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Review Article

Prevention of Combat-Related Infections: A Review of the Literature

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Abstract

Context: Combat-related injuries remain prevalent on the battlefield despite advances in personal protective armor. Infections following these injuries pose a significant concern.
Evidence Acquisition: We used a combination of keywords, including "combat" OR "military", "wound" OR "injury", "infection," and "prevention", to identify relevant articles from major databases, including PubMed/MEDLINE, Web of Science, and Scopus.
Results: Infection risk correlates with the extent and location of the injury. Severe open fractures and penetrating abdominal injuries carry a higher risk of infection than abrasions, blunt traumas, burns, or closed injuries, which are often infection-free. Combat-related infections can manifest early or late, with late-onset infections having a greater likelihood of multidrug resistance. Penetrating abdominal injuries are particularly susceptible to infection due to rapid bacterial colonization in the wounded area and the potential presence of drug-resistant gut microbiota pathogens. Aggressive surgical debridement, along with thorough irrigation and appropriate dressing, proves effective in infection prevention. The timely administration of prophylactic antibiotics is of utmost importance, with continued antibiotic prophylaxis in cases of delayed evacuation.
Conclusions: This review provides a concise summary of current literature on combat-related injury management, emphasizing infection prevention and control strategies.

Keywords: Military Health, Military Medicine, Wound Infection, Wound Healing

1. Context

Infection is a common and deadly consequence of combat-related injuries, with the incidence ranging from 10 to 40% among injured soldiers (1, 2). Owing to advancements in the field of medicine, personal protective equipment (PPE), and antimicrobial agents, such as antibiotics and antifungals, the mortality rate of combat-related infections has decreased, and survival rates and durations have improved. However, as the nature of these injuries remains unchanged, the incidence of infections still remains high. The timely establishment of the chain of support, transfer, prophylaxis, and effective on-site management of these combat-related infections are crucial factors for the overall survival and recovery of injured soldiers (3-6).

The prevention and control of combat-related infections depends on the nature and type of the injury. An evaluation of over three thousand injured American soldiers within 2001 to 2005 revealed that more than 50% of them had suffered from penetrating soft tissue wounds. Additionally, among those injured in the upper or lower extremities, more than 30% had hand injuries; nevertheless, around 50% had lower extremity fractures (3, 7, 8).

According to the classification proposed by Gustilo and Anderson, open fractures are categorized into three main types, with type III fractures having three subtypes. Type I fractures are defined as wounds less than 10 mm in diameter with minimal soft tissue invasion and no contamination. Type II fractures are fractures greater than 10 mm in diameter with mild to moderate soft tissue injury. Type III fractures result from severe injury, leading to massive bone fractures or loss. Type IIIa is characterized by fractures with adequate soft tissue coverage, type IIIb involves bone exposure requiring soft tissue coverage, and type IIIc involves combined soft tissue and bone exposure with an immediate need for vascular reconstruction and repair (9, 10). More than 50% of combat-related injuries fall into the category of type III (a, b, or c), with an infection rate ranging from 5 to 40%. Additionally, 1 in every 10 soldiers loses an arm or leg due to amputation following type III injuries (11-14).

Combat-related wounds or injuries are often considered complex, non-targeted injuries, primarily due to the extensive tissue damage that can occur as a result of uncontrolled tissue targeting. This is characterized by the lack of centralized organization in the wound, which can lead to the colonization of opportunistic or pathogenic bacteria and other microbial strains. This colonization occurs due to the penetration of the skin and subsequent loss of sterility (13, 14). Although wound infections can result from exposure to exogenous agents, such as projectiles, bullets, soil, contaminated clothing fragments, and dirty water, they can also arise from contamination with the host's microflora. The course of wound infection can be further complicated by the simultaneous presence of hypoxia and ischemia resulting from vascular damage, creating a highly favorable environment for bacterial proliferation (15-17).

These wounds are highly susceptible to local and systemic infections, especially if antibiotics are not administered within 3 hours of the wound's development. In addition to exposure, several predisposing factors can contribute to the development of polymicrobial aerobic-anaerobic infections (12). These factors include, but are not limited to, age, pain, hemorrhage, hypoxia, and shock. In most cases, combat-related wound infections are caused by Gram-positive aerobic cocci, including *Staphylococcus* spp., *Streptococcus* spp., and *Enterococcus* spp., Gram-negative facultative aerobic rods, such as *Enterobacteriaceae*, Gram-negative bacteria, such as *Pseudomonas aeruginosa*, and anaerobic Gram-positive sporogenous rods, such as *Clostridium* spp. (18, 19). Based on the current literature and guidelines, this study aimed to summarize the critical aspects of combat-related infections and the necessary steps for prevention and control.

