

THESIS IMMUNOLOGY AND INFECTIOUS DISEASES

INFECTIONS AND HEALTH
OUTCOMES OF COMBAT-
RELATED INJURIES

CURRENT KNOWLEDGE AND UPCOMING
CHALLENGES

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ABSTRACT

Infections in war wounds remain of crucial importance in today's military medicine. Infections are impacting both mortality and morbidity in military personnel. Furthermore, treatment costs are rising because of increasing incidence of MDR infections. The spread of highly resistant strains from military to civilian health care facilities is also disturbing. The paper identifies the major shortcomings in military infection control measures as the main reason behind the increasing antibiotic resistance in clinical relevant bacteria. Several recommendations to improve antibiotics susceptibility and to prevent further spreading of MDR organisms to civilian facilities are made.

INTRODUCTION

Combat wounds differ from injuries in civilian setting [1, 2]. War weaponry has tremendous wounding power causing massive soft tissue and organ damage. All wounds become grossly contaminated with bacteria and environmental debris (i.e. clothes, pavement, dust and dirt), increasing the risk of developing infection.

For centuries combat related wound infections have proved to be a major factor contributing to morbidity and mortality in war in both military personnel and civilians. In order to prevent these secondary complications, topical anti-bacterial ointments have been used for millennia [3, 4].

Mortality however remained high until the discovery of bacteria as the cause of infection and the following introduction of wound debridement. After the introduction of effective antimicrobial treatment, a further decline in mortality was established

Since the outbreak of the War on Terror in 2001, 1.4 million military personnel have been deployed in the wars in Afghanistan and Iraq. Over 41,000 of them got wounded in action [5]. Wound infections still account for a notable part of morbidity and hospitalization in this population [6-8]. Moreover, recent studies also show a considerable increase of highly antibiotic resistant bacteria strains [6, 7, 9], amplifying the need for adequate reviewing of current therapy and bacterial origin involved in infection.

Reviewing current practice and determining the upcoming challenges in wound microbiology care is important in establishing new treatments and to cut increasing health care costs attributable to the treatment of infected wounds. Thorough understanding and propagation of knowledge of wounding and the associated bacteriology is essential to prevent new generations of surgeons repeating the mistakes of their predecessors as had been the case in the past [10].

This paper aims at providing an overview of current knowledge of infections in combat wounds, causative bacteria and available infection control measures, thereby indentifying the major shortcomings of current practice. From this knowledge, several recommendations to improve the standard of care will be made. The main focus will be on infections in soft-tissue injuries. Burns, although common in combat casualties, pose a different array of infections and are not included in this study.

PATIENT CHARACTERISTICS

Military trauma patients differ from their civilian care counterparts. In contrast to patients presented in civilian setting, military trauma patients are generally young and without underlying comorbidities that complicate wound care.

Modern war wounds are characterized by massive devitalized tissue and compromised fluid circulation, usually inflicted by explosives or bullets. Military trauma patients are likely to suffer from a mixture of penetrating and blunt trauma, often mingled with burns and blast overpressure injuries [11]. Because of enhanced personal protection and improved medical care, even casualties with devastating injuries, who would have not made it in previous wars, survive and seek medical attention [12].

Mechanism of injury and infectious susceptibility varies between weaponry, therefore a short overview of most often encountered wounds is given.

PATTERNS OF INJURY

In general, bullet penetration wounds are caused by a combination of shear, tensile and compressive forces [13]. After the bullet enters human tissue, direct tissue destruction is inflicted in the path of the bullet. Bullets also cause temporary cavitation by pushing tissue away around the bullet track, which damages non-elastic tissue in the process. Bullets often tend to wobble and deform after impact depending on the morphology of the missile, thereby causing increased internal damage. For example bullets fired from the Russian made Ak-47 fly relatively point-forward for up to 25 centimeters inside human tissue, as of this stability relatively minimal tissue disruption is inflicted. Standard bullets from the AK-74 and M-16A1, yaw 90° after 7 and 12 centimeter respectively, creating complicated wound cavities [1].

Bullet entry wounds are morphologically different from exit wounds (Figure 1). Entry wounds are characterized by round-like lacerations, whereas exit wounds are markable bigger and irregular of shape [14]. During the whole track, bullet fragments, clothing and environmental debris are driven into the wound [13]. Microorganisms are transported by these particles from the entry wound along the whole bullet tract. However it has also been shown that a retrograde transport of skin particles and debris from the exit wound is present [14].

Explosions may cause a wide variety of injuries. Blast injuries can be divided into four categories [15, 16]. Primary trauma results from the compression of air filled anatomical structures. Secondary wounds are inflicted by scattered debris and bomb shrapnel. Tertiary trauma is inflicted when victims are hurled through the air, wounding them as they descent. Finally blasts may cause burns, destabilize buildings and can harm airways due to toxic inhalation. Primary and secondary injuries are the most common injuries after explosions and are often complicated by infection, as environmental dust and debris are propelled into the wound during the explosion.

