Clin Orthop Relat Res (2008) 466:1356–1362
DOI 10.1007/s11999-008-0212-9

SYMPOSIUM: PAPERS PRESENTED AT THE 2007 MEETING OF THE MUSCULOSKELETAL INFECTION SOCIETY

# Multidrug-resistant Organisms in Military Wounds from Iraq and Afghanistan

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Published online: 18 March 2008


**Abstract** Mortality from battlefield wounds has historically declined, thanks to better surgical management, faster transport of casualties, and improved antibiotics. Today, one of the major challenges facing U.S. military caregivers is the presence of multidrug-resistant organisms in orthopaedic extremity wounds. The most frequently identified resistant strains of bacteria are Staphylococcus aureus, Klebsiella pneumoniae, Pseudomonas aeruginosa, and Acinetobacter calcoaceticus-baumannii complex. Overuse of broad-spectrum antibiotics may be an important factor in building resistant strains. Acinetobacter infections appear to hospital-acquired and not from an initial colonization of the injury. More research is required to give military physicians the tools they require to reduce the infection rate and defeat multidrug-resistant organisms.



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## Introduction

The urgency of responding to wartime medical needs has for decades driven the pace of improvements in the treatment of orthopaedic trauma [13]. This is true not only regarding surgical techniques, but preventing and treating wound infection, advances in transportation, and aseptic practices. In Afghanistan and Iraq, the military has an excellent record of providing rapid and highly advanced care aimed at fighting infection. However, a decrease in mortality rates due to the use of improved body armor and rapid evacuation in treatment has been accompanied by a substantial risk of developing infections with multidrug-resistant organisms (MDROs).

We offer a brief historical perspective on the U.S. military's efforts to prevent wound infection, detailing how mortality rates have decreased from World War I to the present through improved surgical techniques, transport, and antibiotic usage. We then review recent literature regarding the rise of specific multi-drug resistant infections in U.S. military deployed in Iraq and Afghanistan, with a particular emphasis on A. calcoaceticus-baumannii complex.

The major issues raised by the rise of MDROs in military wounds are in regard to the specific resistant strains involved; how military caregivers currently deal with them; the most likely mode of transmission; whether antibiotic usage is fostering patterns of resistance; and what areas researchers should focus upon in attempting to address this problem [31].

## Materials and Methods

We selected peer-reviewed articles based on their relevance either to historical trends involving treatment of

infection in wartime; current trends in U.S. military care in Iraq and Afghanistan; or their relevance to antibiotic use in wound infection in general settings. A PubMed search of "war wounds infection" returned 433 articles; narrowing the search by adding the modifier "United States" resulted in 66 articles for consideration. Information from selected sources was used to develop a historical perspective.

The terms "war infection Iraq" narrowed the results to 60 items; 42 of which overlapped with the previous search. The terms "surgical site infection" yield more than 5,000 results, but narrowing the search to "surgical site infection antibiotic" results in a more manageable 163 articles, from which two authors (JHC, MM) selected based on the following criteria: their relevance to infected extremity wounds; whether they provided guidelines for treatment; and timeliness.

A coauthor (CKM) has previously published several reports [24, 26, 63] regarding bacteria isolated from patients returning from Iraq. Selected results from three studies were deemed of particular significance to this topic and were incorporated. In the first study, predominant bacteria and antimicrobial susceptibilities were surveyed from a deployed tertiary care facility in Baghdad, Iraq, serving U.S. troops, coalition forces, and Iraqis, from August 2003 through July 2004, including cultures of blood, wounds, sputum, and urine, for a total of 908 cultures [63]. In the second study, investigators retrospectively reviewed Type III open diaphyseal tibial fractures U.S. military service members wounded in Iraq or Afghanistan who were admitted to Brooke Army Medical Center (BAMC), Fort Sam Houston, Texas, between March 2003 and September 2006 [26]. In the third study, investigators selected 142 nonduplicate Acinetobacter baumannii-calcoaceticus complex isolates from patients at BAMC and performed susceptibility tests using broth microdilution [24].

## Historical Perspective

Before the 20th century, deaths from disease regularly exceeded those arising from war wounds. During the French Revolutionary and Napoleonic Wars (1792–1815), the British Army's ratio of disease-related deaths to battle-related deaths was 7:1. The American forces in the Mexican War (1846–1848) and the Spanish-American War (1898) saw a similar mortality rate from disease. It was not until World War I (1914–1919) that battlefield deaths reached parity with disease-related deaths [50]. Improvements in the surgical management of wounds led to the gradual disappearance of clostridium-associated gas gangrene through the first half of the 20th century. In World War I, the incidence of gas gangrene was 5% with a 28% mortality rate; in World War II, incidence was 1.5% with 15% mortality; and in the Korean War, 0.08% with no mortality [23].

