MENTORS IN ORTHOPEDICS

MULTI-DRUG RESISTANT BACTERIA AND THE ROLE OF BACTERIAL BIOFILMS IN WAR-RELATED MUSCULOSKELETAL INFECTIONS: A NARRATIVE REVIEW.

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SUMMARY

Background: Combat-related musculoskeletal injuries often involve high-energy trauma, open fractures, and extensive soft tissue damage. These injuries are increasingly complicated by multidrug-resistant (MDR) pathogens and bacterial biofilms, which compromise clinical outcomes and increase morbidity in both military and civilian populations within conflict zones.

Objective: This narrative review synthesizes current literature to evaluate the incidence of MDR bacteria in war-related musculoskeletal infections (W-MSIs), the role of biofilms in infection persistence, and the clinical drivers of antimicrobial resistance in battlefield settings.

Key Points: Data from various conflict theaters indicate that MDR incidence in W-MSIs can reach 81% in cases of osteomyelitis. Predominant isolates include Acinetobacter baumannii, Pseudomonas aeruginosa, and Staphylococcus aureus. Biofilm formation is a critical factor in chronic infection, providing a protective niche that facilitates horizontal gene transfer and resistance to host immune responses. Identified risk factors for MDR colonization include large soft tissue defects, blast-related mechanisms of injury, and prolonged evacuation chains. Notably, evidence does not consistently support the superiority of combined antimicrobial prophylaxis over single-agent regimens. Effective management requires a multidisciplinary strategy incorporating aggressive surgical debridement, meticulous removal of necrotic bone fragments, and stringent antimicrobial stewardship.

Conclusion: The rising prevalence of MDR bacteria and biofilms in W-MSIs necessitates a shift toward targeted therapeutic interventions and rapid diagnostic protocols. Improving clinical outcomes in orthopedic trauma depends on early surgical intervention, optimized infection control, and a deeper understanding of the mechanisms driving microbial adaptation in battlefield environments.

KEYWORDS

Fractures, Open; Osteomyelitis; Drug Resistance, Multiple, Bacterial; Biofilms; Blast Injuries

INTRODUCTION

In the crucible of conflict, where the chaos of battle unfolds, the toll on human life and limb extends far beyond the immediate violence of warfare. Amidst the debris of shattered landscapes and fractured societies, another silent adversary lurks, imperiling the lives of those wounded in combat: multi-drug resistant bacteria (MDR).

The convergence of traumatic injuries, compromised healthcare infrastructure, and the indiscriminate use of antimicrobial agents has catalyzed the emergence of MDR pathogens, posing a grave threat to military personnel and civilian populations alike. Nowhere is this threat more acutely felt than in the domain of war-related musculoskeletal infections, where the intricate interplay between microbial colonization, host immune responses, and environmental factors shapes the trajectory of disease.

To appreciate the magnitude of this challenge, one must first understand the formidable arsenal of resistance mechanisms deployed by MDR bacteria. The advent of antibiotics heralded a golden age of modern medicine, offering a panacea for infectious diseases that had long plagued humanity. However, the indiscriminate use and misuse of these agents have fueled the evolution of resistance among pathogenic bacteria, rendering once-potent antibiotics impotent against their targets. The genetic plasticity of bacteria, coupled with the selective pressure exerted by antimicrobial agents, has engendered a relentless arms race between the forces of medicine and microbial adaptation. [1]

In the theatre of war, where the exigencies of combat demand rapid and decisive action, the consequences of antimicrobial resistance are particularly dire. Traumatic injuries sustained in battle often involve extensive soft tissue damage, open fractures, and foreign body contamination, creating an ideal milieu for bacterial colonization and subsequent infection. Moreover, the chaotic nature of warfare may impede access to timely medical care, leading to delays in wound management and increasing the risk of infection. [2] This is also facilitated by the fact that military personnel are always in stressful situations, often experiencing hunger and thirst. Their sanitary condition, especially soiled clothing, leaves much to be desired.

In every army around the world, strict rules exist for providing assistance to the wounded, including a system for evacuating the wounded from the battlefield to medical facilities. Staged evacuation of the injured is the process of transporting wounded individuals from the site of injury to larger or specialized medical facilities to provide them with appropriate medical care. During staged evacuation, patients go through several stages of assistance and transportation, starting from primary medical care on the battlefield and ending with hospitalization in specialized hospitals or clinics. At each stage of evacuation, in addition to providing medical care to the patient, broad-spectrum antibiotics can be administered inadequately.

