

Review

Infection in conflict wounded

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Although mechanisms of modern military wounding may be distinct from those of ancient conflicts, the infectious sequelae of ballistic trauma and the evolving microbial flora of war wounds remain a considerable burden on both the injured combatant and their deployed medical systems. Battlefield surgeons of ancient times favoured suppuration in war wounding and as such Galenic encouragement of pus formation would hinder progress in wound care for centuries. Napoleonic surgeons eventually abandoned this mantra, embracing radical surgical intervention, primarily by amputation, to prevent infection. Later, microscopy enabled identification of microorganisms and characterization of wound flora. Concurrent advances in sanitation and evacuation enabled improved outcomes and establishment of modern military medical systems. Advances in medical doctrine and technology afford those injured in current conflicts with increasing survivability through rapid evacuation, sophisticated resuscitation and timely surgical intervention. Infectious complications in those that do survive, however, are a major concern. Addressing antibiotic use, nosocomial transmission and infectious sequelae are a current clinical management and research priority and will remain so in an era characterized by a massive burden of combat extremity injury. This paper provides a review of infection in combat wounding from a historical setting through to the modern evidence base.

Keywords: war; wound; infection; trauma; antibiotic; nosocomial

1. INFECTION IN CONFLICT WOUNDED— HISTORICAL BACKGROUND

Wherever man, warfare and organisms coincide, wound infection is apparent. In ancient times, while the Babylonians demonstrated evidence of wound care [1], the first written evidence of a connection between inflammation, wound healing and suppuration is accredited to the Egyptians by Breasted as cited by Henry *et al.* [2]. The use of honey for chemical debridement of wounds was also the practice of Egyptian physicians, and is a treatment continued into modern times [3,4].

While a papyrus gives evidence of wound care in Ancient Egypt, it is a poem that records similar practices in Ancient Greece as Homer's *Iliad* describes the treatment of wounds in the Trojan Wars as cited by Pruitt [5]. The Greeks, like the Egyptians, favoured suppuration and actively encouraged what we now recognize as infection in some combat wounds. Infection was so common that clinicians characterized several forms of pus, viewing 'benign' pus formation as a positive factor in decreasing wound complications.

This notion of encouraging suppuration influenced the practices of military surgeons for subsequent centuries including that of the 'Gladiator Surgeon'—Galen of Pergamum [6,7]. The combined effects of Hippocratic and Galenic influence alongside ecclesiastical restrictions on surgical practice ensured little advance in wound care until the late middle-ages [5].

A resurgence of interest in battlefield surgery followed the introduction of gunpowder into Europe in the fourteenth century AD [8]. Fragmentation and gunshot resulted in a new type of conflict wound, one featuring retained metallic and organic debris. Endeavours of battlefield surgeons of the time had little impact however on ultimate morbidity of these new combat wounds. A lack of surgical training and adherence to Galenic principles compounded by poor post-operative care meant that limb wounding in war had significant life-threatening consequences [5]. It was the experiences of Larrey and others, during conflicts of the Napoleonic era such as Waterloo, Borodino and the Crimean War that led to changes in battlefield surgery and improved outcomes.

Timely evacuation of injured soldiers, radical debridement of wounds by prompt amputation and improved sanitation in hospitals all contributed [9,10].

Thus military wound care underwent a *volte-face* from ancient times. Wounds were no longer bandaged and splinted to encourage suppuration and instead,

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One contribution of 20 to a Theme Issue 'Military medicine in the 21st century: pushing the boundaries of combat casualty care'.

rapid amputation became the key to infection prevention. The wounded were no longer left to die on the battlefield and systems were developed to ensure that medical care was delivered in what we would today recognize as reasonable conditions. Further significant advances also occurred with the advent of microbiology heralded with the discovery, by microscopy, of microorganisms. These 'strange little animals' (p. 4) described by Antony van Leeuwenhoek and cited by Toledo-Pereyra [11] would be the subject of further scientific enquiry, becoming implicated in the infection of wounds.

Further using microscopy, Pasteur demonstrated that spontaneous generation of such microorganisms—the accepted theory of the time—was a flawed concept. He found that biogenesis in fact was the key and that bacteria were involved in putrefaction: hence proving the germ theory of disease [12]. Completion of the link between microorganisms and *clinical* illness was first shown by Friedrich Loeffler, a protégé of Robert Koch, in describing criteria for disease causation that are still in use today [13,14].

Application of scientific process to the care of injuries enabled Lister to make the vital clinical link between Pasteur's and Loeffler's laboratory observations and wound care antiseptics, through the application of the chemical agent carbolic acid. Lister introduced antiseptics into the treatment of open fractures, revolutionizing the outcome of these injuries and permanently influencing battlefield wound care [15].

As a result of these discoveries and the parallel developments of anaesthesia in war surgery, the use of immediate amputation for badly injured extremities gradually became less widely practised. The arrival of the specialty of Microbiology also enabled more detailed study of the natural history of battle wounds, and the nature of infections subsequently described allowed different patterns to be recognized during conflicts of the twentieth century.

World War One (WW1) was the conflict that established the concept of the 'evolving' war wound as Fleming described how the microbial constituents of wounds and their discharge exhibit changes over time [16]. Combined with Fleming's description of war wound flora, the relationship between early infection by *Clostridium* species, gas gangrene and the requirement for timely wound care was established. This conflict was also notable for the resurgence of debridement as a military surgical practice. While benefits of early surgical intervention were evident from the Russo-Turkish war [17], it fell to Antoine Depage to resurrect and define the art of debridement. Key to his practice was the recognition that debridement was a two-stage process: exploration (or incision) and *excision*. He recommended the removal of all debris along with devitalized tissue which he proposed would form a nidus for infection if left *in situ* [18].

During the Second World War (WW2), Miles *et al.* [19] demonstrated the predominance of Gram-positive bacteria in wounds two weeks after injury, and decreased presence at this time of *Clostridium* species. The anaerobic bacteria were thus confirmed as being inoculated at point of injury. Miles *et al.* [19] discarded the belief however that *all* bacteria found within a

wound at a later examination must have been implanted at the time of injury stating that this would:

'...discount the opportunities for infection that arise every time the wound is exposed for treatment or inspection, and to ignore the open reservoir of pathogenic bacteria demonstrable in the patients and staff of a hospital'

([19], p. 855).