Typically, compression leads to skin disruption resulting in stellate lacerations. These lacerations are associated with widespread disrupted blood supply and increased susceptibility to infection compared to wounds caused by shearing forces [13].



Figure 1. Most common encountered types of injuries caused by bullets and explosives. Bullet entry wound in the right shoulder (upper left), bullet exit wound in the right axilla (upper right), shrapnel injuries to the back (lower left), mine injuries to the right leg (lower right). Images modified from [16, 17].

Secondary wounds result from missile-like objects and therefore resemble wounds found in gunshot wounds, depending on projectile characteristics. Hand grenade and small caliber mortar rounds produce numerous small and mostly irregular fragments of the explosive's casing (Figure 1). These fragments fail to penetrate more than a few millimeters, due to low mass and unfavorable shape with regard to aerodynamics. Small caliber explosives will therefore mainly inflict soft tissue lacerations, depending on the proximity of detonation. In addition, these explosives fail to inflict compression injury [18]. Deep penetration and traumatic amputation are generally only seen after heavy blasts from artillery shells, improvised explosive devices (IEDs) or landmines (Figure 1).

OVERVIEW OF CURRENT WOUNDING PATTERNS

In modern warfare, almost half of injuries are caused by fragmentation from blasts. Only a quarter of injuries are related to small arms fire [19]. The current wars show the lowest proportion of trauma related to bullets and ballistic trauma in history. This trend is continuing during the current Iraqi insurgency where fragmentation weapons account for approximately 80% of all injuries, with improvised explosive devices being the most common cause [15, 20, 21].

Combat wounds are primarily found on the extremities (65%), followed by head and neck injuries (15%) and thorax (10%) and abdomen (7%) wounds [8, 19, 22]. Especially the incidence of abdominal and penetrating chest trauma was low early on in the recent conflicts compared to previous combat zones [19]. This reflected increased protection due to improved body armor [23]. Unfortunately, surgeons now find that IEDs are causing blast injuries that extend upward under the armor, causing increasingly more abdominal injuries [24].

The three most common injuries are soft tissue injuries (42%), fractures (17.7%) and burns (4%). The remainder is made up of skeletomuscle injuries, contusions, crush injuries and nervous disorders [19].

During the major combat phase in Iraq, casualties were on average diagnosed with 2.2 different types of injuries on 1.6 anatomic locations [19]. This number increased to 2.38 injuries on 2.70 locations during the current insurgency [20].

MILITARY CASUALTY EVACUATION CHAIN

LEVELS OF CARE

In Western countries, military health care constitutes a complex system, composing of five levels of care with increasing sophisticated therapies available. All casualties will proceed through several levels before being discharged depending on injury severity.

The first level comprises field based first aid treatment provided by nearby medics. Forward Surgical Teams (FSTs) at level II provide first triage on the battlefield. The FSTs focus on life-saving resuscitative interventions and preparing casualties for further evacuation to in-theater Combat Support Hospitals (CSHs). CSHs perform initial return to duty surgery or stabilization for further evacuation. Severely injured casualties are further evacuated out of the theater of war to fixed army hospitals in Germany, Spain or Kuwait (level IV) and finally to hospitals in the country of origin (Level V) [1].

The strength of the evacuation chain is that casualties will receive definitive surgery and revalidation in the country of origin, thereby relieving medical personnel in the frontline. For this to succeed, swift evacuation is paramount. Time to admission after injury is approximately 30-90 minutes, which resembles figures seen in civilian health care [25, 26]. Completing the whole chain of evacuation from the time of injury to the admission in a specified hospital in the United States has been cut back from 8 to 4 days since the start of the conflict [24, 25].

Over 41,000 soldiers have been wounded in action during the current conflicts. All of these casualties sought medical care. Around 29,000 could return to duty, the remaining 12,000 needed to be evacuated [5]. Of these evacuees approximately 57% suffered from gunshot wounds and only 20% of explosives' trauma [15], although explosions are the most common cause of injury. The return to duty rate is probably higher in explosion injuries, because many soldiers who survive the initial blast only sustain concussion and minor shrapnel injuries.

Not only battle related casualties are processed through this system. Of all evacuees, only 20% were wounded in action. The remainder suffered from diseases (60%) or non-hostile injuries (20%) [27].

EVALUATION OF EVACUATION FUNCTIONING

Only a few studies have looked upon the functioning of this evacuation chain in respect to infection control measures [28, 29]. According to these studies points of improvement were possible on several domains.

Both studies found that working conditions are generally suboptimal. The current deployed hospitals are housed in adapted old buildings, or purpose-built temporary facilities. Most facilities suffer sandstorms. In addition, high temperatures are complicating the work.

