamination of wounds from ground material or other matter placed in the devices (e.g. animal carcasses, discarded dirty syringes, or fecal material). Although it has been argued that the heat generated from firing high-velocity weapons sterilizes bullets, this has proven not to be true.13 Overall, the management of combat casualties and finding methods to prevent infections is challenging to healthcare providers throughout the military medical system.
Levels of Medical Care

Medical care capability increases as a casualty is transported from point of injury to level (formerly echelon) I through level III and outside the combat zone to level IV and V (Table 1). Level I provides care as close as possible to the time of injury, and consists of immediate stabilization and evacuation to an initial aid station. Level II offers short-term holding capacity and initial resuscitation.3 This level of care is currently subdivided into IIA and IIB, reflecting the absence or presence of acute, life-saving surgical care. The Army can augment a level II facility with a Forward Surgical Team (FST).14 The Air Force has Mobile Field Surgical Teams (MFST) to provide level II surgical care. Level III, such as the Army’s Combat Support Hospital (CSH), the Air Force Theater Hospital (AFTH), and Navy’s hospital ship that provided care during the early stages of OIF, supply complete resuscitative and hospital care. Assets at this level of care include a myriad of surgical specialties and support and are equivalent to a well-staffed community hospital.16 Care provided at level IV during the current conflict is delivered at the Landstuhl Regional Medical Center, Germany, rendering more definitive surgical care outside the combat zone.6 Level V care is the most definitive rehabilitative and tertiary level of care and is provided in military and Veterans Affairs medical centers located in the United States.

Medical care within the combat theater is provided to both US and non-US personnel, including coalition forces, host nation personnel, and detainees.17 The AFTH at Balad Air Base, Iraq, had 10,953 total hospital admissions between September 2004 and August 2006.18 Of these admissions, 4,323 were not US or coalition patients. Typically, US and coalition forces are evacuated out of country as little as 48 to 72 hours from time of injury in Iraq. Usually, evacuation time to the patient’s final US facility is around 7 days. This contrasts sharply to evacuation times in many previous US conflicts.18,19 Non-US personnel receive therapy at level III facilities until they are stable for transfer to a local healthcare facility or until care is completed, which take weeks.20,21

Wound Bacteriology

Staphylococcus aureus and aerobic gram-negative bacteria such as Pseudomonas aeruginosa have traditionally complicated battlefield injuries.11,22,23 Near the early stages of OIF/OEF, there was a notable increase in casualties developing infections with resistant bacteria (multidrug resistant organisms such as Acinetobacter baumannii calcoaceticus complex (ABC).24 At one US military treatment facility, the incidence of blood-stream infection with ABC in 2005 was 0.3 cases per 1,000 admissions in contrast to 2002, when the incidence was 0.087 cases per 1,000 admissions (personal communication, Kim Moran). Other notable gram-negative bacteria infecting combat casualties in these US facilities included multidrug resistant P. aeruginosa and Klebsiella pneumoniae. Infections with multidrug resistant bacteria were also reported on the USNS Comfort at the beginning of OIF, mostly among non-US personnel.25 A total of 211 trauma patients were managed from March to May 2003 of which 56 were infected. Of these infected patients, 85% were Iraqi, with an average of 4.2 days elapsing from injury to presenting to the Comfort. Sites of infection were wounds in 84% of cases and blood in 36%. The most common pathogens recovered were ABC (33%), Escherichia coli (14%), and P. aeruginosa (14%). Assessments of bacteria from blood, urine, wound and other sites during 2003 and 2004 at a CSH in Iraq revealed a preponderance of gram-positive bacteria among US patients.26 In contrast, non-US patients mostly had gram-negative bacteria, including P. aeruginosa, K. pneumoniae, E. coli, and ABC, largely multidrug resistant in nature.

One of the most disconcerting facts about the bacteria complicating combat casualties is their increasing antimicrobial resistance.27,28 Between 2002 and 2005, in ABC, P. aeruginosa, and K. pneumoniae there was increased resistance to nearly all antibiotics tested at one treatment facility.28 This has resulted in a steady decline in the number of available antimicrobial agents. In ABC isolates collected between 2003 and 2005 in a US military treatment facility, the difference in broad spectrum antimicrobial resistance between personnel injured in OIF/OEF and nondeployed patients was statistically significant, with higher resistance in those isolates from OIF/OEF injuries.27 Over time, resistance increased against all antimicrobial agents tested; however, only imipenem resistance was statistically significant at the end of the study period in comparison to the beginning (56% vs. 87% susceptible). In isolates recovered from deployed personnel, only colistin and minocycline agents were effective more than 75% of the time. Minocycline is not currently available in the United States in an intravenous form, limiting its application in the severely ill. Colistin is associated with toxicity and ABC can develop resistance during treatment with this agent.