Compounding these challenges is the insidious nature of bacterial biofilms, complex microbial communities encased within a self-produced extracellular matrix. Biofilms exhibit a remarkable resilience to antimicrobial agents and host immune defenses, rendering traditional treatment modalities ineffective against chronic and recurrent infections. Within the context of war-related musculoskeletal injuries, biofilms serve as clandestine sanctuaries for MDR pathogens, perpetuating the cycle of infection and thwarting attempts at eradication. [3] The particular danger of these biofilms lies in their ability to colonize large bone fragments and pieces of necrotic tissue resulting from high-energy trauma caused by bullets and shrapnel.

To address the growing threat of MDR bacteria and bacterial biofilms in war-related musculoskeletal infections, a multidisciplinary approach is imperative. Clinicians, microbiologists, epidemiologists, and policymakers must collaborate to develop innovative strategies for prevention, diagnosis, and treatment.

This narrative review aims to synthesize the existing literature on this topic, shedding light on the relevance of antimicrobial resistance and the role biofilm formation in the context of combat-related injuries.

METHODS

Full-text papers and those with an abstract in English published from 2004 to December 2023, identified through international databases, were investigated with the following keywords variably pooled: "Multidrug-resistant bacteria in battlefield wounds", "Antibiotic resistance in combat zones", "MDR", "Antibiotic resistance" "Bacteria", Infection", "Osteomyelitis", "War", "Battlefield", "Wound", "Biofilm".

Those reporting the incidence of MDR bacteria in battlefield wounds were included as well as those papers investigating the role of bacterial biofilms in war-related MSIs. Organisms were classified as MDR if they were resistant to 3 or more classes of antibiotic agents (aminoglycosides, betalactams, carbapenems, and fluoroquinolones) or if they expressed extended-spectrum b-lactamases or carbapenemases. Methicillin-resistant Staphylococcus aureus and vancomycin-resistant Enterococci were also considered MDR.

Data were pooled for further analysis in order to answer the following questions:

1. What is the impact of conflicts on the mortality rate in the world today ?
2. What is the incidence of war-related musculo-skeletal infections (W-MSIs)?
3. What is the role, if any, of bacterial biofilms in W-MSIs ?
4. What are the main drivers that sustain the occurrence of MDR bacteria in W-MSIs and which preventive measures can be effectively be applied?

The impact of conflicts on the mortality rate in the world today

The number of armed conflicts globally peaked a record high with 182 wars and minor conflicts recorded in 2017, according to the Uppsala Conflict Data Program (UCDP) (cf. https://www.uu.se/en/department/peace-and-conflict-research/research/ucdp/). As of our last update in June 2024, several ongoing conflicts and areas of instability persist around the world. Here are some of the main ones:

1. Syrian Civil War: The conflict in Syria has been ongoing since 2011, with various factions, including the Syrian government, rebel groups, Kurdish forces, and extremist organizations, vying for control. The war has resulted in significant humanitarian suffering and displacement.

2. Yemeni Civil War: Yemen has been engulfed in a civil war since 2014, with Houthi rebels fighting against the internationally recognized government supported by a coalition led by Saudi Arabia and the United Arab Emirates. The conflict has led to a dire humanitarian crisis, including widespread famine and disease outbreaks.

3. Conflict in Afghanistan: While the United States officially withdrew its troops from Afghanistan in 2021, the country remains embroiled in conflict. The Taliban has regained control of much of the country, leading to concern about human rights abuses.

4. India-Pakistan conflict: the confrontation arose out of the 1947 Partition of British India, enshrined in the Indian Independence Act. The Partition established a Muslim-majority Pakistan and a Hindu-majority India and provided the diverse regions of Jammu and Kashmir the opportunity to choose which country to accede to. The maharaja (Kashmir's monarch) ultimately agreed to join India in exchange for help against invading Pakistani herders, triggering the Indo-Pakistani War of 1947-48 and subsequent conflicts. Violence along the India-Pakistan border never completely subsided and continues with incidents reciprocal accusations.