WW2 was also notable for the emergence in 1942 of penicillin use on the battlefield, an act that would change the management of combat wounds for ever [20,21]. The mortality rate from lower extremity wounds decreased from 7.7 per cent during WW1 to 2.1 per cent during WW2, in part owing to the use of penicillin. The use of topical sulphonamide antimicrobials is also described, but this did not appear to reduce the rate of infection and was discontinued [22]. Independent of antimicrobial use, the benefit of rapid debridement continued to be highlighted, with decreased rates of infection seen in wounds treated less than 6 h from injury [23].

During the Korean War, helicopter medical evacuation reduced average battlefield evacuation times to 3.5 h [24,25]. Combined with the availability of forward surgery through Mobile Army Surgical Hospitals, this allowed for improvements in trauma care that accounted for a continuing decrease in the rate of post-evacuation mortality from 4 per cent in WW2 to 2.5 per cent in Korea [26].

Although the terrain differs radically between Europe and SouthEast Asia, *Clostridium* species remained the predominant early microbial war wound isolate and it became routine practice in Korea to administer large doses of penicillin and tetanus toxoid to the wounded [27]. Gas gangrene was rarely seen and death rates from wounding were almost half those seen in a conflict ending only five years before [24].

Despite such advances, aside from haemorrhage, infection was still the leading cause of death after wounding during the Vietnam War [28]. Tong [29] provides a temporal analysis from microbiological samples taken at initial debridement, and at days 3 and 5 post-injury. An initial mixed picture of growth of Gram-positive and Gram-negative organisms was seen, with *Pseudomonas* species being the most frequent isolate identified in the later swabs. All those with evidence of bacteraemia had strains reported to be resistant to antibiotics. These findings of mixed wound flora, an ultimate predominance by *Pseudomonas* species and emerging drug resistance corroborated previous anecdotal reports from wounds in injured servicemen [30,31].

Wounds analysed during evacuation from Vietnam to Japanese Base Hospitals showed the presence of *Pseudomonas* species, but in lesser proportions than *Staphylococcus aureus* and *Escherichia coli*. All organisms showed increased resistance to nearly all antibiotics against which they were tested [32]. On repatriation to the United States, Heggors *et al.* [33] found that wounds had become populated almost exclusively by a single organism, either *Pseudomonas aeruginosa*, *S. aureus*, *Proteus* species or *Klebsiella* species.

In the Falkland Islands conflict of 1982, battles were often fought at night, over formidable terrain in inclement weather. Helicopter transport was sparse and evacuation times for many casualties were prolonged. Wounded soldiers receiving antibiotics within 3 h of wounding had no reported septic complications.

In contrast, where surgery was delayed and antibiotics not administered, a 33 per cent infection rate resulted [34].

While antibiotics are not a global panacea and cannot replace early surgery, there may thus be a role in pre-hospital care when there are prolonged evacuation times.

2. INFECTION IN CONFLICT WOUNDED—EVIDENCE FROM RECENT CONFLICTS AND CURRENT SURGICAL PRACTICE

With regard to anatomical distribution of injury, from ancient battles through to contemporary warfare, military trauma is predominantly limb trauma. Over 70 per cent of modern war wounds involve the limbs [35] and recent military operations in Afghanistan continue to be characterized by a significant burden of extremity injury. A major factor accounting for this observation is the mechanism of wounding: explosive munitions account for 75 per cent of all recent war injuries [36], and the widespread energy transfer and fragmentation associated with the detonation of such devices defines modern ballistic wounding. A significant association with these injured extremities is wound infection, which remains the greatest risk to life and restoration of function in the combat casualty who survives beyond the first few hours from point of wounding [29,37]. It is also the commonest reason for infectious disease consultations in military hospitals [38].

(a) *Initial surgery and delayed primary closure*

The increased risk of infection in war wounds is influenced by a number of factors including the mechanism of injury, presence of embedded foreign material, physiological compromise, wound site, wound volume, presence of fracture, neurovascular insult and the adequacy of initial surgery [39]. While some ballistic injuries can be managed conservatively [40,41], early operative intervention is the norm for prevention of infection in the majority of combat wounds [42].

Such primary or initial surgery involves debridement of necrotic tissue and removal of environmental contamination, followed by delayed primary closure (DPC) [43].

A recurring theme for discussion in management of war wounds has been the timing of closure of high-energy combat wounds.

Civilian reports describe successful debridement and primary closure of some open fracture wounds [44]. Heavy contamination and the tissue destruction inherent with combat wounding, however, mean that this approach is unlikely to be successful in the ballistic wound. Attempts to primarily close combat extremity wounds often result in infection and further unnecessary debridement [45–48]. Early closure is more likely to be associated with septic complications, but late

closure may lead to increased risk of scarring and contractures. The balance between these two forms the basis for modern wound care [46].

DPC historically is performed at 4–5 days after the initial procedure because this is the predicted time when the bacterial count in the wound is at its lowest [49]. This is supported by military clinical studies, which report improved wound healing in patients undergoing DPC at this time [50]. Closure may be achieved if the wound appears clean with no evidence of necrotic tissue. If at the second procedure this is found not to be the case, further debridement is carried out and the wound is dressed but left open. Evidence to support one type of wound dressing over another following primary debridement of combat wounds is limited. Recent experience in contemporary conflict and from the International Committee of the Red Cross (ICRC) supports the use of fluffy dry gauze to lightly dress the wound [51]. This may seem counterintuitive as gauze sticks to wounds and discharge will readily leak through. However these apparent disadvantages are an important aspect in the management of combat wounds. Excessive leakage is evidence that the wound is suppurating, indicating inadequate initial debridement. Adherence is useful when the dressings are removed—pulling away the surface of the wound to complete the debridement and presenting a healthy base for closure or reconstruction.