Infectious Complications of Combat Trauma

Extremity Injuries

Extremity injuries have been seen in the greatest number of casualties from OIF/OEF, but small single hospital reviews suggest that a large percentage of these wounds are complicated by infections. Data obtained from Brooke Army Medical Center reveal that between January and June of 2006, 223 OIF/OEF persons were evaluated at Brooke Army Medical Center with 66 (30%) evaluated for orthopedic-related trauma, of which 26 (40%) received courses of antibiotics for various bacteria, including ABC (13), Klebsiella spp. (9), P. aeruginosa (6), Enterobacter spp. (5), and methicillin resistant S. aureus (MRSA) (6). Antibiotics included expensive and potentially toxic medications such as colistin, imipenem-
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* Formerly termed echelons.
cilastatin, and vancomycin for extended periods of time. Another study evaluated 62 open tibial fractures in combat casualties injured between 2003 and 2006. This study identified 40 patients with type III fractures, in whom 35 had data available for analysis. Twenty-seven of the 35 patients had at least one organism present in initial deep wound cultures at admission. The most frequently identified pathogens were ABC, *Enterobacter* spp, and *P. aeruginosa*. Thirteen of the 35 patients had healing times longer than 9 months, which appeared to be associated with infections. None of the gram-negative bacteria identified in the initial wounds were recovered again at the time of repeat operation; however, all patients had at least one staphylococcal organism and three had *P. aeruginosa* at that time. Five of 35 patients ultimately required limb amputation, with infectious complications cited as the reason in four. Interestingly, another study early in the conflict (2001–2003) out of Afghanistan assessed 52 casualties with orthopedic injuries revealed only a 3.8% infection rate. One patient was infected with *Pseudomonas* and a second was infected with *Acinetobacter* and MRSA. In an unpublished study that assessed osteomyelitis among combat casualties from OIF/OEF from 2003 to 2006, 110 patients with 139 hospitalizations were identified (personal communication, CKM). Ninety-nine of these patients had lower extremity, 44 had upper extremity, and two had axial injuries. The pathogens initially noted in the wounds were ABC (71%), *K. pneumoniae* (24%), *P. aeruginosa* (26%), methicillin susceptible *S. aureus* (MSSA) (15%), and MRSA (10%). After adequate surgical and antimicrobial therapy, those with recurrent or relapses had a clear transition from predominantly gram-negative bacteria to gram-positive bacterial infections. ABC, *K. pneumoniae*, and *P. aeruginosa* each represented 5% of these latter infections, whereas MSSA produced 22% and MRSA 28%.

Although ABC has received substantial emphasis as a key pathogen complicating combat casualty care, associated outcomes reveal low virulence. In an assessment of 232 active duty soldiers (151 were OIF/OEF) admitted with injuries to one military treatment facility between March 2003 and May 2004, ABC was recovered in 48 of 84 soldiers cultured, of which 30 were clinical infections, including 23 with osteomyelitis or wound infections or both. In this group, all patients cleared their infection even if they received inadequate antimicrobial therapy.

Unfortunately, because of the scarcity of data regarding care and associated infectious complications of non-US personnel treated in Iraq or Afghanistan, it is difficult to determine the extent of infection in that population. Among non-US personnel treated between September 2003 and August 2006 at the AFTH in Iraq, there were 134 extremity injuries with vascular damage. In that report, there were five wound infections among 192 major vascular injuries. Another study assessed 88 injuries to non-US personnel treated at the AFTH that included 59 with upper or lower extremity wounds treated with standard surgical techniques, antibiotics, and wound VAC. There were no reported infectious complications of these extremity injuries, although follow-up was limited.

**Central Nervous System (CNS) Injuries**

Numerous casualties have had CNS penetrating trauma during OIF/OEF. Although there have been no systematic evaluations of the infectious complications of these wounds, there are two case reports of multdrug resistant bacteria CNS infections. Both describe ABC infections that cleared with appropriate management including the use of broad spectrum antimicrobial agents.