5. Tigray Conflict (Ethiopia): Since November 2020, Ethiopia's Tigray region has been the site of a conflict between Ethiopian federal forces and the Tigray People's Liberation Front (TPLF). The conflict has led to widespread displacement, reports of atrocities, and a humanitarian crisis.

6. Conflict in the Sahel Region: Countries in the Sahel region of Africa, including Mali, Burkina Faso, Niger, and Chad, are facing ongoing instability due to the presence of jihadist groups, ethnic tensions, and governance challenges. Military interventions and peacekeeping efforts are ongoing to address the crisis.

7. Nagorno-Karabakh Conflict: The conflict between Armenia and Azerbaijan over the disputed region of Nagorno-Karabakh flared up in 2020, leading to a brief but intense war. A ceasefire brokered by Russia has been in place, but tensions remain high, and sporadic clashes continue.

8. Conflict in Libya: Libya has been mired in conflict since the overthrow of Muammar Gaddafi in 2011, with various armed groups vying for power and control. Efforts to broker a lasting ceasefire and political reconciliation are ongoing

9. Conflict in Eastern Ukraine: Since 2014, Ukraine has been locked in a conflict with Russian-backed separatists in the eastern regions of Donetsk and Luhansk. Despite ceasefire agreements, a major conflict emerged as of February 2022, leading to a direct confrontation between Russia and Ukraine, supported by several western Countries, leading to hundreds of thousands of casualties and displacement.

10. Israeli-Palestinian conflict dates back to the end of nineteenth century. As the most recent development of this ongoing conflict, Hamas launched a deadly attack on Israel on October 7, 2023, prompting the Israel government to engage in aerial campaigns and ground operations within the Gaza Strip. As a result, almost two million Gazans—more than 85 percent of the population—have fled their homes since October 2023. Recent casualty estimates from the Hamas-run Gazan Health Ministry place the death and wounded toll in Gaza to tens of thousands, with a raise of tensions among countries in the Middle-East and beyond.

These are just a few examples of several ongoing conflicts around the world, and the situation in each region is complex and dynamic, with various factors contributing to instability and violence (Figure 1).

Figure 1: Major ongoing conflicts and instability areas in the world as of June 2024 (source: https://www.cfr.org/global-conflict-tracker)

Death toll related to armed conflicts varies across continents from 19 to 307 per 100.000 habitants (Figure 2). Excluding battle-related deaths, wars have been found to be associated with an increase in age-standardized all-cause mortality of 81.5 per 100,000 population.