(b) *The wound with a fracture*

Combat extremity wounds are frequently complicated by fractures [36] and their stability is key both in the prevention of death from sepsis and subsequent morbidity from osteomyelitis. An 80 per cent reduction in mortality was reported following open femoral fractures if stabilization was achieved using a Thomas splint [52]. The splint's original design by Hugh Owen Thomas has changed little in over a century and still has a major role in battlefield casualty management [53].

Techniques for fracture stabilization include the use of plaster of paris, skeletal traction and internal and external fixation [54]. Internal fixation is generally the preferred method in the civilian setting, but its use in combat wounds is limited as heavy environmental contamination introduces an unacceptably high risk of infection [55]. This axiom is however being challenged within recent reports of internal fixation use in the battlefield [56,57].

(c) *Microbial flora at point of wounding and the use of wound culture samples in war surgery*

Examining the bacteriology of war wounds at the time of injury in contemporary conflict, Murray *et al.* [58] evaluated 61 wounds in 49 casualties by inserting culture swabs into the wounds during early resuscitation, prior to any operative intervention. In contrast to the work of Tong [29], where time of first culture was 2.5 h, the majority of these samples were taken within 40 minutes of injury. Having observed an increase in multi-drug resistant (MDR) wounds in casualties repatriated to the Continental United

States (CONUS), the authors hypothesized that sampling would detect these organisms, hence implicating them as wound pathogens at point of injury.

They found no such evidence: 93 per cent of organisms recovered were Gram-positive skin bacteria, predominantly coagulase-negative staphylococci. Organisms associated with late wound infections and MDR such as *P. aeruginosa*, *Klebsiella* species and *Acinetobacter* species were not present in any of the samples.

In contrast to the findings of Fleming [16], *Streptococcus pyogenes* was not seen at this early stage.

This study was limited by small numbers. Anaerobic cultures were not obtained so that no comment about important pathogens such as *Clostridium* species, could be made. Some wounds also received irrigation and antimicrobial therapy prior to culture. Despite these limitations this does provide some information about the early microbial flora of modern combat wounds. It suggests that in American Field Hospitals nosocomial transmission of MDR organisms was an important factor in those repatriated, since they were not observed in the initial inoculation [58]. Although 'combat-related' MDR infections have become a feature of modern warfare [59–62], such organisms may not be introduced at time of combat wounding, hence questioning the appropriateness of the term 'combat-related' for infections owing to these organisms.

In addition, in the absence of clinical evidence of infection, routine collection of peri-debridement culture samples is inappropriate in combat-related extremity injuries [17].

(d) Infection control in the war wounded: nosocomial transmission during evacuation to home nation

Evacuation times for coalition forces injured in Iraq or Afghanistan are rapid in comparison to previous conflicts, especially considering the geographical disparity between hospitals in the UK, CONUS and Afghanistan. Although on occasion more rapid, typically, evacuation out of country occurs within 48–72 h and in the case of American troops, evacuation to the final medical facility for definitive care happens within 7 days of injury.

A link is made between war wounds, the evacuation chain and nosocomial transmission of pathogens by Kaspar *et al.* [63]. In a longitudinal extension of the work by Murray *et al.* [58] they investigated the association of bacterial colonization of wounds, the skin, oropharynx and perineum of combat injured personnel at the time of presentation and subsequent 30 day colonization or infection by sampling at each stage of the evacuation chain. While there was significant loss during follow-up owing to the logistics of combat evacuation, a clear trend is seen. Of casualties screened in Iraq, one of 54 had a positive swab for methicillin-resistant *S. aureus* (MRSA) in the oropharynx. No other alert organisms that were specifically looked for were detected. When swabs were taken on arrival in Germany after aeromedical evacuation, one patient had a positive result for *Acinetobacter*

baumannii—*calcoaceticus* complex (ABC). Of the 43 patients repatriated to home nation on average 7.2 days following injury, six wounds were colonized (with MRSA, ABC and *Klebsiella pneumoniae*) and eight were assessed as being infected (seven ABC, one *K. pneumoniae*).

The evacuation chain may therefore contribute to the infectious complications associated with war wounds of the extremities, and this could be related to the different microbiological flora of other casualties. In an analysis of 211 battlefield casualties evacuated after forward surgical care in Iraq, Petersen *et al.* [64] detail the microbiology of 53 war wounds, predominantly to the extremities. Eighty-five per cent of overall admissions were Iraqi nationals. There was a preponderance of Gram-negative infections with ABC most commonly isolated. In contrast to the work of Murray [58], these samples were taken on average 4.2 days from point of injury.

During the Iraq conflict, local civilians and detainees accounted for up to 50 per cent of patients in deployed field hospitals [65,66]. While coalition troops may stay in deployed hospitals for a few hours before evacuation, the time spent by local troops, civilians and detainees may be considerably longer. Lack of local medical infrastructure and security issues may even necessitate these individuals staying for the duration of their treatment. This situation is reminiscent of the 'open reservoir of pathogenic bacteria' as detailed by Miles *et al.* [19].

Such an open reservoir resonates in contemporary practice in Iraq by Yun *et al.* [67]. In samples of sputum, wound sites, urine and blood, coagulase-negative staphylococci were the most abundant flora recovered from both coalition forces and local civilians. This is the only similarity. The local, predominantly Iraqi population accounted for 80.6 per cent of all samples analysed, which, aside from coagulase-negative staphylococci, were dominated by Gram-negative bacteria. These patients accounted for 93, 97, 95 and 80 per cent of *P. aeruginosa*, *A. baumannii*, *K. pneumoniae* and *E. coli* strains recovered, respectively, and antibiotic resistance was widespread. Aside from the ubiquitous coagulase-negative staphylococci, Gram-positive infections due *S. aureus* or *S. pyogenes* were commonest in US personnel at the same hospital.

While highlighting an important potential source for the nosocomial transmission of Gram-negative organisms, this study does have at least two significant limitations. There is no clear distinction made between colonization and clinical infection. This is important, since it cannot be implied that the local patients had a greater amount of wound or other infections caused by Gram-negative organisms, just that they were present in wounds on laboratory testing. Another drawback is the absence of longitudinal data from later samples, particularly for US personnel. It would have been valuable to the microbiological profiles of wounds when examined in CONUS to see what (if anything) had changed, particularly in the light of the earlier findings of Kaspar *et al.* [63].

