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REVIEW ARTICLE
Microbiology and risk factors associated with war-related wound infections in the Middle East

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SUMMARY

The Middle East region is plagued with repeated armed conflicts that affect both civilians and soldiers. Injuries sustained during war are common and frequently associated with multiple life-threatening complications. Wound infections are major consequences of these war injuries. The microbiology of war-related wound infections is variable with predominance of Gram-negative bacteria in later stages. The emergence of antimicrobial resistance among isolates affecting war-related wound injuries is a serious problem with major regional and global implications. Factors responsible for the increase in multidrug-resistant pathogens include timing and type of surgical management, wide use of antimicrobial drugs, and the presence of metallic or organic fragments in the wound. Nosocomial transmission is the most important factor in the spread of multidrug-resistant pathogens. Wound management of war-related injuries merits a multidisciplinary approach. This review aims to describe the microbiology of war-related wound infections and factors affecting their incidence from conflict areas in Iraq, Syria, Israel, and Lebanon.

Key words: Middle East, microbiology, multidrug resistance, wound.

Introduction and Background

The Middle East region is frequently associated with wars and military conflicts of which the Arab–Israeli wars and recent Arab uprisings are good examples [1]. There is a strong association between military conflicts and infectious diseases and historically classic 'war pestilence' such as plague, cholera, typhoid, typhus, dysentery, and smallpox are cited as being responsible for most of the deaths during wartime. However, improvements in sanitation and public health infrastructure along with better practices relevant to troop deployment have led to a substantial decline in mortality associated with such infections [2]. The last century has also witnessed a significant drop in mortality resulting from infections caused by battle wounds [3]. Efforts to prevent or minimize morbidity and mortality resulting from combat-related injuries include better personal protective equipment, training of medical personnel to provide lifesaving procedures on the battleground, and setting medical care facilities with surgical capabilities close to point of injury. The ability to enhance survival rates in soldiers and civilians with war injuries has, nevertheless, resulted in an increase in the risk of wound infections

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in this group [4]. Experience gained during the Great War (World War I) helped in reducing the incidence and subsequent complications of battle wound infections. Taking patient mortality as a measure, aggressive surgical debridement, delayed primary closure, early surgical intervention, flaps, and external fixators, although on a limited scale, all contributed to better patient outcomes in World War II compared to World War I. The main lesson gained from World War II, where up to 86% of hospitalized patients experienced an infection, was the importance of nosocomial acquisition of bacteria thus emphasizing the importance of infection control and aseptic techniques [4, 5].

The microbial aetiology of combat-related injuries differs between various stages of management. Generally, bacterial transition occurs over time, from in the early stages an even balance of Gram-positive and Gram-negative flora, to the later predominance of antibiotic resistant Gram-negative species during treatment [6]. It is believed that antibiotics administered early at the time of injury exert a selection pressure leading to antimicrobial resistance [4]. The first large-scale utilization of antibiotics in battles was during D-Day in 1944 where penicillin was effectively used to protect injured soldiers from developing *Clostridium* infection and subsequent tetanus, but later in the Korean war, penicillin combined with streptomycin was the most widely used antibiotic regimen. Antibiotics were often administered prophylactically, but at a cost that only became apparent in retrospect, as resistant bacteria were increasingly reported from infected war wounds 3–5 days after injury. The significance of *Pseudomonas aeruginosa* and resistant Gram-negative and Gram- positive isolates was most obvious during the Vietnam war [7, 8].

War injuries are not restricted to military personnel and since 1945, more than 100 million people, with 25 million deaths, have been recorded in military conflicts worldwide [9]. Characterizing and defining war-zone injuries is a complicated process due to difficulty of access to those affected, limited healthcare personnel and facilities at site of injury, and the widespread use of antimicrobial drugs. Complete patient histories are also difficult to obtain in crisis settings, limiting the healthcare worker's ability to describe all prior interventions. Furthermore, injuries sustained during war are at high risk of infection due to environmental contamination [10].

The aim of this review is to describe the microbiology of war-related wound infections and factors affecting their incidence from conflict areas in Iraq, Syria, Israel, and Lebanon.