World War II and the Korean War saw the introduction and increasing use of antibiotics. Initially, sulfanilamide powder was the standard of care in World War II. Soldiers carried it with them and in the field simply dumped it into the wound [22]. Penicillin was first used in late 1942; initially, the British focused its use on the sterilization of wounds, while U.S. medics reserved supplies for systemic administration. By the end of the war, penicillin had become an important adjunct for wound management and aggressive débridement [28]. One of the foremost lessons from World War II, however, was the importance of preventing nosocomial transmission, with the promotion of masks for patients and caregivers, use of sterile instruments, and other infection control practices commonly accepted today [12, 38, 40].

In Korea, penicillin and streptomycin were commonly used in wound prophylaxis, but at a risk that only became evident in retrospect, as increasingly resistant bacteria were reported from infected war wounds 3 to 5 days after injury [30, 58]. The wars in Korea and Vietnam also demonstrated the tremendous advances in transport and treatment that remain a key strength in today's U.S. military. Helicopter evacuation was first used in Korea and then more widely in Vietnam, and surgical hospitals were designed with an emphasis on mobility.

Military physicians and infection specialists and their civilian counterparts continue to work to enhance combat casualty care through a number of collaborative efforts, such as joint projects under the Orthopaedic Trauma Research Program (OTRP). The Fiscal Year 2006 Defense Appropriations Bill established the OTRP as a part of the Medical Research and Materiel Command (MRMC) medical research program. Administered by the United States Army Institute of Surgical Research (USAISR) at Fort Sam Houston, Texas, the program, funded at $7.5 million, was the first program created in the Department of Defense (DOD) allocated exclusively to funding peer-reviewed orthopaedic trauma research [45]. Additionally, military and civilian specialists have participated in symposia such as the 2006 "Extremity War Injuries: State of the Art and Future Directions (EWI)" [45]. In 2004, the surgeons general of the U.S. military, the U.S. Central Command, and the U.S. Army Institute of Surgical Research initiated a theater trauma system to organize medical assets and identify deficiencies within the current system [14]. The data gathered in this effort have helped the military adjust to changing wound patterns and deliver new products to the battlefield, such as hemostatic dressings and tourniquets [19, 57, 59]. One of the key challenges facing military and civilian researchers, however, remains the problem of multidrug-resistant organisms.

## Infected Battlefield Extremity Wounds in Iraq and Afghanistan

Improvements in military medicine, combined with particular aspects of the nature of the war on the ground in Iraq and Afghanistan, have brought the problem of infection control back to the forefront. Since the beginning of U.S. military operations in the two countries, there have been more than 30,000 injuries to U.S. service members [52]. Early, aggressive, meticulous débridement is the primary tool used to fight contamination and soft-tissue injuries [37]. Broad-spectrum antibiotics are generally not administered in early treatment, as culture-directed antibiotic therapy is used when soldiers are admitted to U.S. military hospitals. Treatment of the wounded is delivered on a multi-tiered basis at a variety of locations by a relatively small number of surgeons. While troop numbers in Iraq have ranged from 130,000 to 160,000 at any time, 120 surgeons are on active duty in the theater, and 10 to 15 of them are orthopaedic surgeons. In the early weeks of the war, Army Forward Surgical Teams (FSTs) moved swiftly behind the lines of combat and rapidly established mobile hospitals. As the nature of military operation in Iraq changed, facilities with more operating room and intensive care capabilities were established throughout Iraq. At this writing, there are four Combat Support Hospitals in Iraq, one in Kuwait and two in Afghanistan; these numbers are subject to change based on evacuation routes and troop strength. These hospitals are capable of 24/7 operations and provide a standard of care similar to that of a major trauma center in the United States [18].

In addition to methicillin-resistant Staphylococcus aureus (MRSA), other resistant strains of pathogens have been found in U.S. war wounds [42, 63]. A 2003–2004 survey of infections from Combat Support Hospitals in Iraq showed bacteria most commonly isolated from clinical infections in U.S. troops were coagulase-negative staphylococci, accounting for 34% of isolates, S. aureus (26%), and streptococcal species (11%). The 732 cultures obtained from the predominantly Iraqi population included mostly Gram-negative bacteria, Klebsiella pneumoniae (13%), Acinetobacter calcoaceticus-baumannii complex (11%), and Pseudomonas aeruginosa (10%). Both Gram-negative and Gram-positive bacteria were resistant to a broad array of antimicrobial agents [63].