Other infrastructural limitations are challenging adequate infection control as well. Negative pressure rooms to isolate patients are not universally available. Furthermore, patients with expected prolonged hospitalization ought to be housed away from newly

admitted patients, but this practice could not universally be implied, usually as of bed shortage [28]. Iraqi patients comprise between 60% and 80% of the total patient population in an average CSH [11]. Indigenous civilians always need prolonged hospitalization, as they are not evacuated out of theater. This implies that military and civilian casualties are treated side-by-side.

Infection control measures are often not up to basic standards due to limited facility capabilities and a periodic overflow in casualties, stretching hygiene compliance to the breaking-point. Compliance to hand washing protocols is not always optimal, both because of individual intention poverty and the lack of appropriate infrastructure to enable hygiene performance.

INFECTION RATES

Many casualties develop infection during hospitalization. It is important to determine whether infection is present, as this will decide if a patient requires surgery or a re-evaluation of prescribed therapy [1]. This is especially paramount in cases where patients have been prescribed unnecessary toxic antibiotics to treat supposed multi-drug resistant (MDR) infections [30, 31].

There is no general definition of infection in war wounds. Traditionally, diagnosis is made upon morphological inspection by looking at evidence of pain, redness, warmth and swelling (i.e. dolor, rubor, calor, tumor). Blistering of the skin and sup-epidermal gas formation could indicate severe infections as necrotizing fasciitis or gas gangrene.

Infection is sometimes retrospectively diagnosed upon the presence of bacteria [31]. This is however not appropriate as all wounds harbor bacteria. It is not the presence of bacteria but their interaction with the host that determines the influence on the healing process and the development of infection [32, 33]. For example, recent work shows that although 40% of wounded in action patients had positive cultures during hospitalization, only 65% of this patient group met criteria of infection [6]. Another study in civilian setting stated that none of the bacteria noted on initial cultures were the organisms ultimately recovered from infected wounds [34].

OBSERVED INFECTION RATES

The infection rates described by recent literature vary considerably with the type of injury and anatomical location. Overall, current infection rates are between 2% and 4% [25]. Blast injuries are significantly more prone to infection than gunshot wounds, minor burn wounds and blunt trauma [6]. Out of all blast injury casualties, 4% will develop infection compared to 2.6% in cases of gunshot wounds [19]. Abdominal and extremity wounds show the highest risk of developing infections, in contrast to thoracic injuries which are not significantly associated with infectious complications [6]. Open tibial fractures still account for a high infection rate. Up to 77% of soldiers cultured positive on deep wound culture and 37% of these soldiers developed infections after a first course of antibiotics [31, 35].

BACTERIOLOGY

It has been shown that infection remains a problem in casualties returning from the current conflicts in Iraq and Afghanistan. Likewise it is important to know which pathogens are causative to these infections and to identify the source of bacterial contamination.

Providing a review of encountered wound bacteriology is problematic as no nation-wide data on infections in combat casualties exist. Scientific studies provide some knowledge concerning this topic. However, most studies only provide retrospective analyses of single wound cultures and limited numbers of patients are included. In addition, due to limitations of the facilities deep wound cultures and ensuing anaerobic culturing conditions were often not available.

Microbiological identification of cultures may take up to several days, at that time casualties have long been moved to higher levels of care. Microbiological data can therefore not be compared with clinical patterns and thus can only be used as an indicator of bacterial colonization, not of infection.

LEVEL-DEPENDENT VARIATION

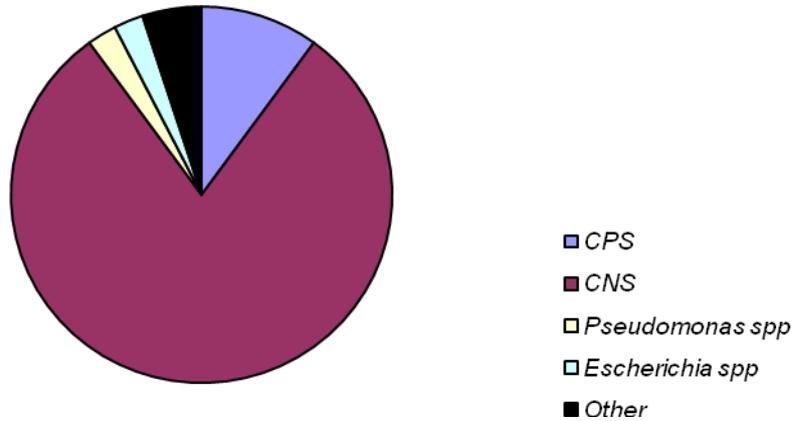
Research shows that most wounds are contaminated by a polymicrobial mixture of anaerobic and aerobic organisms [31, 36]. About half of all wounds show more than one organism present [6].