Iraq

Operation Iraqi Freedom/Operation Enduring Freedom resulted in a large number of injuries among both civilians and the military. The value of surveillance cultures was evaluated in a published report on 213 combat-related open Gustilo and Anderson type III diaphyseal tibia fractures among 192 US military personnel between March 2003 and September 2007 [11]. Surveillance cultures were positive in 64% of extremities and 93% of them grew Gram-negative isolates. By contrast, at 9 months following injury, 27% developed a wound infection with mainly Gram-positive bacteria. In those with initial surveillance culture-positive wounds, 38·7% developed an infection compared to 11·5% with negative surveillance culture wounds. Moreover, in subjects who subsequently developed a wound infection and had initial cultures taken, 26·2% showed a match of at least one of the initial surveillance organisms. The contradiction between initial surveillance cultures and subsequent infected wound microbiology was attributed to the use of early antibiotic treatment, which suppressed the growth of susceptible flora and selected for more resistant organisms. The study concluded that patients culture positive on surveillance cultures were more likely to develop a wound infection and osteomyelitis. Even though positive surveillance cultures were not predictive of the infecting organism in subsequent infection, they were associated with development of wound infection, osteomyelitis, and ultimate need for amputation [11].

A smaller study of 49 US military casualties in Baghdad, Iraq during spring 2004, with acute open traumatic injuries that underwent aerobic culture of their wounds, found a bacterial contamination rate of 49% of cultures [12]. Gram-positive bacteria, mostly skin-commensal flora, constituted 93% of positive cultures with only two isolates identified as methicillin-resistant *Staphylococcus aureus* (MRSA) while Gram-negative bacteria were quite rare (5%). These findings suggested that early wound bacteriology is composed predominantly of Gram-positive organisms of low virulence and pathogenicity, and that the use of broad-spectrum antibiotics against multidrug resistant (MDR) Gram-negative bacteria is unnecessary in early wound management [12].

MDR is defined as non-susceptibility to at least one agent in $\geqslant 3$ antimicrobial categories [13]. The role of

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MDR bacteria in causing wound infections and even bacteraemia was apparent in US military personnel in Iraq. Highly resistant pathogens mainly *Acinetobacter baumannii-calcoaceticus* complex (ABC), *P. aeruginosa,* extended spectrum *β*-lactamases (ESBLs) producing *Klebsiella pneumoniae*, *Escherichia coli,* and MRSA were frequently isolated from wound and bloodstream infections in American soldiers [14–17]. Data from combat support hospitals in Iraq during 2003 and 2004 revealed that coagulase-negative staphylococci accounted for 34%, *S. aureus* for 26%, and *Streptococcus* spp. for 11% of isolates. By contrast, cultures from the predominantly Iraqi population showed mainly *K. pneumoniae* (13%), ABC (11%), and *P. aeruginosa* (10%) [18]. The total number of Gam-positive and Gram-negative isolates is not reported, but both showed resistance to a broad array of antibiotics [18]. In another study of US soldiers in Iraq and Afghanistan, the isolation of *Candida* spp. from penetrating wound injuries was associated with an increased risk of mortality [19]. However, a retrospective study of 48 British soldiers with an open fracture of the femur reported that four patients developed deep wound infections requiring surgical treatment and despite the low numbers of cases, the degree of bone loss rather than deep tissue infection was the factor most associated with outcome [20].

Little has been published about infections associated with war-related trauma in Iraqi soldiers and civilians. A study by the non-governmental organization Doctors Without Borders, found sepsis to be the most common cause of death in 1169 Iraqi patients admitted to a burns unit and 92% and 63% of Gram-positive and Gram-negative isolates, respectively, were classified as MDR [21]. The most common Gram-negative organisms were *P. aeruginosa* (34%), *K. pneumoniae* (12%), ABC (9%), and *Enterobacter cloacae* (8%), with *S. aureus* (26%) and *S. epidermidis* (11%) being the predominant Gram-positive species [21].