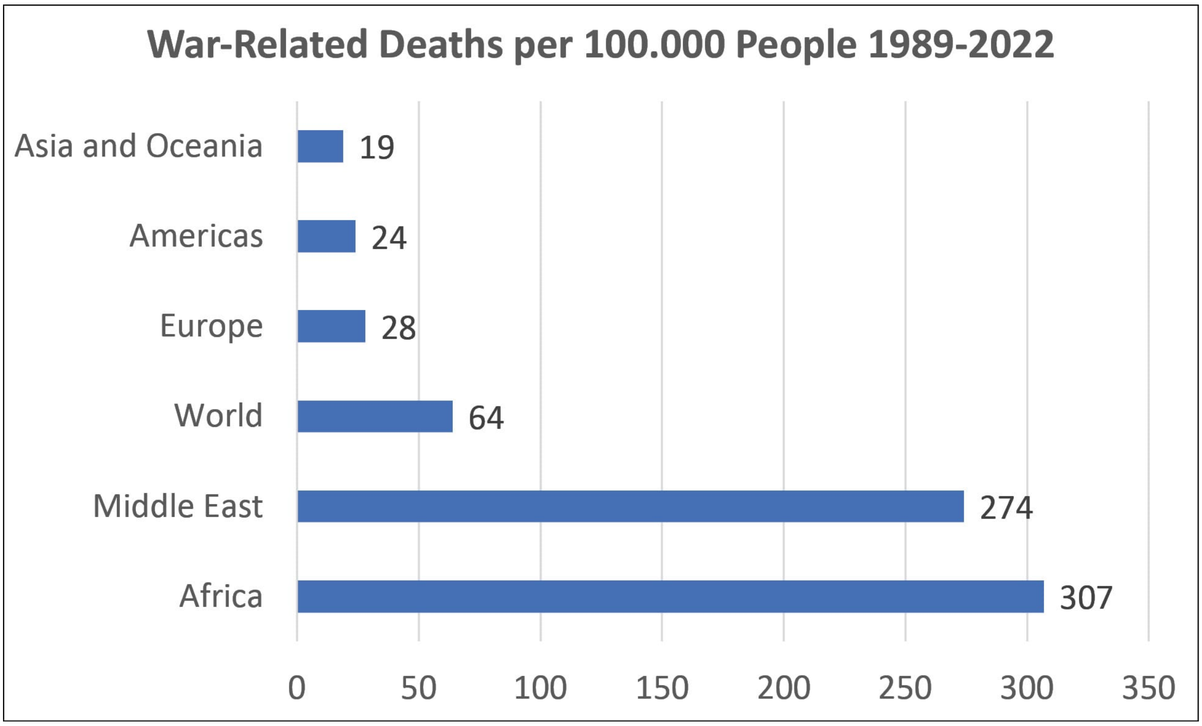

Figure 2: . Death rates in armed conflicts based on the continent they occurred, 1989-2022. Deaths of combatants and civilians due to fighting, per 100,000 people of the population in 1989. Included are all armed conflicts that were ongoing over that time. (source: Uppsala Conflict Data Program (2023); Natural Earth (2022) – processed by Our World in Data; https://ourworldindata.org/war-and-peace#all-charts)

For comparison, according to the World Health Organization [4] the 10 leading medical causes of death, globally, in 2016 showed the following crude death rate, per 100,000 population:

1. Ischaemic heart disease, 126
2. Stroke, 77
3. Chronic obstructive pulmonary disease, 41
4. Lower respiratory infections, 40
5. Alzheimer's disease and other dementias, 27
6. Trachea, bronchus, and lung cancers, 23
7. Diabetes mellitus, 21
8. Road injury, 19
9. Diarrhoeal diseases, 19
10. Tuberculosis, 17

Incidence of MDR bacteria in War-related MSIs

Obtaining precise incidence and prevalence data specifically for MDR bacteria in W-MSIs is challenging, due to the variability of conflict settings, healthcare infrastructure, and reporting mechanisms. [5]

In fact, the most common pathogens found in war-related musculoskeletal infections can vary depending on factors such as the geographic location of conflict, the nature of injuries sustained, and the healthcare resources available for treatment. However, a number of studies have identified certain pathogens that are frequently implicated in these infections.

Nine original articles reporting the incidence of MDR bacteria in W-MSIs and one study dealing with the impact of bacterial biofilms in war-related injuries we included in our analysis (cf. Table 1).

Author	Year of publication	Battlefield theatre(s)	Number of patients
Murray et al. [6]	2009	Iraq and Afghanistan	2242
Weintrob et al. [7]	2018	Iraq and Afghanistan	1807
Tribble et al. [8]	2019	Iraq and Afghanistan	1359
Fily et al. [9]	2019	Iraq, Yemen and Syria	727
Kiley et al. [10]	2021	Iraq and Afghanistan	51
Yaacoub et al. [11]	2022	Syria, Iraq, Lebanon, Palestine, and Yemen	3204
M'Aider et. [12]	2022	Iraq	174
Soderstrom et al. [13]	2023	Afghanistan	316
Moussally et al. [14]	2023	Gaza	n/a

Table 1. Papers reporting the incidence of MDR in W-MSIs.

Data were collected by the following battlefield theatres: Iraq, Syria, Lebanon, Palestine, Yemen, Afghanistan. Analysis of the available studies revealed that the majority come from few groups of researchers, with an absolute prevalence of papers published from US and German military centres.

According to our search, both Gram positive and negative MDR bacteria are frequently associated with W-MSIs in various battlefield theatres.

Some of the most common pathogens found in war-related musculoskeletal infections include:

1. Acinetobacter baumannii: This gram-negative bacterium is notorious for its ability to survive in hospital environments and cause nosocomial infections. It has been frequently isolated from wounds of military personnel injured in combat, particularly in regions such as Iraq and Afghanistan.