Wound cultures show profound level-dependent differences in bacteriology (Figure 2). A recent study reviewed the bacteriology of war wounds within 40 minutes after injury [36]. Of all casualties evacuated to the CSH, 49% showed viable bacteria present in wounds. Gram-positive bacteria were the predominant organisms isolated, of which only two methicillin-resistant *Staphylococcus aureus* (MRSA) strains were found. Multidrug resistance was not found in any of the Gram-negative organisms cultured.

Another study monitored bacteriology in patients admitted to a level III hospital ship, with an average time to admission of 4 days. An evidently change in bacteriology was recognized. *Acinetobacter spp* was shown to be the most common isolate in wounded servicemen. Of all wounds, 33% showed *Acinetobacter spp* presence, 17% *Pseudomonas spp*, 18% *Escherichia spp*, and 9% *Enterobacter spp*. *Coagulase Negative Staphylococci* (CNS) were only found in 3% of cultures. Thirty-eight percent of patients whose wounds were infected showed positive blood cultures, of which 41% were caused by *Acinetobacter* species [6].

A study in a level V facility again showed that *Acinetobacter spp* was the most common organism in wounds. *Staphylococcus aureus* was the second most common organism isolated. Notably, all patients had already undergone debridement and most received antibiotic courses before arriving at this facility [37]. A retrospective study in a similar facility yielded identical results in which 10% of casualties showed *Acinetobacter* presence, 7% MRSA and 5% *Klebsiella pneumoniae* [25]. The isolation rates of clinical relevant pathogens were significantly higher in patients returning from Iraq compared to soldiers wounded in the United States.

Bacteriology at time of injury



Bacteriology 4 days post-injury

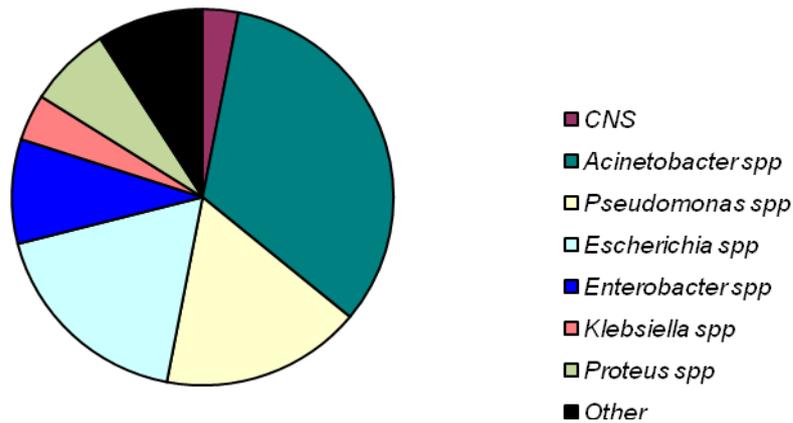


Figure 2. Assessment of bacterial presence in war wounds at time of injury and 4 days post-injury. CPS: coagulase-positive *Staphylococcus* species, CNS: coagulase-negative *Staphylococcus* species. Modified from [6, 36].

A separate level V study in the USA showed a different pattern. Isolates from wound infections showed 32% of wounds harbored *MRSA*, 16% *CNS*, methicillin-sensitive *Staphylococcus aureus* and *Pseudomonas aeruginosa* each. *Acinetobacter baumannii*, *Enterobacter cloacae*, *Proteus mirabilis* and *Streptococcus salivarius* were each isolated in 4% of the cases. [Dau]. It is possible that wounds from the later level V study were sampled later during the admission course, as previous studies revealed that a surge in MDR Gram-positives could be identified in recurrent infections [35, 38].

OTHER VARIATIONS

Regional or seasonal differences depending on the theater of war is conceivable [36], but no differences in bacteriology in war wounds have been found between Iraq and

Afghanistan yet. This is partly due to the fact that in higher levels of care, casualties from both combat regions are admitted together. On the other hand this lack of difference could be explained by the relatively comparable climates in both regions. During the Korean War (1950-1953) and the Vietnam War (1955-1975), seasonal patterns in pathogens isolated was indeed observed [39, 40]. This pattern has not yet been found in the current conflicts, although there is a large variation in monthly isolation rates. A possible explanation of this pattern might be of lower compliance of infection control measurements in times of greater casualty influx [25].

In theater sampling did reveal striking differences between US and non-US patients admitted to a CSH. Gram-positive bacteria were common among US patient, whereas non-US casualties showed mostly MDR Gram-negatives with *Klebsiella spp*, *Acinetobacter spp* and *Pseudomonas spp* species dominating. It is not clear whether this discrepancy is due to prior colonization of indigenous patients with MDR organisms, or that it is due to their longer time from injury to admission compared to coalition casualties [25]

ANTIBIOTIC RESISTANCE

Bacteriology at time of injury constitutes antibiotic-susceptible Gram-positive organisms [36]. However, MDR organisms have been isolated in many casualties and the isolation rate steadily increased since the outbreak of the current conflicts [7].