Syria

The Syrian civil war, now in its fifth year, has resulted in >200 000 deaths, 500 000 wounded, and at least 9 million refugees [22, 23]. This war is an example of a military conflict that affects both civilians and soldiers and which has led to the destruction of the healthcare infrastructure in a limited-resources environment. A study by Doctors Without Borders of 61 Syrian orthopaedic patients with suspected infections found that 74% had at least one positive wound culture, 13% of which were polymicrobial. Gram-negative organisms accounted for 56% of cultures with *P. aeruginosa* in 23%, *E. coli* in 19%, and ABC in 14%; Gram-positive bacteria, including MRSA, represented 44% of isolates. Overall, 69% of patient harboured MDR organisms with MRSA representing 42% of staphylococcal isolates [10].

Since February 2013, the Syrian civil war has resulted in an influx of 1300 wounded, both fighters and civilians, into Israeli borders seeking medical treatment [24]. Among such patients, the incidence of MDR isolates ranged from 47% to 66%, the most common being ESBL-producing and/or carbapenem-resistant Enterobacteriaceae (CRE), MRSA and ABC; two of the CRE isolates produced New Delhi metallo-*β*-lactamase [25, 26]. Data for the first 100 patients from Syria admitted to the Ziv Medical Centre between February and October 2013 show that sepsis, due to delayed definitive wound care, was the main determinant of the clinical outcome. No correlation between time from injury to arrival to the trauma room and the incidence of septic complications was evident but an increased probability of sepsis was noted in wounds that had undergone primary closure to control haemorrhage and/or wrapped in soiled blankets before definitive care. For this reason, primary closure wounds warranted reopening, debridement, and vacuum-assisted closure systems [24].

Cited factors responsible for the increase in MDR organisms include delay in appropriate management, wide use of antimicrobial drugs without prescription in the community, and the presence of metallic or organic fragments in the wound [10, 27]. It is recommended that in patients undergoing surgery such fragments must be removed or monitored for a long period of time [9]. However, several studies have shown that this does not apply for the central nervous system (CNS) injuries as no relationship was found between the presence of retained fragments and the development of either a seizure disorder or a CNS infection warranting the conclusion that it is unnecessary to re-operate for retained bone fragments, as they do not increase immediate or late complications [28–31]. The hospital setting is the major source of MDR organisms associated with blast injuries and nosocomial patient-patient transmission as well as faecal colonization with ESBL-producing Gram-negative bacteria often being responsible for acquisition of infection [25, 32]. Turton *et al.* showed the ABC strains responsible for wound infections in the United States and UK in American and British soldiers, respectively, who had shared exposure to various medical facilities, were genetically identical [33]. Nosocomial transmission has been reported to be a greater contributing factor to wound infection over environmental contamination at the time of injury [33–35].

This increase in MDR organisms has also translated to novel resistance at the molecular level. Carbapenem resistance in 66% of ABC isolates in Syria has been reported [36] and this was ascribed to the $bla_{\mathrm{NDM-1}}$ gene in isolates from four Syrian patients, wounded in Syria, while being treated in Lebanon, which was the first time it was described in that country [37]. The $bla_{\mathrm{NDM-1}}$ gene was first described in New Delhi in 2008 in Enterobacteriaceae [38] and differs from the most common acquired OXA-type resistance mechanism against carbapenemases [37, 39]. Data from Syrian hospitals on carbapenem resistance are lacking possibly due to the severe damage to healthcare infrastructure and the fact that Syrian doctors and health professionals are overwhelmed and understaffed dealing with the huge patient-care burden [40, 41].

Israel

Israel has witnessed numerous wars with bordering Arab countries. Medical military authorities during the Yom Kippur war recommended prophylactic penicillin administration to all wounded soldiers within 30–60 min after injury. In addition to penicillin prophylaxis, many hospitals added 1 g/day of streptomycin followed by oral 3–4 g/day of each of cloxacillin or ampicillin [42, 43]. During that war, infection rates ranging from 4·9% to 58·3% were reported with *P. aeruginosa* being the most common pathogen [43–45], and this species was again the most prevalent in the ensuing 1982 war with Lebanon [46]. In both theatres the increased incidence of infection was associated with penetrating abdominal wounds involving the colon, extensive soft tissue loss, burns involving >25% of the body surface, multiple operations, open drains inserted in the first operation, and wounds located below the diaphragm [42, 44, 46]. Infections due to penetrating abdominal wounds involving the colon can be due to heavy colonic bacterial flora mainly *Bacteroides* spp. and Enterobacteriaceae. For this reason, Simchen & Sacks [44] recommended the prompt administration of clindamycin and gentamicin in combination for all abdominal injuries and treatment was continued for 48–72 h if colonic involvement was shown at laparotomy.

