

Warzone trauma and surgical infections

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Abstract

The evolution of the type and management of combat injuries has continued over the last two decades of global conflict. The association between microbiology and war injury is not new and can be traced as far back as Hippocrates who said 'He who wishes to be a surgeon, must go to war'. Modern combat injury is caused by the improvised explosive device, that results in significant tissue destruction as well as a massive systemic inflammatory response. This systemic injury complicates the immune response to early and later bacterial infection. It also makes patients susceptible to prolonged fungal infection. Review of combat injuries from Korea, through Vietnam and to Iraq and Afghanistan identifies some common trends of early and late combat injury. The former combat operations were marred by ballistic injury over blast. Managing these complex infections requires regular microbiological assessment, targeted antibiotic therapies and early marginal surgical debridement of tissues. The aim of this article is to assess the current evidence for combat infections and the literature supporting the current management of infections as a complicating factor of traumatic injury.

Keywords Infection; Sepsis; Trauma; War surgery

Introduction

The evolution of microbiology and the surgeons understanding of infection has long been entwined with conflict. While many observers would attribute individual piecemeal advances to the challenges of conflict, the underlying common thread for the evolution of war surgery is a stepwise advancement in the understanding of infections and their relationship with mortality.

Hippocrates is credited with several key advances in this area. Not only did he recognize the relationship between fingernail length and disease transmission, his text *'On Wounds'* highlighted the key to effective healing was through washing in water or wine, maintaining a moist wound bed as well as rest and immobility. He also references techniques to facilitate pus drainage (the pus puller) from an abscess cavity. However, like many after him he considered pus fundamental to the process of wound healing – despite being an advocate of the reduction of inflammation within the wound. The obsession with 'laudable

pus', as a mechanism to encourage wound healing, was championed by the gladiator surgeon Galen of Pergamum (120-210AD). Galen's writings on this subject were to form opinion for centuries (Until 1267).¹

Recent conflicts have been dominated by the effects of the improvised explosive device (IED), resulting in a significant disruptive complex tissue wound with multiple contaminants (Figure 1). This differed from the penetrating wound of a bullet, particularly in the degree of contamination. The former patients were significantly injured, sustained a substantial systemic inflammatory response and were susceptible to both invasive fungal and bacterial infections. This predisposed them to both early and late contamination.²

The aim of this article is to understand the relative injury and contamination pattern of such patients, which therefore will allow a grasp of their microbiological management.

The bacteriology of the warzone

Prior to the 20th century therefore, death from disease non-battle injury outweighed those from battle war wounds. As a comparison, the British armies disease to battle related death ratio was 7:1 in the Napoleonic wars. As surgical management of their wounds improved, the gas gangrene mortality decreased from 28% in World War I, 15% in World War II to no mortality in Korea.

As antibiotics become more widespread, so did antibiotic resistance. Furthermore the need to prevent nosocomial transmission became paramount. The improvement in evacuation of patients, that was markedly seen in Vietnam and Iraq (Korea timelines were more than 3.5 hours), meant many patients who traditionally would be killed in action were brought into hospital.³ This group increased exponentially in operations in Afghanistan.⁴ As such these catastrophically injured patients are associated with a number of infectious complications, immunomodulation from massive transfusion and a variety of bacteriology.

Evolution of infection rates

In Vietnam, sepsis was the third leading cause of death overall out of 132,996 admission in 19 hospitals, accounting for 12% of deaths. In the first 24 hours, sepsis was the second most common cause of death, whereas after 24 hours it becomes the most common cause of death (38%). It was commonly associated with large soft tissues and colonic abdominal injuries. In Vietnam, sepsis accounted for between 2 and 9% of preventable deaths.

In Afghanistan and Iraq the infection rate has been estimated at 34% and 28%, respectively. The common misconception is that the deep contamination from conflict-related injuries, such as blast, gunshot wound or penetrating foreign body, results in a deep wound contamination that is responsible for longstanding infection. Evidence disproves this theory on several fronts. Firstly, soldiers injured in conflict may have deeply contaminated wounds, whether from faeculent matter found in wadis or soil being driven into tissue planes from the blast injury (Figure 2). However, evidence by Lee et al. has demonstrated that there is little correlation between pre- and post-debridement

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Figure 1 Blast injury to a hand showing the degree of contamination.