There is no standardized definition of multidrug resistance. The Walter Reed Army Medical Center's department of pathology stipulates that a Gram-negative bacterium is considered to be MDR if it exhibits resistance to at least three out of the five following classes of antibiotics: aminoglycosides, carbapennems, cephalosporins, penicillins and quinolones [9]

Acinetobacter baumannii isolates displayed high resistance to all five classes [6, 41]. Resistance patterns of *Escherichia spp*, *Pseudomonas spp*, CNS, *Enterobacter spp*, *Klebsiella spp* and *Proteus spp*, are very similar to the once seen in *Acinetobacter*, although these organisms are generally more sensitive to these agents [7]. However changing resistance patterns were shown since the outbreak of the conflicts.

From 2000 to 2006, an increase in resistance was observed for 13 out of 16 antibiotics tested from 5 classes in *Klebsiella pneumonia*, for *Escherichia coli* for 12 antibiotics and for all agents in *Acinetobacter baumannii*. Notably, susceptibility of *Acinetobacter baumannii* to amikacin, tobramycin, and trimethoprim-sulfamethoxazole decreased by more than 50%, susceptibility to ampicillin, cefepime, ceftazidime, ciprofloxacin, gentamicin, levofloxacin and piperacillin-tazobactam decreased by more than 75%. Even the susceptibility to imipenem, one of the last resorts available, decreased from 100% to 61%. During the same period, total MRSA isolates increased from 28.3% to 49.7% to total *Staphylococcus aureus* isolates. A similar raise was observed in vancymycin-resistant *Enterococcus* which showed an increase from 1.5% to 9.3% respectively (Figure 3) [9].

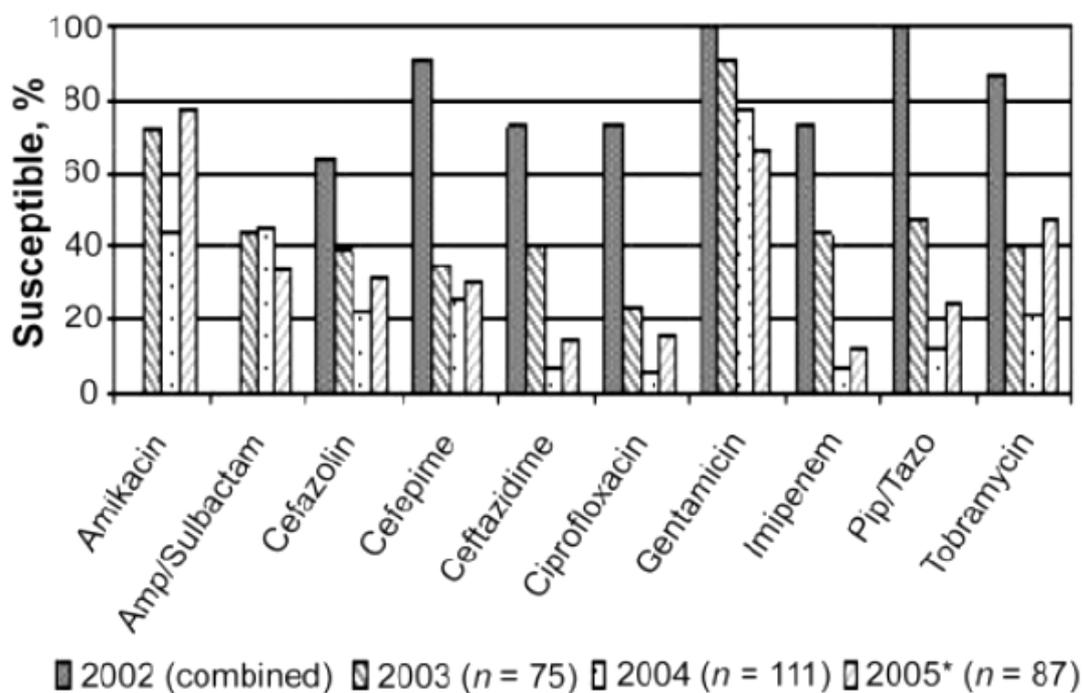


Figure 3. Changes in antibiotic susceptibility in *Acinetobacter baumannii* between 2002-2005. Susceptibility to common available drugs declined dramatically during the study period [7].

ORIGIN OF BACTERIA

The major challenge after identifying the bacteria species in wound infections is to identify the source of contamination. Protective measures can only be undertaken once the origin of MDR organisms has been established. Several contamination routes have previously been proposed. Bacteria causing infection could originate from preexisting colonization of the patient at the time of injury, inoculation by the injury mechanism and from nosocomial transmission during hospitalization [42].

Acinetobacter species may indeed be present in human flora, especially on moist areas like the toe webs and groin [43]. However, infection through colonial predisposition is unlikely as healthy servicemen proved to be colonized with different bacterial strains than the ones causing infection [44].