2. Evidence Acquisition

To identify relevant articles, we searched three major literature databases using a string of keywords combined as (combat OR military) AND (wound OR injury) AND infection AND prevention, setting the primary search field to Title/Abstract/Keywords in all literature databases. The initial search was conducted by a reviewer, resulting in a total of 221 records from Web of Science, 91 records from PubMed/MEDLINE, and 263 from Scopus. These 575 records were subsequently independently reviewed by two reviewers to eliminate duplicates and irrelevant entries. Utilizing EndNote Reference Manager as the primary tool for screening titles and abstracts, 142 duplicate records were identified and removed, leaving 433 records for further assessment. Of these records, 284 were excluded as they were deemed irrelevant and did not properly address the primary question of the review. The remaining 149 records were then reviewed by a third reviewer. Only a portion of these articles (47 records) was ultimately used in the writing of the present review article, as many of them had similar content, although they were relevant. Since this work was not intended to be a systematic review, the references were selected to meet the requirements of the intended text.

3. Results

3.1. Microbiological Aspects of Combat-Related Infections

Early contamination is primarily attributed to the normal human microbiota rather than external pathogenic agents (2, 20). The microflora of various body regions, such as the oral cavity, skin, colon, and intestines, typically consists of Gram-positive bacteria, which can easily initiate infections. Visceral injuries are susceptible to infection by certain aerobic and anaerobic species, such as *Bacteroides fragilis* and *enterococci*. Wounds in the upper region might become infected by *streptococci* or *staphylococci*, which are predominantly found in the skin, oral cavity, and airway tracts. Injuries resulting from massive explosions carry a higher risk of infection due to increased exposure to dust, debris, and infectious agents during the initial stages. Explosion-related injuries also have a greater likelihood of fungal infections, which are commonly found in soil. Based on a comprehensive study of American injured soldiers, infections stemming from early contamination with microbiomes have a potential for antimicrobial resistance, with a higher likelihood of Gram-positive infections, such as *Bacillus cereus, B. subtilis*, and *P. aeruginosa*; nevertheless, Gram-negative species are rarely the cause of infection at this stage (15-18).

Late-onset infections are associated with secondary contamination during the chain of support. It is important to note that late-onset infections often exhibit greater resistance to antimicrobial agents than early-onset infections. Based on several studies conducted among soldiers in Iraq and Afghanistan, various resistant species, including *Acinetobacter baumannii, Enterobacteriaceae, S. aureus, P. aeruginosa, enterococci*, and yeasts, have been reported as the causes of resistant infections. Drug-resistant organisms are classified as methicillin-resistant *S. aureus* (MRSA), vancomycin-resistant *E. faecium* (VRE), extended-spectrum beta-lactamase-producing enterobacteria (ESBLE), carbapenemase-producing enterobacteria (CPE), and ceftazidime-resistant species. These resistant microorganisms are most frequently encountered in referral or tertiary care centers due to the extensive use of broad-spectrum antibiotics in these healthcare facilities. Prolonged hospitalizations can significantly increase the risk of late-onset resistant infections (19, 21-23).

3.2. Early Surgical Intervention and Irrigation

Early surgical intervention is a crucial step in preventing infection after combat-related injuries. The primary goal of surgical intervention is to minimize the risk of infection by eliminating the conditions necessary for the growth of pathogenic microorganisms. This should involve aggressive debridement, including the removal of necrotic tissue, external objects, and contaminated superficial clots. During debridement, healthcare personnel must exercise caution to avoid damaging viable, healthy tissue, as this can exacerbate the injury or wound and reduce the chances of recovery (2, 24). The use of proper PPE, such as gloves, masks, and gowns, is highly recommended, if available, as it reduces the risk of cross-contamination between the injured soldier and healthcare personnel and vice versa. Additionally, if possible, pre- and post-debridement cultures should be taken as they provide data for further analysis and assist the medical team in case of encountering a resistant infection. There is no consensus on the ideal timing for debridement; however, the literature suggests it should be performed as early as possible, ideally within 12 hours after injury, with the majority of cases debrided within 3 to 6 hours after injury (25-28).