Figure 2 IED blast with bilateral traumatic lower limb amputation. There is extensive soil contamination of the wound.

cultures in those that go on to have infections in lower extremity injuries.

Secondly, the species cultured in early and late infected wounds differ substantially. This points towards a lack of correlation between the organisms found on primary cultures from the local environment and those that result in long standing deep infection. In fact, some evidence suggests that the common early organisms cultured are more likely to be local skin flora than environmental organisms. Tong et al.'s seminal study on US marines in Da Nang, Vietnam, highlighted that nearly half of the 63 specimens were Gram-positive on admission.⁵ At day 5 Gram-positive organisms accounted for only 23 of 146 specimens. As time from injury and length of hospitalization increased, Gram-negative organisms became the predominant isolates from culture. *Pseudomonas aeruginosa*, for example, which accounted for

only three specimens on day 5, become the most common Gram-negative culture by day 5. In addition, species such as *Enterobacter*, *Proteus*, *Escherichia coli* and *Acinetobacter baumannii* were also isolated. Tong postulated that there was some seasonal variation in the causative organisms of wound infection and blood sepsis. While Gram-positive skin flora represented the majority of initial wound cultures during the winter months, the summer was shown to be dominated by enteric Gram-negative organisms. Gram-negative sepsis, with isolates strongly correlating with wound cultures, was a recurrent common problem with species such as *Enterobacter*, *ABC*, *Klebsiella*, *Pseudomonas*, *E. coli* and *Proteus* being responsible. Interestingly it was reported that of the 17,726 patients admitted to Army hospitals in Vietnam, only 4% developed in patient wound infections. Furthermore, lower extremity wounds were had a higher rate of infection (27%), compared with upper extremity wounds (10%). Again, at the Brooke General hospital between 1965 and 1968 in a group of 84 patients with open tibial fractures due to gunshot wounds (GSW) and lower velocity metal fragments, their causative agent for osteomyelitis was *Staphylococcus aureus* and *Pseudomonas*.⁶ The comparison between Vietnam and Iraq data is challenging, as the former analysis often does not include long-term follow up specimens, whereas the latter often takes place in the continental united states.

As an update a similar study from Iraq was also performed. In 61 wounds, 93% of cultures were positive for Gram-positive bacteria.⁷ This contrasted with the even distribution of Gram-negative and -positive bacteria often seen in Vietnamese wounds. Any initial Gram-negative colonizing bacteria were proven to be low virulence strains from the local environment. In these studies it was noted that as patients were evacuated along the echelons of care there was a pendulum shift from Gram-positive and saprophytic Gram-negative agents to nosocomial and resistant Gram-negative cultures such as *Acinetobacter*, *Klebsiella*, *P. aeruginosa* and *E. coli*.

Early versus late infections

Early infections are therefore related to the local skin flora of the host, rather than to the environmental organisms found in combat. Late infections and their complications, such as further amputation, appear to be related to nosocomial transmission between patients in hospital. In essence there are two different groups with 'late' infections. Those who have nosocomial transmission and develop a multi drug resistance strain colonized in wounds, as was the case with the *Acinetobacter-Calcoaceticus-Baumannii* (ABC) complex bacteria. Then there is the population who had a late osteomyelitis and require further surgical intervention, often a more proximal amputation.

As patients were often evacuated out of the country (Iraq or Afghanistan) within 48–72 hours, it is difficult to define where early infection ends and late infection begins. Kaspar and colleagues links the evacuation chain, wounds and nosocomial transmission.⁸ This group looked at 30-day colonization from point of wounding. In their study of 54 patients, one patient had a positive culture for MRSA on testing in Iraq, One positive for ABC on arrival in Germany, and six patients were colonized with MRSA, *Acinetobacter* and *Klebsiella* (43 repatriated to home

nation), and eight were considered infected with *Acinetobacter* or *Klebsiella*, thus demonstrating the strength of evacuation chain as a causative factor in nosocomial infection. This tendency towards colonization or infection with ABC can also be seen in a study done by Peterson on Iraq nationals. In his group of 53 war wounds to the extremities, the majority were infected with Gram-negative *Acinetobacter* 4.2 days post injury.