Contamination is a term used liberally in the discussion of wounding. While this is commonly applied to

the presence of microbes, dirt, clothing and other materials carried into a wound are also by definition wound contaminants.

Although there are numerous definitions, in microbiological terms wound colonization is the term applied to the presence of non-replicating bacteria on the wound surface that do not initiate a host response. Colonization may be attributable to environmental contamination at the time of injury, associated with high-speed inoculation by debris, dirt and soil. In the case of gas gangrene for example it is contamination at point of injury by dirt containing clostridial spores from animal faeces that may lead to later wound infection.

Wound infection is defined as the invasion and multiplication of microorganisms in a wound resulting in tissue injury and a host reaction. Features suggestive of infection are increasing pain, erythema and heavy discharge from the wound, which may be accompanied by systemic features of haemodynamic instability, fever and elevated inflammatory markers. As such, a distinction between infection and colonization is imperative: *infection is a clinical diagnosis*. For example, if a swab of a healthy healing wound is taken from a patient whose skin is heavily colonized with MRSA, then the wound swab will grow MRSA. In the presence of a healthy healing wound, this does not imply MRSA infection, but merely the presence of the organism. Systemic antibiotic treatment would not be indicated in such a case and could indeed be detrimental [68].

Of all the organisms implicated in nosocomial transmission in recent conflict, the one gaining the greatest attention is the genus *Acinetobacter*. In order to simplify its taxonomy, recently the four more common species (including *A. baumannii* and *Acinetobacter calcoaceticus*) have been referred to as the ABC complex [69]. *Acinetobacter species* are Gram-negative, aerobic, non-fermenting bacteria. *Acinetobacter baumannii*, the most clinically relevant of the species, is characterized by the ability to survive for prolonged periods in the hospital environment, increasing its potential as a nosocomial agent. Unusually for Gram-negative bacteria, it is also resistant to desiccation, which may account for its common association with wounds involving environmental contamination. It is noted for its ability to acquire resistance to antimicrobial agents and some strains resistant to all known antibiotics have been reported [69]. The potential impact of this is evident as *A. baumannii* remains the most commonly recovered pathogen from admission screening cultures in deployed hospitals [70] and is the Gram-negative pathogen with the greatest prevalence of MDR seen from these facilities [71].

Investigating an outbreak of MDR *A. baumannii* infection, Scott *et al.* [62] analysed soil specimens, the skin of casualties and also samples taken from within the hospital environment itself. Their results indicated *A. baumannii* presence in only 0.6 per cent of skin swabs, 2 per cent of soil samples but in 100 per cent of hospital samples. This adds to the evidence of colonization by the organism being the result of transmission within the US healthcare environment.

Griffith *et al.* [61] investigated factors associated with recovery of *A. baumannii* in a deployed hospital in a retrospective analysis using only *A. baumannii* isolates associated with clinical infections. Reporting findings in line with those of Yun *et al.* [67] and Petersen *et al.* [64], the authors demonstrated that the organism was commonly found in the deployed hospital environment, and particularly in those hospitals dealing with patients who were local nationals. They found that infection with *A. baumannii* strongly correlated with the number of host nation patients being treated both in the intensive care unit and on the wards. He concludes that 'these patients may serve as a reservoir for *A. baumannii* in the combat support hospital', a sentiment again echoing experiences with early infection control in WW2 [19].

Repatriated casualties colonized with MDR organisms enter home-nation health systems and the war casualty potentially becomes a source that may transmit to the home-nation population. Outbreaks have been associated with repatriated soldiers from recent conflicts [72,73], and transmission from combat wounded has led to fatalities in immunocompromised civilian patients [74].

Reaching the end of the evacuation chain, it is possible to comment on late wound infections—those seen primarily at the stage of reconstruction surgery. In a study of severe tibial fractures, Johnson *et al.* [75] provide an insight into the late stages of combat injuries and their flora. On arrival in CONUS, the wounds were characterized almost exclusively by Gram-negative organisms, including *Acinetobacter species*, *Enterobacter species*, and *P. aeruginosa*. None of these organisms were subsequently found at the second procedure, but instead at this key point in their reconstruction all patients had at least one *Staphylococcus species* identified. Late infection with the Gram-positive organisms was implicated as the reason for definitive surgery in four of five limbs ultimately amputated.

This predominance of late Gram-positive staphylococcal infections reported from the US has also been observed in the UK, where *S. aureus* is the commonest organism causing late infection in combat casualties [76].

Acknowledging an increase in MDR infections with *Acinetobacter species*, *Klebsiella species* and *P. aeruginosa* predominantly associated with cross-contamination from non-US forces, Hospenthal & Crouch [77] established a series of infection control priorities following assessment of deployed US medical facilities. Lack of infection control expertise was identified throughout and a number of basic hygiene measures could be improved. Simple measures of hand hygiene and segregation of long-stay, local national patients from those admitted for only short periods were also recommended as well as development and adherence to infection control protocols. In contrast, the UK Field Hospitals have a well-developed infection control process, with a dedicated Infection Control Practitioner working directly with the Hospital Commander. Combined with the shorter evacuation times, this may account for the lower rates of healthcare associated infections seen in UK battle casualties from Afghanistan.

Like its predecessor in previous conflicts, the modern combat wound appears to have a series of distinct microbiological phases. The evacuation chain and co-location of local nationals impacts considerably on nosocomial transmission particularly in the continuing spread of MDR Gram-negative organisms. The need for strict infection control and surveillance, although not a new concept, is of paramount importance in combat wound care.

While hospital acquired infection through nosocomial transmission may have been identified as a driver in the development of MDR in casualties of war, it shares this role with another key aspect of management of the combat wounded—the use of antimicrobial agents.

(e) *Driving resistance? Antimicrobial use in combat casualties*

Although responsible for decreasing the infection burden of combat injury, the widespread use of antimicrobial agents has also created the latest challenge in wound care: MDR bacteria.