A retrospective study of Type III open diaphyseal tibial fractures conducted at BAMC from March 2003 to September 2006 showed 27 of 35 patients had at least one organism in initial deep wound cultures upon admission to a U.S. military hospital. The most frequent pathogens were A. calcoaceticus-baumannii complex, Enterobacter spp. and P. aeruginosa. The initial organisms including the multidrug-resistant Gram-negative bacteria recovered from the wounds were successfully treated, while recurrent infections were predominately due to new staphylococci, and these had delayed union or amputation [26]. Five patients ultimately required amputation of the limb, and in three of these cases, amputation followed a recurrent infection. A fourth patient's initial cultures were negative but underwent amputation following infection from methicillin-sensitive Staphylococcus aureus and pseudomonas [26].

One of the pathogens with the most notoriety during Operation Iraqi Freedom/Operation Enduring Freedom is A. calcoaceticus-baumannii complex (ABC), a Gram-negative bacillus commonly isolated from the hospital environment and hospitalized patients and noted for its resistance to a broad range of antimicrobial agents. It has recently emerged as an increasing cause of infection in personnel returning from overseas conflicts after care in deployed military hospitals [1, 3, 11, 41]. The susceptibilities of 142 ABC isolates (of which 95 were from wounded U.S. soldiers deployed overseas) to 13 antimicrobial agents were determined by broth microdilution. The most active antimicrobial agents ($\geq$ 95% of isolates susceptible) were colistin, polymyxin B, and minocycline. Broad antimicrobial resistance was observed among the isolates tested, with deployed patients' isolates more resistant than nondeployed patients' isolates. However, resistance patterns increased over the study period from October 2003 to November 2005. Resistance to imipenem was increased ($p < 0.01$) at the end of the study period in comparison to the beginning (87% versus 56% of isolates susceptible). A noted area of concern from the study was that some ABC isolates developed resistance to colistin during testing [24].

Several studies demonstrate multidrug-resistant Acinetobacter is a common cause of nosocomial infection in burn patients [2], and patients with the infection have more severe burns and comorbidities with longer lengths of stay [2]. However, in two studies, Acinetobacter infection was not independently associated with mortality [2, 11]. Acinetobacter outbreaks have been seen in a variety of settings and geographical locations, and have included the injured from earthquakes and tsunamis; hospital-acquired infections in Turkey, Brazil, and Baltimore, MD; ventilator-assisted pneumonias in Lebanon; and intensive care units in Kuwait [17, 27, 32, 34, 43, 46]. Acinetobacter infections in particular among combat casualties appear to be primarily the result of nosocomial transmission and not from colonization of the casualty at the time of injury or environmental contamination of the wound at the time of injury [20, 21, 49]. Wounds are typically colonized with Gram-positive bacteria or pan-susceptible Gram-negative bacteria at the time of injury [42].

## Antibiotic Use and Drug Resistance

The growing phenomenon of antibiotic resistance and multiresistance, a topic familiar to civilian researchers, is of great concern in military settings as well. The need for reliable empirical therapy in any trauma setting is well-established, given the risk of mortality rises markedly if primary empirical therapy fails to cover suspected pathogens that later appear in cultures of severe infections [4, 15, 25, 35, 53]. Findings of antibiotic resistance appear as early as the Korean War, in which standard therapy prior to evacuation to Tokyo consisted of surgical débridement and the use of penicillin with streptomycin. An evaluation of neurosurgical cases from the Tokyo Army Hospital between 1951 and 1952 revealed resistance to penicillin in 48 of 58 cases, and to streptomycin in 49 of 58 cases [58]. Seven cases were resistant to all agents tested (penicillin, streptomycin, tetracyclines, and chloramphenicol). The authors reported inadequate débridement was the most common cause of infection in 25 of 58 cases; however, they also concluded that prophylactic antibiotics were associated with a high incidence of drug-resistant microorganisms. A review of practices during the 1973 Yom Kippur War warned against overuse of antibiotics, stating, "Unfortunately, the nature of wounds received during combat is characterized by extensive tissue damage and the wounds are most often contaminated by environmental bacteria. This leads towards the temptations to 'sterilize' the wound with massive doses of antibiotics and favors a false security with less reliance on good surgical technique" [29].