In a study by McDonald et al., they identify late infection by analysing those patients who may have had recurrent infections post primary discharge. In their cohort of 337 patients, 33% had trauma-related infections during their initial hospitalization. Following discharge 38% had a subsequent infection post discharge, with 29% occurring after they had left military service; 43% of infections were soft tissue infections, 14% were osteomyelitis and 13% pneumonia. Soft tissue and blood stream infections were more common among those who had had more than three infections. Sepsis had a median duration from injury of 5 days, whereas soft tissue infection had a median interval of 17 days and osteomyelitis 25 days. Patients in this study who developed a new infection post discharge were associated with large volume (>10 units) blood product transfusions and an ISS of >10 during their primary trauma. In work by Huh et al. looking at infectious complications and late amputation,⁹ patients who had undergone an amputation more than 12 weeks post injury were correlated with requiring both a soft tissue coverage procedure and a high rate of infectious complications. In a comparative study by Fairhurst (who defined late amputation as those >11 months post injury), five of eight amputations were performed due to recurrent osteomyelitis. Thiagarajan in 1999 defined the relationship between amputation and underlying diagnosis in 49 patients. Amputation within 1 month was shown to be due to vascular reasons, 1–12 months likely due to persistent sepsis, and after 1 year due to chronically infected bone unions. The microbiology of these infections was not recorded. In a study by Penn-Barwell et al. in UK military patients the most common organism associated with infection was *S. aureus* in 59% of patients.¹⁰ The degree of bone loss from the fracture was correlated with infection. Timing of infection was not reported in this study; however, their findings correlate with comments from Yun et al. who reported that Gram-negative pathogens predominate early in the military osteomyelitis group being replaced with *Staphylococcus* spp, despite clinicians using Gram-positive antimicrobial therapy.⁷

Microbiology from the US military burn centre revealed that whereas patients demonstrated cultures for *S. aureus* and *Acinetobacter* on arrival 4 days post injury, the cultures shifted to predominately *P. aeruginosa* and *Klebsiella* species after 15 days of hospitalization. While there is an increasing tendency for Gram-negative colonization with military patients with prolonged hospital stay, late infections in traumatic injuries are due to Gram-positive agents such as *S. aureus*.

Sheppard and colleagues from the national naval medical centre in Bethesda, argued that the majority of US combat casualty soft tissue wounds are not infected or colonized when arriving at a continental US military medical facility. In their work 242 wound biopsies were taken from 34 patients, 69%

showed no growth and only 31% showed a positive growth.⁸ The incidence of polymicrobial and colonized cultures ($<1 \times 10^5$) was shown to be low and likely reflects the success of frequent and aggressive measures with regards to wound lavage and antimicrobial treatment. Their data identified predominance for *A. baumannii* and Gram-negative species on arrival at a continental US treatment facility. In their data this prevalence decreased during the hospitalization which points away from nosocomial transmission being responsible.

The mixed nationality of casualty populations may also be responsible for what can be seen as the changing pattern of early infections. In a report from a US deployment to the Persian Gulf in 2003 there was an overall trend towards *A. baumannii* as the predominant isolated organism in infected wounds (34% of subjects). In reports from a medical treatment facility in Baghdad it was identified that there was an early propensity of Gram-positive cultures in US soldiers as opposed to Gram-negative species in non-US injured.⁷ The practice of empiric broad-spectrum antibiotics in injured soldiers and nosocomial transmission at medical treatment facilities is thought to be responsible for the change in the bacteriology of war wounds in the early period.

The focus on early causative organisms in Iraq and Afghanistan can also be seen in Johnson's work on 62 patients with an open type III tibial fracture.¹¹ In their study on 40 included fractures, 27 had one organism present in initial deep wound cultures and these were again found to be *Acinetobacter*, *Enterobacter* and *Pseudomonas*. In those that had prolonged union due to infection none of the original organisms were isolated at secondary surgery. Instead, *Staphylococci* was found to be the responsible organism.

Yun et al. looked at sputum, wound sites, urine and blood from patients in Iraq and demonstrated an abundance of coagulase-negative *Staphylococci*.⁷ The local Iraq population made up 80% of this sample and also grew Gram-negative bacteria, including *Pseudomonas*, ABC, *Klebsiella* and *E. coli*. Conversely US soldiers grew *S. aureus* and *Streptococcus pyogenes*.