Perhaps owing to the lingering spectre of infection resulting from war wounds, antibiotic administration is still regarded in some corners as a panacea for all wounding. However, antimicrobial agents are *merely an adjunct to wound care*, to be chosen and administered only after due consideration of the clinical and logistical situation. The ICRC [78] puts this in perspective: ‘the best antibiotic is good surgery’ (p. 263).

One area of concern is the pre-hospital administration of antibiotics to those injured in combat, where there is a lack of robust evidence on which to base recommendations. Some animal experiments have suggested the benefit of early (approx. 1 h after injury) antibiotic administration, which has driven the quest for provision of antibiotics to those forward on the battlefield [79]. This is supported by some civilian clinical data identifying early antibiotic administration as the single most important factor in reducing infection in open fracture wounds [80]. In combat, the use of early (within 3 h) antibiotics to decrease infective complications was supported by reports from the Falklands war [34]. While it may appear intuitive to administer early antibiotics to reduce subsequent infection, there has been a trend towards use of large doses of antibiotics to ‘sterilize’ the wound in the pre-hospital setting. Reports exist of such approaches, particularly where the tactical situation may preclude rapid evacuation [81]. This is not however supported by any evidence base.

The ICRC identify that the bacteria posing the greatest threat to those surviving military wounding are the beta-haemolytic streptococci and *Clostridium* species. This notion of selecting therapy to target agents posing the greatest threat to those recently injured is similarly championed by Hutley and Green [68].

They note that early access to surgical facilities and surgical wound care is key:

‘use of antimicrobials does not sterilize or clean the wound. Their purpose is purely to prevent the patient rapidly developing and dying of toxæmia and

septicaemia before surgery. It follows therefore that pre-hospital antibiotics must target those organisms that are capable of producing this clinical picture of severe and life-threatening early sepsis’.

[68], p. 317).

The authors recommend the administration of benzylpenicillin to casualties in whom surgery may be delayed greater than 4 h and discourage the use of broader spectrum agents. For in-hospital use they recommend benzylpenicillin for extremity wounding, co-amoxiclav for visceral injury and ceftriaxone and metronidazole for open head injury.

Recommendations from the USA identify that antibiotic administration early in the evacuation chain should be *pre-emptive*, in contrast to home nation care where antibiotic use should be solely for infected wounds with clinical microbiology guidance, or as a peri-operative adjunct under routine care. Differing from practice in the UK by recommending the administration of the first generation cephalosporin cefazolin (instead of benzylpenicillin), agreement does exist on the discouragement of enhanced, routine Gram-negative cover [63].

Global recommendations building on evidence from previous conflicts and current experiences are available [82] and may be summarized as follows:

(i) *Care at point of injury*

- Bandage wounds with a sterile dressing and stabilize fractures.
- A single dose of intravenous antibiotics to be given, *only* if evacuation is going to be delayed such that surgical intervention is not possible within 4 hours.
- Instigate evacuation to surgical facility as soon as the tactical situation allows.

(ii) *Care at surgical facility*

- Surgical evaluation of injuries to determine requirement for operative intervention: consideration for conservative management with wound toilet and antibiotics for a limited number of soft tissue wounds only [83–85].
- Intravenous antibiotics to be commenced within 3 h of injury with as narrow a spectrum as wounding pattern allows. Routine Gram-negative cover for all wounds is discouraged. Recommendations for agent of choice and duration of cover differ; however, regardless of choice, duration should be short (48–72 h) following initial procedure with a subsequent short course to cover DPC at which point antibiotics are stopped. Any further antibiotic therapy should be guided by clinical and microbiology assessment. Tetanus immunization status should be addressed.
- Aggressive, accurate debridement encompassing wound track excision, compartment decompression and removal of all devitalized tissue, debris and munition fragments that can be reached. Extension of wound beyond the zone of injury to allow comprehensive assessment. Extremity fractures to be stabilized by external fixation or traction depending on individual injury. All

wounds are to be left open, being dressed with saline-soaked gauze and crepe bandage or topical negative pressure wound therapy (TNPWT) if available and logistic chain permits. Routine pre and post-debridement cultures are not to be taken.

- Instigation of strict infection control practices including absolute segregation of ‘transiting’ coalition forces from local national in-patients and the staff caring for them wherever possible.
- Evacuation from surgical facility as soon as logistical support and physiological condition allows. Antimicrobial therapy should not be extended to cover open wounds, drains or external fixation devices during evacuation.

(iii) *Care at home nation/reconstructive surgery*

- Continuing close attention to infection control practices commenced in the war zone. Antibiotic therapy and sampling based solely on clinical assessment. Increased awareness of the possibility of contamination and /or infection with MDR organisms and the likelihood of Gram-positive organisms as a cause of late infections.

3. INFECTION IN CONFLICT WOUNDED—FUTURE DIRECTIONS IN RESEARCH AND POLICY

(a) *Pre-hospital antibiotics*

The evidence behind the administration of military prehospital antibiotics is based on limited animal studies [79] and on timeframes suggested in a study of only 49 cases [34]. In the civilian literature, while antibiotic administration for significant extremity trauma gains widespread support [80,86], this is largely based on ‘expert opinion’ and the timing and nature of its administration is not clear. There exists a need therefore to develop more robust animal models to investigate both the efficacy of antimicrobial agents and their delivery systems. Such models need to encompass injury not just by bullets and metallic fragments but also by blast to reflect current combat wounding. Inoculation with all the various species of bacteria associated with point of wounding [58] would be possible as well as more unusual organisms such as fungi recently reported in some severe wound infections of casualties from Afghanistan [68]. Until such time that more up to date, military specific evidence is available, standard practice with narrow spectrum agents only for delayed evacuation remains best practice.

(b) *Prospective, longitudinal evaluation of wound bacterial profile and skin flora*

In order to be efficacious, antimicrobial therapy must be informed. Numerous authors [16,29,58,63,67] provide an insight into the bacterial profile of the war wound both close to wounding and at various subsequent time points. These studies have little methodological similarity however, being largely opportunistic descriptions of small numbers of cases, some colonized and others infected. In most

operational settings where war wounds occur there is little opportunity to undertake scientifically robust investigation, since forward medical care (including laboratory support) is usually limited. Scarce resources are typically directed at patient survival as opposed detailed microbiological study, which has minimal impact on immediate patient care.