The recommended standard of care for bone fractures is the external fixation method, as internal fixation can significantly increase the risk of infection in the injured area. Internal fixation should only be used in a very select number of patients after evacuation, in well-equipped care centers, and should not be performed in military facilities or on-site hospitals. In the absence of infection, coverage is not necessary. Complete coverage is typically not intended until the first week after injury in the absence of infection. The injured site can be left open with proper drainage and dressing. The healing process can be improved through the appropriate use of negative pressure. A recent study demonstrated successful outcomes in reducing the risk of infection by using the vacuum-assisted closure method among American soldiers. This technique reduces on-site edema, enhances drainage, and promotes angiogenesis and tissue formation (1, 29, 30).

Irrigation with antiseptic agents and saline is of utmost importance. According to one study, successful irrigation should meet five essential criteria: The type of irrigants, the applied amount, the delivery method, the timing of delivery, and the use of adjuvant agents. Based on the current literature, the amount of saline used for wound irrigation ranges from 3 to 9 liters, depending on the type of injury and fracture. Severe types, such as type III fractures, require a higher amount of irrigant; nevertheless, milder types, such as type I fractures, require around 3 liters. Irrigation with a bulb syringe, in addition to low- and high-pressure lavage, have all been found effective in reducing the risk of infection. A study comparing the efficacy of tap water versus saline for wound irrigation showed that saline was more effective in controlling and preventing infection. However, tap water, along with high-pressure delivery, can be used when saline is not available. Regarding the timing of irrigation, although no randomized trials are available, the current literature suggests that irrigation should be performed within 3 hours after the initial debridement (31, 32).

3.3. Medication, Prophylaxis, and Antibiotic Treatments

It has been shown that early antibiotic therapy and prophylaxis effectively decrease the risk of infection. However, due to the lack of controlled studies, recommendations regarding medications, prophylaxis, and post-injury antibiotic therapy are mainly based on expert opinions. These recommendations differ in terms of the choice of antibiotic, the timing of administration, and the agent of choice. The sole purpose of antibiotic administration is to reduce the chance of gangrene and infections at grossly contaminated sites. The primary species to be targeted are clostridial species, such as *C. perfringens*, along with staphylococci and streptococci species, such as *S. pyogenes* or *S. aureus*. It should be noted that minimally invasive wounds, blunt injuries, and burns should not be treated with antibiotics, and these recommendations only apply to combat-related open injuries (2, 33).

There is no consensus regarding the timing of antibiotic administration. Recommendations range from 30 minutes after injury to 6 hours after injury. However, there is an agreement that antibiotics should be administered as soon as possible after the injury. The initial effective time span should be within 3 hours after injury; however, some data suggest that administration after 6 hours can also be effective. The rule of thumb here is to administer antibiotics as soon as possible. In case of any delay, they can be administered up to 3 hours after injury but not later than 6 hours after injury (2, 33-35).

Certain criteria should be kept in mind when choosing a preferred antimicrobial agent. Based on the data gathered from drug-resistant infections in combat-related injuries, Gram-negative antibiotic coverage is not necessary for early administration, as resistant infections occur later in advanced medical care facilities. The use of broad-spectrum antibiotics at this stage might increase the risk of the formation of drug-resistant colonies. High doses of drugs with acceptable diffusion are the preferred choices, as optimal dissemination is of crucial importance. The antimicrobial agent should have a long half-life, which helps reduce the number of administrations. There is no consensus regarding intravenous or oral administration; however, due to the unstable setting of administration, intravenous injections are mostly used. Oral administration can be used if the injured soldier is conscious and able to swallow. These drugs should be easily stored with minimal thermal care. They should also be highly tolerable with a very high threshold of toxicity (2, 33, 36-38).

Penicillin is still the recommended antimicrobial agent in combat injuries. However, in cases of long delays, typically more than 2 to 3 days, this regimen could be combined with metronidazole. The United Kingdom experts have recommended amoxicillin-clavulanate; nonetheless, the United States Armed Forces recommended intravenous cefazoline administration of 2 g 3 times a day. Additionally, in case of delayed evacuation, cefotetan or ertapenem are suggested. The standard of care recommended by the French military forces, however, differs from the aforementioned guidelines. The French version recommends amoxicillin-clavulanate (intravenous dose of 2 g and q8h for one day) as the standard of care for first-line prophylaxis therapy. The underlying justification is the higher activity of amoxicillin-clavulanate than penicillin against certain species, such as *C. perfringens, Escherichia coli, Klebsiella pneumoniae, Citrobacter koseri, B. fragilis*, and *Proteus mirabilis*. It should also be noted that amoxicillin-clavulanate does not affect *P. aeruginosa* and *B. cereus*, against which penicillin is active. These two species can be found in early-onset combat-related infections (2, 33, 39, 40).