In one study on obligate anaerobes by White and colleagues, they demonstrated 59 patients with 119 obligate anaerobes identified 7–13 days post injury from lower extremity wounds (43%) that were largely *Bacteroides* (42%) and *Clostridium* (19%) species.¹² There was an association between pelvic wounds and *Bacteroides* species and concomitant resistant Gram-negative aerobes. Comparatively Fleming showed the *Clostridium* was found in more than 80% of wounds. Miles demonstrated in a study of wound flora that *Clostridium* was isolated from 52% of wounds within 3 days of injury, 28% at 4–12 days and not isolated after 12 days. In Korea, *Clostridium* was found within 4.5 hours post injury in 36–84%³ and in Vietnam in 63 wounds 3% were associated with the anaerobes *Clostridium* and *Bacteroides* on the day of injury. Gas gangrene rates have therefore dropped from 5% to no reported cases in the Vietnam war.

Globally therefore it can be seen that one-third of combat casualties from Iraq and Afghanistan develop infections during their initial hospitalization. The causative agents being skin, soft tissue and bone infections in 24% of cases, growing *Enterococcus faecium*, *Pseudomonas*, *Acinetobacter* and *E. coli*.¹³



Figure 3 Fungal infection causing progressive myonecrosis; this required more proximal amputation to control.

Fungal infections

Fungal infection has also been a complicating factor in the microbiology of combat trauma (Figure 3). They carry increased mortality, morbidity and prolonged hospitalization for patients. The military crude mortality from fungal infection was presented at 8% within the first 2 years of conflict. In a study that focused on the clinical significance of *Candida* colonization it was shown that there was a median of 7 days from injury to isolation of *Candida* species, with a 14 day lag time to culture of non-albicans *Candida* species – which were often associated with a prior antifungal exposure. In this study *Candida* isolation had a 7.1% mortality rate. In data by Murray and colleagues an unspecified candidiasis (n = 20) was the most common coded fungal organism, followed by *Aspergillosis* (n = 15) and *Mucormycoses* (n = 16).

The management of these fungal infections from the outset is crucial, as many patients grow more than one mould. Early surgical examination, wound washout and debridement is critical as is dressing with Dakin-soaked Kerlix. Instillation of 0.25% Dakin through vacuum therapy may also be indicated in these patients. The use of intravenous antifungals over oral is thought to increase IV bioavailability, in particular for delivery of amphotericin B and a broad-spectrum triazole (the clinical experience has been with voriconazole). Broad-spectrum antibiotics covering Gram-positive and -negative organisms is also indicated (often vancomycin and meropenem).

The role and use of antimicrobial therapy

The fallout from the management of complex extremity injuries and their infections is an evolution of antibiotic resistance leading to multidrug resistant organisms in military wounds. While World War II saw an increasing use of sulphanimide powder, the introduction and adjunct use of penicillin was to be a turning point in infection management. In Korea, penicillin was combined with streptomycin as a wound prophylaxis, the repercussions of which would only be seen in retrospect. At days 3–5 these wounds would show increasingly resistant bacteria as highlighted by Wannamaker and Kovaric.

The advent of the guidelines on the management of open extremity injuries, as well as antimicrobial prescribing practices in combat injuries, has seen preponderance for the use of prophylactic intravenous antibiotics prior to debridement. In UK practice open fractures are treated with 1.2 g of IV co-amoxiclav every 8 hours, with clindamycin being added with patients without definitive microbiology. Ciprofloxacin can also be utilized to cover for atypical Gram-negative bacteria such as *Aeromonas hydrophilia* from irrigation channel contamination. The advent of such antimicrobial practice has therefore increased the incidence of multidrug resistant organisms including methicillin-resistant *S. aureus* (MRSA).

In one survey from Iraq the most commonly found infections were coagulase-negative *Staphylococci* (24% of isolates), as well as *S. aureus* (26%) and *Streptococcus* (11%). In the local national population the leading strains were Gram-negative *Klebsiella*, *Acinetobacter* and *Pseudomonas*. All of these bacteria were resistant to a vast array of antimicrobials. The susceptibility of ABC to imipenem decreased and in some cases even to Colistin, therefore demonstrating its move to being a multidrug-resistant organism. The majority of isolates were susceptible to colistin, polymyxin B and minocycline. It is also believed that this multidrug-resistant nosocomial infection is more common in burns patients and those who have comorbidities with a longer length of stay. Nevertheless *Acinetobacter* has not been independently shown to be associated with mortality.