Methodologically sound, ethically approved assessment of skin and wound colonization from point of first surgical intervention for both deployed combatants and host-nation patients is required and studies are in development using the unique military environment and medical support to Allied operations in Afghanistan [68]. Such research will provide clinicians with a detailed microbiological picture of inoculation, colonization and subsequent infection of wounds in that geographical area. This will enable evaluation of standard wound profiles and also anecdotal seasonal variations in microbial patterns, allowing therapy to be better directed when infection occurs. Such information will also inform those charged with producing doctrine governing the provision and nature of hospital care for both local nationals and deployed personnel and assist in informed evacuation of the wounded.

There is a requirement to strengthen the microbiological support available to clinicians in the deployed theatre. Until recently the focus of deployed laboratory medicine has been immediate casualty care, with basic haematology and clinical chemistry being the priorities, along with transfusion of blood and blood products. With most coalition casualties being evacuated within 24 h of wounding, the requirement for field microbiology has been considered minimal. However the recognition that many local nationals are also injured, who remain in deployed medical facilities for often extended periods, means that enhanced microbiological support is necessary. Such long-term patients may be readily colonized with MDR organisms and act as a source for transmission to other patients including those present for short periods prior to repatriation.

This translates to increased manpower, better training for deployed biomedical scientists, and improved technology to aid diagnostic capability. Novel technologies to enable rapid identification of organisms and resistance profiles that are suitable for use in field conditions are areas of current research.

(c) *From Scutari to Sangin: infection control and deployed medical care*

The impact of sanitation, hygiene and basic nursing care so evident in the Crimea remains as relevant in modern military hospitals. Nosocomial transmission of hospital-acquired organisms remains a significant threat to all patients, and all the recent advances in trauma care amount to little if patients survive only to succumb to late infection. Healthcare associated infections may be associated with transmission from other patients, medical attendants or the physical environment itself. Infection prevention and control within the medical chain is now recognized as a high priority and mirrors similar changes in attitude

within civilian practice. Key areas identified to reduce infection risks include:

- informed design and construction of medical facilities;
- appropriate infrastructure and resources;
- resupply of consumable items—apparently a trivial matter, but a critical issue with respect to infection control;
- enhanced microbiological support and active surveillance of both infections and ‘alert’ organisms;
- education at all levels—control of infection is every individual’s responsibility;
- leadership—both professional from clinical leads, and managerial; closure of a hospital facility through poor infection control is the responsibility of the Commanding Officer; and
- trained infection control personnel, both as part of the deployed hospital strength and ‘reach-back’ capability to home country subject matter experts (SMEs).

Absence of this capability has been demonstrated to adversely impact on patient care in the deployed military setting, and seems to account for the discrepancy between the high rates of healthcare associated infections in US medical facilities when compared with British military hospital care [77].

(d) *Surgical wound care and infection: irrigation as an adjunct to debridement*

Animal studies show that wound irrigation can reduce post-operative contamination and subsequent rates of infection when compared with those wounds created in a similar manner in which no irrigation is performed [87]. Irrigation is now generally accepted as part of clinical care, but there remain a number of variables regarding its use that cause considerable debate: namely quantity, nature and delivery method of the irrigant fluid.

Although considered by many to be a relatively new entity, irrigant delivery by high pressure systems has been under investigation for over 30 years. Initial pre-clinical work popularized the use of pulsatile lavage (PL) for irrigating contaminated wounds [88,89].

This approach received initial support from investigators comparing bulb syringe and PL irrigation of a complex contaminated musculoskeletal wound comprising a bioluminescent strain of *P. aeruginosa*. Irrigating with normal saline, they found a statistically significant difference in bacterial counts between PL and low pressure delivery after both 6 and 91 of lavage. PL also resulted in the same quantitative drop of bacteria numbers with 3 l of irrigant that was achieved in 9 l using the bulb system. The authors concluded that PL was a more effective and efficient method of irrigation to remove bacteria than a conventional irrigation technique [90].

Using the same model, Svoboda *et al.* [90] compared the use of water against normal saline using PL [91]. Six hours after injury and inoculation with bacteria, wounds were irrigated with 9 l of either tap water or normal saline. There was no difference in

bacterial counts between groups, with both methods decreasing bacterial load by 71 per cent.

Using the same model a subsequent research team reported two studies comparing both the delivery mechanism of low versus high-pressure irrigation and the use of different solutions [92]. Six litres of normal saline, castile soap, benzalkonium chloride or bacitracin solutions were delivered using PL. Initial, post-debridement and lavage bacterial counts favoured the use of castile soap, but a significant (120%) rebound in bacteria was seen after 48 h.

Similar but smaller effects were seen with all other solutions, apart from normal saline. The saline group demonstrated the least drop in bacteria numbers initially, but at 48 h there was the smallest rebound increase in counts of all the fluids used.

In a second study, the authors found that using normal saline delivered either by bulb syringe or PL, similar drops in bacteria counts were seen post-treatment. At the 48 h point, however, there was a significant rebound in numbers of bacteria (up to 94% of the original level) in the PL group compared with 48 per cent in the bulb group. The authors concluded that none of the tested solutions performed better than sodium chloride, and that a low pressure device using saline solution to irrigate wounds was the best choice [92].

With regard to timing of lavage, the complex wound model was used to try to establish the effect of early wound irrigation. Investigating delays of 3, 6 and 12 h, Owens & Wenke [93] found that irrigation with 6 l of normal saline via PL decreased bacteria counts by 70, 52 and 37 per cent, respectively, and concluded that earlier irrigation was more likely to have an effect.

Military work using irrigation animal models has looked at the effects of dilute sodium hypochlorite solutions, water and sterile saline in a porcine open fracture model contaminated with *S. aureus* or *E. coli*. Gaines *et al.* [94] found no difference in bacterial count reduction between the water or saline groups. A significant reduction in *S. aureus*, but not *E. coli* was seen with the sodium hypochlorite solution. This suggests that drinking water might effectively be used as an irrigant in far-forward or austere surgical environments. Further study of the effects of sodium hypochlorite solutions are required, particularly in terms of its Gram-negative activity.