In cases where coverage for Gram-negative species is needed, an aminoglycoside, such as gentamicin, should be added to amoxicillin-clavulanate through intravenous administration. According to the French guideline, this should be done for type III open fractures and abdominal perforations. As gentamicin has a synergistic effect with amoxicillin-clavulanate, the antimicrobial effect should be enhanced. However, the United States Armed Forces guidelines do not support this recommendation. In the case of abdominal and visceral perforations, the addition of gentamicin to the conventional amoxicillin-clavulanate regimen is of higher value, as amoxicillin-clavulanate alone cannot act against certain species of enterobacteria with a high rate of penicillinase production. Post-abdominal-perforation infections usually have an early onset, as the gut microbiota can grow inside the perforated area in a very short time span. This situation can worsen as the gut microbiota commonly comprises several multidrug-resistant enterobacteria (2, 33, 41).

In case of allergy to amoxicillin-clavulanate, the conventional regimen can be replaced by intravenous administration of clindamycin with a loading dose of 600 mg four times a day. Clindamycin has higher activity against anaerobes and Gram-positive species than amoxicillin-clavulanate. Likewise, clindamycin is also ineffective against enterobacteria and Gram-negative species. Gentamicin should be added in the case of perforating abdominal trauma and type III open fractures (2, 33, 38, 42).

The duration of prophylactic therapy can range from 24 hours after injury to 5 days after injury. Based on available reports, a 1-day regimen can be equally efficacious as a 3 to 5-day course. Longer durations can be associated with multidrug-resistant combat-related infections. Usually, the duration of administration should end 24 hours after surgical debridement. However, in the case of extended and more severe injuries, such as abdominal perforations and higher types of open fractures, the administration of amoxicillin-clavulanate can extend to 5 days, and the aminoglycoside agent can be administered for 3 days (2, 33, 38, 43).

As mentioned earlier, the French guidelines differ in antimicrobial agents of choice from the American equivalents. According to the recommendation by the Infectious Diseases Society of America and the Surgical Infection Society, the standard of care is intravenous administration of 2 g of cefazoline 3 - 4 times a day for 24 hours after debridement. In cases of more severe injuries, such as open fractures and perforating abdominal injuries, intravenous administration of 500 mg metronidazole is added to the cefazoline regimen. The alternate antibiotic of choice, in case of allergy, is the same as the French guideline and is clindamycin. However, in the case of penetrating chest injury with the disruption of the esophagus or perforating abdominal injuries, the antibiotic of choice is ertapenem, along with moxifloxacin. Ertapenem should be administered intravenously with a loading dose of 1 g, and moxifloxacin should be administered intravenously with a loading dose of 400 mg.

In addition, the American guideline recommends erythromycin or bacitracin for ophthalmic injuries, and in case of injury, fluoroquinolone is recommended. For more severe and penetrating ophthalmic injuries, levofloxacin is recommended. Additionally, for deep partial-thickness burns, silver nitrate is recommended to be added to the conventional dressing until complete healing or the closure of the injury. In the case of delayed evacuation and delayed medical care, moxifloxacin, ertapenem, levofloxacin, or cefotetan can be administered orally, intravenously, or intramuscularly (2, 33, 37, 43, 44).

3.4. General Considerations

Apart from the aforementioned surgical interventions and antibiotic prophylaxis, general infection control considerations should be maintained as rigorously as possible during in-site management of combat-related injuries. Hands should be washed and cleansed before and after mending each soldier via available water-based antiseptic sanitizers (45-47). Gloves, gowns, and masks should be used, if possible and available, to reduce the risk of cross-contamination. The constant and rigorous use of antiseptic agents to disinfect equipment of any visible contamination is of utmost importance. If possible, proper waste disposal should be managed for the safer transportation of the infective waste (2).

4. Conclusions

Based on the currently available literature, infection remains a prevalent and deadly consequence of combat-related injuries. The use of PPE, along with adhering to general considerations, such as hand hygiene and disinfection, is the primary step in infection control. Surgical interventions, such as aggressive debridement and dressing of the wounded region, coupled with antibiotic prophylaxis, can significantly reduce the risk of combat-related infections.

Footnotes

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