Despite its widespread use on the battlefield during the Yom Kippur war, the administration of prophylactic antibiotics did not have a significant impact in preventing wound infection [42]. Furthermore, this practice possibly contributed significantly to an increase in infections due to Gram-negative rods [47–51]. An increase in carbenicillin-resistant *P. aeruginosa* and gentamicin-resistant *Klebsiella* strains was noted in burn patients [45].

Candidaemia among immunocompetent patients following a bomb blast at an Israeli market place, which contained a significantly high concentration of airborne *Candida* organisms, was reported by Wolf *et al.* [52]. This infection was recorded in seven (30%) of 21 patients between 4 and 16 days after the injury and *Candida* spp. was the most frequent cause of bloodstream infections, with inhalation injury appearing to be the best predictor of infection. Mortality in such patients was 43% and underlined the need to monitor patients for fungal infection where injuries were sustained in a similar setting and highlighted the wide range of organisms responsible for infected wounds through environmental exposure at the time of injury [52].

Lebanon

Lebanon has been plagued by wars and military conflicts since 1975 and the country has experienced, on several occasions, violent armed battles ranging from internal civil war to full-blown war with the Israeli Army. Over 40 years, the nature and intensity of military confrontations has varied, but the results remain the same – deaths and casualties among civilians and fighters [53]. Relatively few reports have been published describing battle injuries in Lebanon during the civil war (1975–1978) and the war with Israel (1982–2006) [29, 54–57]. In the civil war, a study of the management of 1021 Lebanese patients over a 10-year period (1975–1984) at a tertiary hospital reported an infection rate of 12% with *S. aureus, P. aeruginosa*, and *E. coli* being the most common organisms, respectively [55]. Another report from the same centre on the outcome of 1500 patients, described a 2·1% incidence rate of sepsis as the second cause of death after haemorrhage (3·7%) [57].

In more recent times Lebanese hospitals have acted as referral centres for war casualties from Syria and Iraq as well as their own national soldiers and civilians. The variability in the source of injuries and the various approaches for early management at the point of injury adds further to the complexity of the treatment of such injuries [58] and risking the possibility of importation of MDR strains. In 2010 two NDM-1-producing *K. pneumoniae* imported from Iraq were detected in Lebanon [59] and between 2011 and 2013 a 60% prevalence rate of carbapenem-resistant ABC was recorded in Tripoli, the largest Lebanese city bordering Syria [60], thus highlighting the need for effective measures to control the spread of such pathogens in the country.

Intracranial infections, including brain abscesses, following missile injuries to the brain were reported by the neurosurgery division at the American University of Beirut Medical Centre in patients treated between 1981 and 1988 [56]. More recently, the 2006 conflict with Israel, resulted in the release of more than four million sub-munitions over Lebanese soil including one million unexploded duds [61]. A study of 350 injured causalities by Fares *et al*. in 2013 revealed an infection rate overall of 19·4% with bacterial infections accounting for 86·8% and fungi for the remainder. *P. aeruginosa* was the most common single isolate (30·5%) followed by *E. coli* [62]. This underlines the common finding that Gram-negative infections are generally more prevalent among war-related injuries compared to Gram-positive organisms and infected wounds are most often located below the diaphragm. Environmental contamination of penetrating pieces of clothes and metallic foreign objects increases the risk of streptococcal, staphylococcal and enterobacterial infections which are commonly found on skin or clothing covering the wound [12, 62, 63].