Bacteriological assessment at the time of injury found no MDR present, therefore MDR inoculation as of mechanism of injury and direct environmental contamination is unlikely [36].

Intramural transmission is plausible as *Acinetobacter* species are able to survive in dry environments for prolonged periods [45]. Research indeed shows that hospitals are the likely source of the *Acinetobacter spp* contamination. In 2007, colonization rates of pathogenic organisms were assessed and compared for combat and non-combat related casualties in the Iraqi conflict. Casualties were screened and followed from admission in Iraq to arrival in Germany and the US. It was found that only one of 74 casualties was colonized with MDR bacteria in Iraq. Ultimately, nine casualties contracted MDR infection in the US [46].

Nosocomial spreading was again confirmed by a recent study comparing *Acinetobacter baumannii* outbreaks in the United Kingdom and the United States of America. According to this study, UK casualties were responsible for the introduction of a highly resistant *Acinetobacter* species in civilian care. These new strains proved indistinguishable from similar isolates introduced to the USA [47]. Another study also identified genotypically identical *Acinetobacter* strains throughout the chain of evacuation [48].

Non-coalition casualties are probably the source of intramural *Acinetobacter* infection outbreaks. *Acinetobacter baumannii* is found to be endemic in countries surrounding Iraq and is thus often isolated from Iraqi citizens being treated in coalition medical facilities [49, 50]. As stated before, coalition and non-coalition casualties are often housed together, making transmission of pathogens between coalition and non-coalition patients plausible.

Nosocomial transmission seems not limited to one hospital or one strain of bacteria, suggesting a wide breakdown of infection control measures [28]. To prevent any further spreading of highly resistant strains as of this breakdown, casualties are now routinely isolated and their wounds cultured upon arrival in the United States [24].

BURDEN OF INFECTION

Infections of war wounds cause numerous complications depending on the location of injury and responsible pathogen.

TYPES OF COMPLICATIONS

Skin and soft tissue injuries may result in wound abscesses, cellulitis, septic arthritis, osteomyelitis and necrotizing fasciitis. Meningitis, brain abscess and other intracranial complications are common after head injuries. Peritonitis due to *Enterococcus spp* and Gram-negative species are often seen after intra-abdominal trauma [1].

Clostridia-caused gas gangrene was the most dreaded complication after wound infection [51], with an associated mortality between 38% and 62%. This condition is not generally seen anymore after the introduction of penicillin and swift debridement.

Necrotizing fasciitis is another severe condition, although rarely seen in modern times. However if it does appear, the progression of infection is fast and is accompanied by bacteremia, toxemia, septic shock, often with fatal outcome [1]. The most notable the most notable causative organism is *Streptococcus pyogenes*, although other organisms may provoke similar pathologies.

Acinetobacter-mediated necrotizing fasciitis is getting more common. This condition is characterized by cellulitis with vesicles in the proximity of the wound and progresses to hemorrhagic bullae and possible fatal outcome when left untreated (Figure 4) [50]. It is however not yet clear if *Acinetobacter* provokes necrotizing infection on its own or that co-pathogens may contribute as well.



Figure 4. Close-up view of *Acinetobacter* soft-tissue cellulitis (*left*). The skin is covered with tiny vesicles, giving it a peau d'orange appearance. If the infection progresses these vesicles will develop into hemorrhagic bullae (*right*), accompanied by sepsis with possible fatal outcome[50].

MORTALITY

There is still much debate about the overall impact of wound infection on mortality rates in wounded servicemen.

Although *Acinetobacter* is one of the most common pathogens in infected wounds, in-theater studies have not yet provided solid data on *Acinetobacter* attributable mortality. According to two studies, *Acinetobacter* infections are not independently associated with increased mortality [41, 52]. Patients are usually very capable of clearing *Acinetobacter baumannii* infections after minimal intervention [41]. A recent retrospective study of trauma related infections in Iraq stated that both mortalities during hospitalization were associated with *Acinetobacter baumannii* infection, but as of sample size no statistical analysis could be performed [6].

In civilian setting significant morbidity is seen after *Acinetobacter spp* infection in the immunocompromised [53-55]. A systematic review found *Acinetobacter spp* attributable mortality in intensive care unit patients ranged from 10% to 43% [53]. It is possible that increased mortality is also seen in the severely injured casualties returning from the front, but that the good health of most soldiers protects them from severe complications, thus tempering statistical effects of *Acinetobacter spp* infection on overall mortality.

A few studies found that *Klebsiella pneumonia* did cause significant morbidity and mortality in patients without relevant comorbidities, compared to patients with non-infected wounds [7, 25]. Whether this is also true for *Escherichia coli* and *Pseudomonas aeruginosa* infection is not clear. Overall mortality rates comparison between infected and non-infected wounds yielded no significant differences [6].