Combining investigation of irrigants in a contaminated wound model treated with topical negative pressure wound therapy (TNPWT), Waterman [95] compared saline, polyhexanide with surfactant and stabilized hypochlorous acid solutions when used with repeat debridements every 48 h. In this model, the hypochlorous acid solution group had significant improvements compared with the other fluids and controls.

Irrigation, topical dressings and antibiotic use are all independent variables, and it can be difficult to create an animal model in which the effects of each can be assessed in isolation. It seems probable on the balance of evidence to date that wound irrigation does have an effect in reduction of the rates of wound infection. A recent military retrospective clinical cohort study demonstrated that compared with

antibiotics and no irrigation, irrigation as sole treatment resulted in a 23 per cent lower infection rate [96]. This supports continuing endeavours to establish with clarity the place of lavage in military wound care.

(e) Surgical wound care and infection: hydrosurgery as an adjunct to debridement

A recent addition to the armamentarium of the military surgeon is hydrosurgery. This technique uses high pressure irrigation in combination with conventional sharp debridement in a single hand tool. While primarily used in burns treatments, it has a potential role in combat wounds particularly for repeat debridement at reconstructive surgery. Opinion is divided both regarding the use of this technique in comparison to conventional sharp debridement [97] and its effectiveness in reducing bacterial contamination in animal wound models [98]. Military work [99] using a contaminated open fracture model described a comparison between hydrosurgery and bulb syringe irrigation. There was a decrease in overall operative time and cost, and a reduction in initial bacterial counts when using a high pressure parallel flow device. Bacterial counts in the two groups of wounds were not significantly different at the 48 h point. Hydrosurgery may have a place in the late management of combat casualties in the future, but at present it seems unlikely that there will be any role in forward surgical care.

(f) Post-operative wound care and infection: TNPWT

TNPWT exposes the wound bed to a negative pressure environment and through deformation of the wound edge, a signalling cascade is instigated which ultimately leads to granulation tissue formation and wound healing [100,101]. It has been suggested that the use of TNPWT in traumatic wounds may lead to increased local levels of cytokines, resulting in accumulation of neutrophils and angiogenesis with resultant neovascularization [102].

Topical negative pressure also allows for the removal of considerable soft tissue exudate from the wound site. The use of TNPWT in civilian trauma is promoted as an adjunct in management of lower extremity wounds. It has been shown to decrease time from injury to definitive wound coverage, which may have an indirect effect on wound infection rates [103]. There is some evidence for benefit as an adjunct to surgical debridement in civilian open high energy fractures [104,105]. The use of TNPWT in military patients has been reported in a number of series [106–109] which are limited in being observational reports. While encouraging, their claims should be treated with caution since they are not formally structured studies—one author claims a 0 per cent wound infection and 0 per cent complication rate [108]. Recent reviews by Hinck *et al.* [110] and Fries *et al.* [111] of the use of TNPWT in combat-related injuries draw limited conclusions. Noting the paucity of high quality evidence they conclude that while appearing safe and probably effective, further work is needed to establish best treatment strategies. One of the

concerns—about the performance of devices during aeromedical evacuation—seems to have been allayed [112], but there remain a number of unanswered questions regarding their use in combat casualties.

In military studies, Lalliss *et al.* [113] describe a comparison of TNPWT and standard dressings in a contaminated open fracture model. They found that the animals with TNPWT had reduced bacterial counts at all time points following debridement and application of the dressings when compared with standard care. Wound oedema was also reduced. In one wound, mechanical tube blockage resulted in a 1200 per cent increase in bacterial counts, which reflects a realistic concern about the use of TNPWT in operational settings. Other work [114] details TNPWT complications related to power outage in the combat environment. In a retrospective analysis of 123 patients, there was a 10 per cent system failure rate owing to power outage, leading to unplanned return to the operating room and substantial late wound complications.

Investigating the impact of TNPWT on cartilage, Kadrmaz *et al.* [115] describe a prospective randomized animal study that demonstrated no alteration in cartilage histology or morphology when TNPWT is applied to an articular surface, either directly or indirectly. This is an important consideration when assessing the potential use of TNPWT for high energy wounds of limbs.

Augmentation of TNPWT with silver dressings has been described in case series of civilian wounds, which attempted to further decrease the bacterial burden. Waterman *et al.* [116] found that addition of a silver dressing into the TNPWT system in a contaminated musculoskeletal wound resulted in lower bacterial counts, although there was no measured effect on rate of wound infection.

Waterman *et al.* [117] also investigated performance of differing TNPWT systems in the contaminated animal wound model and found no significant difference in bacterial count reduction between different pieces of equipment. They concluded that it was the technique rather than specific equipment which was significant.

Having based all previous TNPWT research on a contaminated animal model using *P. aeruginosa*, Stinner [118] investigated if TNPWT had an effect on *S. aureus*. Following debridement and irrigation, animals were inoculated with *S. aureus* and assigned to either TNPWT or traditional dressings. There was no difference in bacterial numbers between the two groups. This observation might prove significant since *S. aureus* is most commonly implicated in late wound infection.

TNPWT continues to be used in injured service personnel since there are anecdotal benefits for wound closure, particularly when dealing with complex, cavitating wounds with copious exudates [119]. Rigorous scientific investigation has yet to demonstrate that TNPWT benefits all wound care problems, and there remains no evidence to support the hypothesis of reduction in infection rates. Its vulnerability to technical failure and lack of effect on the organism implicated in the wounds with the greatest ultimate morbidity is of considerable concern. The need for

further work is apparent in both pre-clinical and clinical military settings.

(g) Post-operative wound care and infection: use of dressings in combat wounds

While TNPWT may be suitable for established hospital facilities, those providing far-forward surgical care cannot benefit from this technology. Other possibilities to optimize wound care are with the initial dressings applied to the wound. Currently no evidence exists regarding the best dressing to use in the initial care of the contaminated military wound, although research is currently in progress.