2. Pseudomonas aeruginosa: Another gram-negative bacterium, Pseudomonas aeruginosa, is commonly associated with war-related musculoskeletal infections. It is known for its intrinsic resistance to many antibiotics and its ability to form biofilms, making treatment challenging and requiring extensive infected bone removal.

3. Escherichia coli: While often associated with urinary tract infections, Escherichia coli can also cause musculoskeletal infections, particularly in the context of penetrating wounds or open fractures sustained in combat. Some strains of E. coli may exhibit multidrug resistance, further complicating treatment.

4. Klebsiella pneumoniae: Like E. coli, Klebsiella pneumoniae is a gram-negative bacterium that can cause a range of infections, including musculoskeletal infections in the setting of trauma. Multidrug-resistant strains of K. pneumoniae have been identified in combat-related wounds, posing challenges for treatment.

5. Staphylococcus aureus: This gram-positive bacterium is a common cause of both community-acquired and nosocomial infections. Methicillin-resistant Staphylococcus aureus (MRSA) has garnered particular attention due to its resistance to multiple antibiotics and its ability to cause severe infections in wounded combatants.

6. Enterococcus species: Enterococci, particularly Enterococcus faecalis and Enterococcus faecium, are gram-positive bacteria that can cause infections in wounds, especially in the context of healthcare-associated infections or in patients with compromised immune systems. Enterococcal infections may be challenging to treat due to intrinsic and acquired resistance to antibiotics.

These pathogens represent some of the most common causes of musculoskeletal infections in military personnel injured in combat. However, the microbiological profile of these infections may vary depending on factors such as the specific circumstances of the conflict, the availability of medical resources, and local antimicrobial resistance patterns.

In fact, obtaining precise incidence and prevalence data specifically for multi-drug resistant bacteria (MDR) in war-related musculoskeletal infections can be challenging due to the variability of conflict settings, healthcare infrastructure, and reporting mechanisms.

According to the data available for our review, the reported incidence of MDR bacteria in W-MSIs was as high as 81% in patients with osteomyelitis, with up to 33% extended-spectrum beta-lactamases found in Gram-negative isolates, and almost 25% Enterobacteriaceae being resistant to carbapenem. In particular, MDR found in skin and soft tissues and bones included Staph. aureus (range 21.3% to 60.5%), Enterobacteriaceae (12.5% to 86.2%), P. aeruginosa (7.6% to 53.4%), Enterococci species (3.2% to 74.0%), A. baumannii (45% to 86.2%). Escherichia coli (78.3%), Klebsiella spp. (45%); Coagulase negative Staphylococcus and Anaerobes showed much lower or null MDR isolates (cf. Table 2).

Microorganism	% of positive isolates	Rate of MDR strains
Staphylococcus aureus	23.2 to 49.1%	21.3 to 60.5%
Coagulase negative Staphylococcus	5.7%	0%
Anaerobes	12.5%	0%
Klebsiella spp.	25%	45%
Pseudomonas aeruginosa	10.3 to 13.5%	7.6 to 53.4%
Enterobacteriaceae	6.1 to 31.5%	25%
Escherichia coli	8.8%	78.3%
Acinetobacter baumannii	2 to 11.0%	45 to 86.2%
Enterococci spp.	3.2 to 8.0%	3.2 to 74%

Table 2. Most frequently isolated pathogens from bone and skin and soft tissue injuries with the relative range of MDR strains, according to the authors reported in Table 1.

The role of bacterial biofilms in W-MSIs

Biofilm formation was significantly associated with infection persistence in a univariate analysis performed in the only study that we could found on this topic. [15] In their research, Akers and co-workers tested for biofilm formation in a total of 235 bacterial isolates from military personnel with deployment-related injuries in a case-control analysis. The authors concluded that, although limited by the relatively small sample size, their study confirmed that biofilm production by clinical strains is significantly associated with the persistence of wound infections.

Various mechanisms may sustain bacterial biofilms formation in war-related bone and joint infections, including:

1. Prolonged Wound Healing: In the chaotic and resource-limited environments of conflict zones, prompt and effective wound management may be difficult to achieve. Traumatic injuries sustained in warfare often involve open comminuted fractures, penetrating wounds, and tissue damage, creating ideal conditions for bacterial colonization and biofilm formation. Bacterial biofilms delay wound healing processes, prolonging the recovery time for injured military personnel and increasing the risk of complications.