Treatment and prevention

The use of prophylactic antibiotics for war-related trauma is controversial. Current guidelines of the Infectious Disease Society of America and the Surgical Infection Society for the prevention of infections associated with combat-related injuries strongly suggest that the use of broad-spectrum antibiotics at time of injury should be discouraged due to their potential to select resistant organisms. Furthermore, they do not support the use of aminoglycosides or fluoroquinolones for enhanced Gram-negative antimicrobial coverage as well as the administration of penicillin to prevent clostridial gangrene or streptococcal infection [64]. Velmahos *et al.* [65, 66] considered that in severe trauma patients the use of broad spectrum antibiotic coverage that includes MDR pathogens such as ABC is not needed at the time of injury, and administration of antibiotics for >24 h does not offer additional protection against sepsis, organ failure, and death, but rather increases the probability of infection with MDR pathogens. However, the guidelines do advocate the administration of systemic antibiotics within 3 h post-injury to prevent infectious complications and sepsis. The choice of antibiotics depends on the location of the wound, with cefazolin preferred for extremity, central nervous system, and thorax wounds, and metronidazole for abdominal wounds; topical silver sulfadiazine and mafenide acetate are suggested for burn trauma [64].

ABC is a common pathogen in wound infections across the Middle Eastern region and the reported most active antimicrobial agents against these organisms are colistin, polymyxin B, and minocycline [67–69]. Imipenem was originally recommended for prophylaxis against ABC organisms in war wounds but its empirical use is now discouraged, and should be reserved for management of a proven or suspected ABC infection [70]. Injuries sustained in certain environmental settings may predispose to fungal colonization thus warranting antifungal prophylaxis with fluconazole [52, 62].

Wound debridement and delayed primary closure including the removal of possible foreign debris, first introduced in World War II [71], have been shown to significantly decrease the incidence of infection on admission [42, 72]. Primary wound closure after debridement creates tension at the wound edges, which consequently compromises blood supply, increases the risk of infection and wound dehiscence [58]. Early drainage of haemothoraces, avoidance of thoracotomy as primary treatment, and the separate treatment of abdominal and thoracic injuries have also contributed to lower infection rates in patients with chest injuries [43, 73]. In countries such as Syria, where bacterial resistance is likely as a result of wide over-the-counter use of antibiotics [26, 74], hospitals in bordering countries receiving casualties are taking extra measures to ensure appropriate infection control practices including routine microbiological screening on admission, the use of a specific trauma room for immediate resuscitation, and the introduction of isolation bays on the wards [24].

A system for the treatment and prevention of war trauma-related wounds has been an evolving discipline since World War I. Currently, the gold standard approach used by the US military consists of four levels of care divided according to proximity to the

Table 1. *Summary of published reports describing the microbiology of war wound infections in Iraq, Syria, Israel, and Lebanon*

Military/civilian	Study sample	Site	Infection rate	Outcome	Most common organism	Study
Iraq						
British military	48	Open femur fractures	8·33%	4% underwent amputation	*S. aureus*	[20]
US military	300	Lower extremity amputations	27%	53% underwent reoperation	n.s.	[72]
British military	182	Chest	10·44%	4·9% overall mortality	n.s.	[73]
US military	192	Diaphyseal tibia fractures	27%	22% underwent amputation	ABC (surveillance) *S. aureus* (infected)	[11]
US military	16 742	Variable	5·5%	0·6% overall mortality	Gram negatives	[6]
Civilian	137	Chronic osteomyelitis	78%	n.s.	*S. aureus*	[32]
Military and civilian	211	Variable	26·5%	3·57% mortality among infected	ABC	[17]
US military	49	Variable	49%	n.s.	Coagulase-negative staphylococci	[12]
Syria						
Civilian	100	Variable	12%	2% overall mortality	n.s.	[24]
Military and civilian	66	Cranial trauma	10·6%	4·5% overall mortality	n.s.	[31]
Military and civilian	345	Variable	18%	n.s.	*P. aeruginosa*	[10]
Military and civilian	186	Cranial trauma	6·45%	31·7% overall mortality	n.s.	[9]
Israel						
Civilian	21	Variable	30% with Candida	43% mortality with candidaemia	*Candida*	[52]
Military	Group 1982: 184 Group 1973: 130	Extremities	Group 1982: 30·5% Group 1973: 31·5%	n.s.	*P. aeruginosa*	[46]
Military and civilian	41	Burns	58·53%	14·61% overall mortality	*P. aeruginosa*	[45]
Military	420	Variable	22%	1·90% overall mortality 1·20% mortality from infection	*P. aeruginosa*	[44]
Military and civilian	142	Chest trauma	4·9%	7·75% overall mortality	n.s.	[43]
Military	624	Variable	12·5%	6 cases of bacterial sepsis	*P. aeruginosa*	[42]
Lebanon						
Military and civilian	350	Total body cluster munitions	19·4%	0·85% bacteremia	*P. aeruginosa*	[62]
Military and civilian	272	Cranial trauma	11·39%	n.s.	n.s.	[29]
Military and civilian	1021	Head and neck injuries	12%	n.s.	*S. aureus*	[55]