MORBIDITY AND MONETARY COSTS

Although increased mortality is debatable, infections do cause delayed wound union and are correlated with increased amputation rates [41]. Hence, infection impacts the duration of ICU stay seen in Iraq. Patients with infected wounds are twice as many admitted to ICUs and need to be kept 3.15 times longer than patients without infection, 7.09 days versus 2.23 days respectively. Also, infected wounds require 1.75 times more surgical procedures, 3.5 versus 2 respectively [6].

Health care charges are significant greater for patients with infected wounds. Treatment costs of *Acinetobacter baumannii* infections were found to be 2.5 times higher compared to treatment of non-infected wounds [56]. Spendings on antibiotic use are an important aspect of this greater resource consumption. Noticeably, due to increasing MDR infections, overall antimicrobial expenditure to combat MDR organisms increased up to 1400% between 2000 and 2006 [9].

CURRENT THERAPY AND INFECTION CONTROL

In civilian health care a thorough assessment of the patient and the wound is made before therapy is started. This assessment includes a full medical history and evaluation of systemic and local factors related to wound healing [33]. However, in wartime this assessment is not possible due to periodic mass influx of casualties and lack of time. Therefore standardized treatments have always aimed at broad-spectrum approaches.

CURRENT TREATMENT GUIDELINES

To date there is only one textbook summarizing the strategies of treating combat casualties [1]. Unfortunately this book limits itself to summarizing statements without evidence-based recommendations and does not incorporate lessons learned from previous conflicts. Furthermore, neither theater-wide nor level-wide guidelines exist and the ones that are in use are hardly appropriate as they have been based on civilian guidelines [11, 28]. These civilian care recommendations on its selves are often based upon assumptions and expert's opinion, rather than on prospective randomized trial data.

Some general statements about provided level-based care can be made. Casualties will be stabilized in the first levels of care before being evacuated out of theater. Medics often provide the first dose of antibiotics, after which casualties are immediately evacuated to the nearest FST and CSH [57]. After exsanguination and shock has been controlled, wounds undergo debridement in CSHs, meaning that surgeons remove all devitalized and necrotic tissue which may serve as a growth medium for micro-organisms. To clean the wound cavity, loose debris is washed away through irrigation. Wounds are then left open for several days, allowing more adequate evaluation of viability of tissue in the proximity of the wound, which is crucial in deciding whether a new course of debridement needs to be performed.

Antibiotic therapy is empirically determined on anatomical location and type of injury, to cover the most likely pathogens present [1]. In case of infection, wounds are reopened, irrigated and a new antibiotic regime will be installed.

Patients will be evacuated to higher levels of care once they are stabilized. At higher levels of care, the cycle of reevaluation of the wound bed and subsequent re-debridement and switching antibiotic regime is repeated until resolution has been achieved.

EVALUATION OF GUIDELINES

There are some remarks on the policy outlined above. First of all, administration of antibiotics at time of injury is recommended by the USA army. Usually broad-spectrum antibiotics like levofloxacin and ceftriaxone are administered, to provide coverage against Gram-negative pathogens [34, 57]. However, Gram-negatives do not usually appear until after admission to level III hospitals, as has been shown before. Pre-hospital administration of antibiotics should only be undertaken if wound irrigation and empirical antimicrobial therapy cannot be performed within three hours post-injury [31]. Gram-negative targeted pre-hospital antibiotic therapy is therefore generally not needed as casualties will be admitted to CSHs within 90 minutes after injury as stated previously. In-field antibiotic therapy should thus aim at preventing infection with highly virulent Gram-positives such as *Clostridia* and *Streptococcus* species.

Wound debridement is often performed by pulsatile lavage wound irrigation. This practice stimulates aerolization of Acinetobacter species and might promote nosocomial spreading [56, 58].

After initial surgery, prophylactic therapy duration of five days has been recommended to prevent peri-operative infection, although this is not supported by literature. Quite the contrary has been established in civilian setting, where 24 hours is found to be sufficient to fence of infection and longer duration of treatment stimulates resistance formation [56, 59].

When MDR organisms are present, doctors have to decide which antibiotic ought to be used. Physicians are forced to choose between marginally effective standard antibiotics or experimental agents with possible higher toxicity [30]. Unfortunately, because no fixed protocols describing antibiotic use exist, this shortcoming may lead to differences of provided care between facilities.

PERSPECTIVES

The aim of this paper was to give a broad overview of infections in war wounds and to evaluate current infection management strategies. Wound infection remains of crucial importance in today's military medicine due to its impact on mortality and morbidity and increasing medical costs. It is vital to accurately determine the source and progression of infection in combat related casualties.

This paper showed that combat zones prove to be difficult research domains as the research data is often sparse and fragmented [60]. Although much has been published concerning infections in war wounds, most published literature is of poor quality. Much of our current knowledge has been derived from opportunistic retrospective studies and case reports, which lack sufficient follow-up or decent patient-control groups. Moreover, published work does not always differentiate between clinical infection and bacterial colonization. Therefore it is still difficult to make solid statements concerning infection control functioning and upcoming challenges.