In the current conflicts in Iraq and Afghanistan, a major source of concern is that the use of broad-spectrum antibiotics for empirical treating of combat wounds results in selection of more resistant pathogens. Also, the use of broader-spectrum agents to treat multidrug resistant infections of non-U.S. personnel in Iraq may create increasing resistance in this reservoir of patients for potential nosocomial transmission. However, the role that current military practices of antibiotic use plays in the development of resistance has not been clearly established. Hawley et al. [24] note that imipenem was previously administered as a prophylactic agent for war wounds, in response to ABC, but empirical use is now discouraged, and the drug is used for management of a proven or suspected ABC infection. Further study is required to refine protocols for antibiotic prophylaxis on the battlefield.

## Discussion

The long struggle against infection in war wounds continues in the present conflicts in Iraq and Afghanistan, despite our historical advances in technology and techniques. The resistant pathogens predominantly identified in studies should be familiar to civilian orthopaedic surgeons: MRSA, ABC, Enterobacter spp. and P. aeruginosa. For military caregivers, treatment is focused on aggressive débridement and culture-directed therapy.

Several factors inherently limit our ability to analyze medical practices in wartime. The first is they are constantly subject to change depending on circumstances in the theater. A second is that data in many cases are fragmentary. However, the current evidence strongly suggests the use of broad-spectrum antibiotics at time of injury is a potential source of resistance and should continue to be discouraged. Current evidence, in both military and civilian settings, supports the conclusion that a single dose of antibiotic, within 1 hour of surgical wound (post injury), is sufficient prophylaxis against infection [8, 9]. Antibiotics with broad coverage that includes multidrug-resistant pathogens such as Acinetobacter are likely not needed at the time of injury. Administration of more than one antibiotic for more than 24 hours does not offer additional protection against sepsis, organ failure, and death, but rather increases the probability of antibiotic-resistant infections [55, 56].

Civilian and military researchers should focus on endeavors to identify new uses for older antibiotics against resistant strains identified in military wounds. Colistin, developed in the 1950s, has shown new utility against Gram-negative organisms in the 21st century [16, 31, 33, 36, 39], and may be useful in treating ABC [44]. Also, new antibiotics may soon prove their usefulness against MDROs. Tigecylcline, a glycyclcycline antimicrobial recently approved for use in the U.S., has broad-spectrum activity against both Gram-positive and Gram-negative organisms and is effective in complicated skin and soft tissue infections and in intraabdominal infections [64]. A report using one animal model demonstrates its effectiveness, in concert with oral rifampin, in treating MRSA [62]. Daptomycin, a lipopeptide, offers rapid bactericidal activity against growing and stationary-phase bacteria, is approved for treating complicated soft tissue infections, and has a low potential for the development of resistance [47, 64]. Linezolid, the first of the synthetic oxazolidinones to be approved for use, has shown great potential against drug-resistant Gram-positive organisms, but further research is needed. Research is currently focused on improving its myelotoxicity profile for long-term use [54]. In testing either new or old antibiotics, or synergy therapies, researchers should look to adapt established animal models (generally rabbits [7, 10, 62], guinea pigs [51], or rats/mice [5, 6, 48, 61]) to a wound model.

The current evidence also suggests that nosocomial infection is a greater concern than antibiotic overuse,

particularly in regard to Acinetobacter. More attention must be paid to instituting new or, more likely complying with, existing infection control protocols. The response to an intensive-care unit Acinetobacter outbreak in June 2007 at the National Naval Medical Center demonstrated that a broad-based, hospitalwide reinforcement of standard practices such as pre- and postcare hand washing, adherence to isolation precautions, and environmental cleaning was the key to limiting nosocomial spread [60].

Research will continue to focus on building a more complete picture of infection patterns in extremity war wounds from Iraq and Afghanistan. The coauthors are investigators in an OTRP-sponsored program to create a registry of wound infection data from patients at BAMC, Walter Reed Army Medical Center, and other major military hospitals [10]. This long-term project should offer clues to the origin of resistant infections and how variations in treatment such as antibiotic usage and surgical débridement affect outcomes.

War wound infections have long posed a major challenge for military medicine, and as the care of casualties continues to enhance survival rates, infectious complications will remain a major cause of morbidity. U.S. casualties from Iraq and Afghanistan often have wounds that are colonized or infected with multidrug-resistant strains of Staphylococcus aureus, ABC, Pseudomonas aeruginosa, and Klebsiella pneumonia. Nosocomial infection and overuse of broad-spectrum antibiotics are the most important short-term concerns facing military caregivers in this regard. Longer-term research must focus on improved antibiotic therapies, employing both new and old agents, and a better understanding of wound patterns and infectious complications.

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