ABC, *Acinetobacter baumannii* complex; n.s., not stated.

battlefield and type of management. The first level consists of initial care in the battlefield and includes stabilizing fractures, bandaging wounds with sterile dressings, and administration of single dose antimicrobials if evacuation is delayed. Level-2 care takes place in a field hospital and consists of tetanus vaccinations and immunoglobulin administration, wound irrigation with saline to remove gross environmental contamination, and topical antimicrobials for burns. Combat support hospitals provide level-3 treatment with inpatient care, intensive care units, and operating rooms; this also includes surgical wound management with external fixation of open fractures, in addition to treatment provided at level 2. Finally, level-4 treatment is provided by regional hospitals or hospital ships, located outside the battlefield area, and covers general and specialized inpatient medical and surgical care [64]. Despite the success of this system in reducing morbidity and mortality, its implementation requires large amounts of financial and logistical resources, which are beyond the capability of most national armies. Wars in the Middle East including the US-led 'War on Terror' increasingly involve smaller nation armies and paramilitary groups that do not have such healthcare systems in place and as a consequence, civilian medical centres and hospitals in countries such as Iraq, Lebanon, and Syria bear the major burden of these conflicts.

Conclusion

The near complete destruction of healthcare-related infrastructure and hospitals in conflict areas, mainly Syria, has obliged injured individuals to seek treatment elsewhere primarily in neighbouring countries. The porous borders between countries in the region and the flight of refugees to adjacent areas have resulted in further draining of the limited public health resources available. In the absence of well-equipped military hospitals, civilian medical centres are bearing the major responsibility of handling those patients.

Table 1 summarizes published reports of conflict wound infections in civilians and military personnel according to country of study and describes the study sample size, wound infection rate, study outcome, and most common organism grown on culture. Study outcomes varied between rate of amputation, mortality, sepsis, bacteraemia, and re-operation. Infection rates range from 4·9% to 78% with *P. aeruginosa*, ABC, and *S. aureus* among the most common organisms reported causing wound infection.

The free movement of injured fighters and civilians has facilitated the transmission of MDR pathogens. The term 'Iraqibacter' used by the Americans to describe the emerging ABC problem following the Iraq war can be applied to many settings including Lebanon, Jordan, and Israel so much so that Iraqi patients are screened for a wide range of MDR pathogens before being released from isolation following admission to Lebanese hospitals. Since these organisms in war-related wounds are on the increase, it is important to disseminate and implement infection control practices to prevent their further emergence and transmission as nosocomial transmission is the most important factor determining the extent of spread in hospitals. Other contributing factors include the environment of injury, site of injury, and initial choice of antibiotics.

The effective management of war-related injuries requires a multidisciplinary approach where surgeons from various disciplines as well as other infectious diseases specialist medical and nursing personnel are involved. Despite the vast discrepancy in available resources, regional health authorities could learn from the American military experience where initial management at the site of injury and rapid transport to the closest available medical facility has been shown to positively affect patient outcome. Unwarranted surgical interventions such as early closure and the overuse of broad-spectrum antibiotics will have a negative impact on the incidence and microbiology of wound infection and the patient's morbid complications.

Despite numerous wars and conflicts in the Middle East, there are few large-scale microbiological studies of conflict-related trauma and appropriate clinical management from the region. As the violence continues, with no sign of abating, more studies with larger sample sizes are needed to build adequate regional and local expertise leading to formation of appropriate guidelines for the region.

Declaration of Interest

None.

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