One of the aims of this study was to determine infection rates in soft tissue injuries. During the Vietnam War (1955-1975), approximately 4% of casualties developed wound infections in theater. In today's armed conflict a similar overall infection rate has been observed of 2% to 4%. This low rate is attributable to the swift evacuation process. In the war in Somalia (1993) evacuation was delayed with a subsequent infection rate of 19% [11]. Noticeably, research on surgical site infections in civilian health care shows infection rates of 2% for clean wounds and 5% for high risk wounds [61, 62]. This data indicate that overall infection rates do not differ much between military and civilian care and that infection rates have been relatively stable for decades, under the condition of swift evacuation.

This review gave some insights in the bacteriology of combat wounds. Gram-positives represented the most common organisms isolated at time of injury, but MDR *Acinetobacter* species were shown to be the most common organisms at higher levels of care. *MRSA* strains were present as well, but generally only seen in recurrent infections. In civilian health care facilities the same MDR species are challenging as in military medicine [63]. Differences in isolation rate do however exist, with higher isolation rates for *MRSA* and *Streptococcus spp* and lower rates for *Acinetobacter* and *Pseudomonas* species. Furthermore, isolates taken from civilian patients are more susceptible to antibiotics.

Highly MDR organisms in military casualties pose a significant risk to both the military and civilian health care facilities, because casualties with MDR organism infected wounds are repeatedly transferred between health care facilities. As of the evacuation process, MDR organisms are introduced throughout the evacuation chain. This is especially disturbing when wounded servicemen are treated in civilian health care facilities, as is seen in Canada and the United Kingdom [17, 47].

Until now MDR related mortality and morbidity in combat casualties are still debated, as conclusive studies of this relationship remain to be performed. It is thought that the general good health of soldiers may protect them from wound infection complication. However, the introduction of highly resistant organisms to the civilian care is alarming as civilian care patients are generally older of age and suffer from comorbidities in contrast

to military patients. The impact of highly MDR infections in the immunocompromised admitted to the civilian facilities could be devastating.

The treatment of *Acinetobacter baumannii* poses a formidable challenge because of its extensive drug resistance. The available drugs to which *Acinetobacter* species are susceptible are depleting rapidly. Unfortunately, no new antibiotics with activity to MDR gram-negative bacteria are to be expected in the near future [30]. It is crucial to immediately mitigate drug resistance, and the ensuing spread of MDR strains to the civilian health care facilities.

The rise in antibiotic resistance is certainly attributable to the suboptimal infection control measures and poor antibiotic regime protocols currently in use in military facilities. All efforts should therefore be directed to ameliorate these shortcomings.

RECOMMENDATIONS

Improvements can readily be made in several domains, which could all have a profound impact on infection rates and the spread of MDR organisms. Most of these measures come without extra costs or radical infrastructural adjustments.

Increased MDR prevalence mandates new infection control measures and rigorous compliance to existing protocols. Especially the impact of proper hand hygiene compliance cannot be overemphasized [64]. Previous studies have shown that perpetual infection control measurements were able to reduce infection rates and more importantly to improve antibiotic susceptibility [64-66].

Pulsatile irrigation should be kept to a minimum to prevent airborne spread of MDR *Acinetobacter baumannii*. A marked decrease in the incidence of recovery of new isolates was possible by minimizing the use of pressure lavage and keeping doors closed [56].

Hospitals should do everything at their disposal to separately treat indigenous and coalition patients to prevent nosocomial transmission of MDR organisms between the two groups. All military patients should be quarantined in cohorts upon arrival in a new level of care, to prevent nosocomial transmission ascending through the evacuation chain. Lastly, casualties evacuated to their country of origin should not be treated in civilian health care facilities, to prevent complications among the immunocompromised.

Although it is commonly accepted that antibiotics contributed to the tremendous reduction of wound complications, systemic antibiotics need reconsideration to tackle increasing bacterial resistance. Firstly, the practice of administering broad-spectrum antibiotics at the time of injury should be addressed. A randomized controlled trial of antimicrobial therapy should be undertaken to determine which antibiotics provides sufficient coverage [34]. In addition, the practice of antibiotics prophylaxis for several days should be revisited. The possibilities of replacing systemic antibiotic therapy by antiseptic agents might be beneficial. Antiseptics are gaining renewed interest and usage because they have a lower propensity to induce bacterial resistance than antibiotics [67]. Agents like mafenide acetate and silver containing compounds have been used for decades for the prevention of infection in burn victims as systemic prophylaxis in these patients is not effective [68].

Efforts should be taken to establish standardized guidelines for all medical personnel. The compliance to these protocols must be monitored to ensure best practice. For the development of these guidelines, decent prospective studies with long follow-up are needed in all research domains.

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