Having detailed the research base pertaining to infection in combat wounded, one feature remains to be discussed. The recent increase in combat wounded survivability, in tandem with increasing ability to pursue limb salvage strategies, has resulted in casualties being repatriated with catastrophic soft tissue and bone defects, particularly in the lower limb. This results in challenges both in regeneration and reconstruction of the soft tissue envelope and also the skeleton. Implicit with these reconstructive challenges is the management and prevention of infection.

(h) Reconstruction and infection: strategies for the management of complex limb wounding

The requirement for early surgical attention to combat wounds is an established tenet of military surgery and early irrigation has been shown to reduce bacterial contamination rates [93]. There is little clinical evidence however for the additional effect of local antibiotic administration in open fractures and bone defects.

Local antibiotic delivery using absorbable, tobramycin-impregnated calcium sulphate pellets has been shown to be effective in preventing intramedullary *S. aureus* infection in a contaminated goat fracture model [120]. These pellets offer not only local antibiotic but also an osteoconductive scaffold, and similar results have been achieved using amikacin [121].

Further work investigated enhancing the regenerative aspect of this treatment while maintaining its antimicrobial effect by introducing demineralized bone matrix to the beads. No infections in the experimental arm contrasted with infections in all but one animals in both control arms of this study [122]. There exists therefore a possibility to provide enhanced osteoconductive and inductive scaffolds for bone regeneration in the same delivery vehicle for local antibiotic. Exploring the effectiveness of both commercially available and handmade beads in a contaminated wound model, Wenke *et al.* [123] found that all of the antibiotic impregnated implants reduced bacterial counts. The calcium sulphate pellets used in this study have the added benefit of not requiring removal by further surgery, in contrast to other techniques.

This *in vivo* work has been augmented by *in vitro* analysis of a novel 'fast acting', rapidly dissolving variant of the standard impregnated calcium sulphate bead which has shown promising results against both *Pseudomonas* species and *S. aureus* [124].

Brown *et al.* [125] examined a rat model with a critical sized femoral defect to evaluate the timing of local antibiotic administration when used in combination with debridement. Following inoculation with *S. aureus* and debridement at varying times, wounds were either closed or else treated with antibiotic impregnated beads and then closed. In this recovery model, bacteriological evaluation at 2 weeks demonstrated that for animals without antibiotics, significantly greater bacterial counts were seen in those receiving delayed debridement. Antibiotic beads were associated with a decrease in bacteria numbers, although timing to debridement even when augmented with antibiotics was still significant. It was concluded that both early debridement and local antibiotic administration might contribute to decreasing late infection.

Conscious of the possible effect of MDR organisms such as *Acinetobacter baumannii* on extremity wounding, a mouse model has been developed to investigate the efficacy of local antibiotic delivery. Crane *et al.* [126] demonstrate that compared with both untreated controls and animals treated parentally, local delivery of antibiotic via beads was significantly effective at reducing MDR bacteria counts. The use of local delivery has recently been reported from clinical cases in an operational theatre. In a retrospective cohort study comparing use of TNPWT versus antibiotic beads, TNPWT was associated with increased rates of late wound infection, more trips to theatre and a far greater cost [127].

Developing on the concept of local delivery with stability, a delivery platform consisting of a polyurethane scaffold impregnated with aminoglycoside antibiotics has been described. This modality has the benefit of being biodegradable while providing a scaffold for re-vascularization and bone formation [128]. It follows that manipulation of the scaffold to enable provision of osteoinductive matter has also been investigated to enable enhanced conditions for bone healing and infection control [129].

There has also been considerable interest in the efficacy of recombinant bone morphogenic protein in the management of contaminated lower extremity injuries although there are few scientific reports to date. Military work has suggested that there may be a beneficial effect in an infected segmental rat femur defect model [130], but quality clinical data is lacking. Osteomyelitis with challenging MDR organisms is likely to become increasingly important in the future [131] and a concern for home nation health providers. This is an area in which basic research is required, supported by subsequent quality clinical analysis of the treatment strategies for complex limb trauma.

4. LIMITATIONS

In presenting a comprehensive review of the contemporary evidence base concerning military wound infection such as the above, a number of caveats must be applied and appreciated. The inability to perform structured robust scientific investigation in war limits the clinical evidence on which modern wound care is based. While prospective data collection and assessment of defined infection-related outcome

measures have now been established, the investigation is in its infancy and as a result current clinical reports are limited in their quality and generalizability. In order to help bridge the chasm of available clinical military evidence, animal models such as those discussed have been developed to investigate extremity injury and infection. Limitations in these models do exist. The concept of attributing infection outcomes primarily to the numbers of organisms present following a series of interventions has dominated military scientific infection studies, both published and recently presented. It must be appreciated that infection is a clinical entity and is not wholly related to bacterial presence in a sample of tissue. While longer term survival outcome models are possible, significant constraints are experienced when attempting to investigate infection through to its end stage, not least with regard to ethical implications.

In order to appraise the breadth of evidence available, a number of unpublished sources have been included. While limited in terms of levels of evidence, they do afford an insight into contemporary research directions in this field.

These limits notwithstanding, valuable evidence is available both to the clinician and the scientist upon which to build improved clinical and laboratory investigation of military wound infection both in current conflicts and in future wars.

5. SUMMARY

This paper provides a historical insight into the infection of combat wounds; it affords a review of contemporary clinical experience and also gives insight into future research direction. The pivotal role of deployed microbiology is highlighted and the importance of nosocomial transmission of organisms to the war wounded is detailed. The presence of 'reservoirs' of such pathogens in combat hospitals, particularly when host nationals are treated alongside military personnel, has been described and forms a central facet of the infection control strategy of any deployed facility.

It is important to differentiate between contaminating and infecting organisms to prevent over-zealous use of broad-spectrum antimicrobials with the risk of development of MDR organisms. Treatment must be limited only to those microorganisms implicated in infectious processes. Although high quality evidence supporting early lavage, serial debridements and prompt administration of prophylactic antibiotics is scarce, this, along with expedited evacuation times and 'life and limb saving' operative techniques, seem to be contributing to a greater number of survivors and more salvaged limbs. Future directions will move to matters such as optimal dressings and use of growth factors in the management of these critical sized, contaminated injuries. It cannot be overstated however that these should be seen as adjuncts to, and not replacements of, good surgical wound care.

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