In a deployable scenario the biggest problem with combat infections has been the increasing reliance on broad-spectrum antibiotics and balancing this with restricted availability of antimicrobials on deployments. The increasing multidrug resistance can be highlighted by the discontinuation of the use of Imipenem as a first line treatment for ABC.

The evidence on the use of prehospital antibiotics is based on limited in vivo work and the timeframes based on studies of only 49 cases. Despite this there is an increasing tendency to push the resuscitative interventions forward to improve survival. The use of antimicrobials in civilian trauma is effectively based on expert opinion. There is a lack of effective in vivo models to investigate the true timings and effects of early antibiotic delivery. This potentially propagates the further rise in multi-drug resistant organisms.

Murray points towards the decision for antimicrobial therapy in combat wounds should be based on understanding the host, the agent and the environment. In combat, this throws up a variety of factors, such as host hygiene, nutritional and

immunological status. Furthermore the virulence and pathogenicity of the fungi, bacteria or virus that has potentially contaminated the wounds. Finally the environmental factors such as any water exposure, faeculant matter or length of exposure are crucial to impacting on the necessary strength and duration of therapy.

The use of targeted guidelines driven therapy has had delivered some control over the development of multidrug -resistant organisms and improving outcomes. In work done by Lloyd et al. a review of expanded Gram-negative and narrow-range antimicrobials was compared on the infection rate in open soft tissue injury.¹⁴ Although the use of expanded Gram-negative agents declined in the study period from 39% to 11%, there was no significant difference between the subsequent infection rates between the two groups despite narrow-spectrum antimicrobials having an infection rate of 3%. Thus the move to targeted therapy is both beneficial to preventing infection without relative risk.

In concern over the development of carbapenem-resistant *Enterobacteriaceae* (CPE) secondary to its overuse a review of such patients was undertaken by Mende et al. In their work on 0.4% of those who cultured positive for *Enterobacteriaceae* were resistant to carbapenem. In this group 44% of the cultures were for *Enterobacter aerogenes*, 4% for *Klebsiella* and 19% for *E. coli*.

An alternative, to limit the development of further multidrug resistance, is to rely increasingly on our surgical management of these wounds. Irrigation has been shown to reduce both post-operative contamination and rates of infection in wounds without the need for destructive antiseptics. Svoboda demonstrated that in 6 hours after injury using 9 litres of tap water or normal saline there was no difference in bacterial counts between irrigation with saline and water.¹⁵ In this study both methods equivocally reduced bacterial load by 71%. Owens and Wenke investigated the timing of lavage over days 3, 6 and 12 hours post injury. That demonstrated that 6 litres of saline with pulse lavage decreased bacterial counts by 70%, 52% and 37%, respectively, and therefore early irrigation was more likely to have an effect.

Appropriate marginal debridement and re-evaluation, specifically in the complex wound, has been advocated by clinicians from conflicts in Afghanistan. The increasing use of negative-pressure wound therapy has limited evidence to support its reduction in wound bio-burden. Furthermore there is research to demonstrate utilizing such therapy on wounds over 7 days propagates bacterial colonization of the wound, thus hampering further wound healing and reconstruction. Further work to clarify the role these adjuncts have on reducing infection rates and temporizing to definitive closure is necessary.

Conclusions

This paper has highlighted the evolution of microbiology and combat care with relation to complex infections. It has highlighted the complexities of combat microbiology in the patient both in the early and late periods. Delivering combat medicine is a complex logistical task that is required to deliver high quality outcomes in austere clinical environments. The challenges of complex reparations across multiple continents over a prolonged period

undoubtedly has an effect on the colonization and infection rate of injured servicemen. The increased use of prophylactic antibiotics to improve survival and early extremity salvage has to be balanced against the need to provide empirical therapy and prevent multidrug antimicrobial resistance. The lessons learnt from the past 100 years of conflict have had profound repercussions and potentially created a future clinical dilemma of complex multidrug resistant acute pathogens in combat trauma.

Combat casualties continue to have a high infection rate which is temporized by early marginal surgical debridement to decrease bacterial loads. This is concurrently treated with a variety of antibiotic regimens that are tailored to the microbiological picture. However, these wounds are also susceptible to late infections which have prolonged effects on the reconstructive elements to these patients care. ◆

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