**Head and Neck Injuries**

Rates of infectious complications for US head and neck casualties has not been described. Among Iraqi patients treated at an Iraqi facility between September 2003 and August 2004 there were 100 patients with multiple and comminuted mandibular fractures. Fifty-three injuries were caused by missiles and 54 patients had comminuted fractures. Three of the patients with comminuted and one with multiple fractures developed infection, for an overall infection rate of 4%. The specific bacteria infecting the wounds were not reported. Of the infected injuries, three were from missiles and one from a motor vehicle crash.

**Thoracic and Abdominal Cavity Injuries**

An assessment of casualties treated on the USNS Comfort during the early stages of OIF revealed on multivariate analysis that abdominal injuries had an odds ration of 2.7 for developing an infection whereas extremity injuries had a 2.4 odds ratio. The bacteria complicating these injuries were multidrug resistant and included ABC and *P. aeruginosa*. Thoracic injury was not associated with infection on univariate or multivariate analysis. There were 175 (5.1%) colon and rectal injuries among 3,442 patients treated between September 2003 and December 2004 at a CSH in Iraq. Sepsis developed in 27 patients (16%) and had significant impact upon mortality. Specific bacterial pathogens were not reported in that report.

**Burn Infections**

Burn patients have comprised approximately 5% of US military casualties in OIF/OEF. Since the onset of these conflicts, there have been numerous burn casualties infected with multidrug resistant bacteria. A retrospective study of all patients admitted to the US Army Institute of Surgical Research burn center from January 2003 to May 2006 was undertaken to evaluate the impact of bacteremia in that population. One hundred twenty-nine of 1,258 patients admitted to the burn center became bacteremic during their hospitalization. Fifty-one of 414 OIF/OEF burn patients had episodes of bacteremia. Ninety-two of the 414 OIF/OEF burn patients had bacteremia with *P. aeruginosa*, *K. pneumoniae*, *S. aureus*, and ABC. Bacteremia with *K. pneumoniae* was inde-
The incidence of ABC infection increased from 2.3% in 2001 to 11.9% in 2005 at the US Army Institute of Surgical Research. A retrospective study examined the clinical impact of ABC. Among the 802 patients included in this study, 59 patients were infected between January 2003 and November 2005, with an additional 52 patients found to be colonized with ABC during that time period. Bacteremia was the most common type of infection (31 of 59 infections). In general, patients with ABC infection had more severe burns, more comorbidities, and longer lengths of stay than those patients with colonization or no ABC recovered. ABC infection was associated with 22% mortality in contrast to 7.7% in those without infection; however, on multivariate analysis there was no mortality attributable to ABC. Most of the ABC isolates had broad spectrum antimicrobial resistance; however, there was no statistical difference in mortality between those treated with effective antimicrobial agents (24.5%) versus those who were not (10%) (p = 0.432).

**Epidemiologic Source of MDRO Infections**

Traditionally, gram-positive bacteria and anaerobes predominate in wounds at the time of injury, and are replaced by gram-negative bacteria after 2 to 7 days, followed by Staphylococci and Strep-tococci after 2 to 3 weeks. Resistant bacteria complicated wounds of combat casualties after the use of prophylactic or preemptive antibiotics given at the time of injury in previous wars. Proposed sources of these multidrug resistant bacteria include preexisting colonization of the patient at the time of injury, inoculation into the wounds at the time of the injury from environmental contamination, and nosocomial transmission during the care of patients within the military healthcare system.

It is known that a person’s skin is colonized with approximately 180 different types of bacteria at any one time. Typically, 25% of persons are colonized with *S. aureus*, and 3% with MRSA. This is true within our military population, and it has been recognized that colonization can lead to infections. *S. aureus*, including MRSA, are associated with colonization at the time of injury and may be introduced into the wound directly from skin colonization. MRSA is also a known nosocomial pathogen.

Several studies have investigated whether ABC colonizes the skin of casualties before injury. An assessment of healthy soldiers with no prior deployment history visiting a troop medical clinic in the United States revealed soldiers were occasionally colonized with ABC, but these isolates were not genetically or phenotypically related to the bacteria recovered from combat casualties of OIF/OEF. In addition, cultures of noninjured military personnel in Iraq or upon arrival to Germany after leaving Iraq without prior exposure to theater healthcare facilities have not recovered ABC. Therefore, it is unlikely that casualties are colonized with ABC before injury.

One study attempted to evaluate if bacteria from environmental contamination were inoculated into the wounds at the time of injury. Forty-nine casualties with 61 wounds were screened at the CSH in Baghdad for wound contamination at the time of injury. Most bacteria recovered were gram-positive (93%). There were only three gram-negative bacteria detected; none were multidrug resistant and this group did not include *P. aeruginosa* or ABC. Although inconclusive based on the small size of the study mentioned, it is unlikely that patients have their wounds inoculated with environmental material such as dirt or debris containing multidrug resistant gram-negative bacteria at the time of injury.

Another possibility for cause of resistant gram-negative bacteria infecting combat casualties is nosocomial transmission. At the onset of OIF/OEF, ABC, and other multidrug resistant bacteria were increasingly being described worldwide as nosocomial pathogens. ABC has been reported to infect injuries of noncombat trauma victims. In addition, ABC was noted to be a nosocomial pathogen in countries surrounding Iraq, including Turkey, Saudi Arabia, and Kuwait. In Jerusalem, recovery of ABC went from 6% of nosocomial bacteremia cases in 1999 to 17% in 2002, representing the most common pathogen producing bacteremia in one hospital. An analysis of the bacteria recovered from a CSH in Baghdad during 2003 and 2004 revealed that non-US personnel had more multidrug resistant gram-negative bacteria than US personnel. This is notable, as non-US patients spend prolonged periods of time within the CSH, possibly serving as a reservoir of these bacteria for nosocomial transmission, especially in the combat zone where implementation of infection control procedures can often be challenging.

Scott et al. performed a key study that supports the role of nosocomial transmission contributing to infections of combat casualties with multidrug resistant bacteria. That study screened dirt obtained in Iraq and environmental samples from treatment areas within CSHs in Iraq for the presence of ABC. It also attempted to link any environmental samples with ABC isolates recovered from patients cared for in Iraq, on the USNS Comfort, at Landstuhl, or WRAMC or both. All field hospitals screened had ABC recovered from treatment areas. By molecular typing, there were 66 different ABC strains noted among 170 clinical isolates and 25 different strains among 34 environmental samples. Although one could not point to one CSH or one particular strain as the cause of the outbreak, there were five cluster groups that matched environmental field hospital isolates to patient isolates. The largest cluster included 45 isolates from 43 patients at four different US military hospitals that matched an isolate recovered from an operating room at a CSH. That cluster included non-US patients and US patients with no deployment history that were OIF and non-OIF inpatients with no deployment.
history in military hospitals in the US. These isolates were related to isolates from the United Kingdom. In addition, ABC strains were similar to some of the isolates previously found infecting patients in Europe. Isolates have also been recovered from hospitals taking care of Canadian soldiers injured in Afghanistan and evacuated to Canadian hospitals.

Although ABC does not appear to cause great harm in healthy military personnel, when transferred too older or immuno-suppressed ill inpatients, this bacteria can cause death. In the US military burn unit, despite aggressive infection control measures, 50 patients (6% of all admissions during the study period) acquired ABC colonization or infection during their hospital stay, suggesting nosocomial spread.

At this time it is not clear what is leading to the increasing antimicrobial resistance in bacteria recovered from our military treatment facilities. One of the major concerns is that greater use of broad spectrum antibiotics to empirically treat wounds of combat casualties in the combat zone or along the evacuation chain is resulting in selection of more resistant pathogens. In addition, the use of broader spectrum agents used to treat multidrug resistant infections of non-US personnel within our hospitals in Iraq is likely driving increasing resistance of bacteria in this reservoir of patients for potential nosocomial transmission.

CONCLUSIONS

As the care of combat casualties continues to improve, allowing enhanced survival after initial injuries, infectious complications will remain a major cause of short- and long-term morbidity. At this time, casualties are undergoing therapy for wounds that are often colonized or infected with multidrug resistant bacteria such as ABC, P. aeruginosa, K. pneumoniae, and S. aureus. The role of nosocomial transmission and the over use of broad spectrum antibiotics resulting in more resistant pathogens should not be ignored. Continuing to improve our understanding of wounding patterns, infectious complications, and modes of transmission will improve care for casualties.

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