2. Foreign Body and Implant-Associated Infections: War-related injuries are frequently associated with retained contaminated foreign body and often necessitate the implantation of orthopedic hardware or prosthetic joints to stabilize fractures or replace damaged tissues. All these materials can serve as substrates for bacterial adherence and biofilm formation.

3. Antimicrobial Resistance: Bacterial biofilms provide a protective niche for MDR pathogens, shielding them from the lethal effects of antibiotics and offering an additional possibility to exchange antibiotic resistance genetic information.

4. Chronicity and Recurrence: The resilience of biofilm-associated bacteria to host immune responses and antimicrobial agents allows infections to persist despite aggressive treatment measures.

5. Diagnostic Limitations: Diagnosing biofilm-associated infections in war-related bone and joint injuries presents significant challenges. Conventional diagnostic methods, such as tissue cultures or imaging studies, may fail to detect biofilm-embedded bacteria, leading to delayed or inaccurate diagnosis. Improved diagnostic techniques, such as antibiofilm pretreatment methods [16]are needed to enhance the accuracy of diagnosis and facilitate targeted treatment.

In summary, bacterial biofilms play a critical, although still underestimated and insufficiently studied, role in exacerbating the challenges associated with treating war-related bone and joint infections. Their ability to promote chronicity, antimicrobial resistance, and treatment failure underscores the importance of developing novel therapeutic strategies tailored to combat biofilm-associated infections in conflict settings.

What are the main drivers that sustain the occurrence of MDR bacteria in W-MSIs and which preventive measures can effectively be applied ?

The main drivers causing the high rate of MDR bacteria in W-MSIs and their relative impact are not completely understood.

Most often reported general explanations, more based on the knowledge deriving from the civil context than from proven evidence in battlefields, include:

1. High Exposure to Bacteria: In battlefield situations, soldiers are exposed to various environments where bacteria thrive, including soil, water, and contaminated surfaces. This increased exposure can lead to higher rates of bacterial colonization and infection.

2. Widespread Antibiotic Use: In combat zones, antibiotics are frequently used to treat injuries and prevent infections. However, misuse or overuse of antibiotics can promote the development of antibiotic-resistant bacteria. Soldiers may receive antibiotics prophylactically or for treatment, which can contribute to the selection of resistant strains.

3. Limited Medical Facilities and Resources: In some combat situations, medical resources may be limited, leading to challenges in wound care and infection control. Improper wound management, unavailability or delayed medical assistance can increase the risk of infection and the spread of MDR bacteria.

4. Complex Wound Types: Battlefield injuries can range from minor cuts and scrapes to severe trauma, such as gunshot wounds or blast injuries. These complex wounds create environments conducive to bacterial growth and can be difficult to treat effectively, especially if MDR bacteria are present.

5. Movement of Troops: Troops in combat zones often move frequently, which can make it challenging to ensure continuity of care and follow-up for wound management. This movement may also result in exposure to different bacterial strains and environments, further increasing the risk of MDR infections.

On the other hand, better scientifically grounded and more specific risk factors are reported in Table 3.

Author	Year of publication	Number of patients	Main identified risk factor(s)
Murray et al. [17]	2011	405	Higher military Injury Severity Score
Weintrob et al. [7]	2018	1807	Amputations, blood transfusions, Injury Severity Score.
Petfield et al. [18]	2022	1271	Open fracture ≥IIIb, blast injuries, foreign body at fracture site (with/without orthopedic implant), moderate/severe muscle damage and/or necrosis, moderate/severe skin/soft-tissue damage
Fayad et al. [19]	2023	n/a	Inappropriate microbial therapies, limited resources, high heavy metal contamination in humans and the environment, lack of access to proper water, sanitation and hygiene (WASH)

Table 3. Main risk factors for W-MSIs reported by various authors.

Interestingly, a number of other potential risk factors were disproven. In particular, more easily modifiable factors such as early operative intervention, combined antibiotic administration [7] and single-dose broad-spectrum antimicrobials at the point-of-injury [20] did not affect infection or colonization rates, confirming neither benefit nor harm. In line with these results, combined antibiotic prophylaxis cefazolin plus fluoroquinolones and/or aminoglycosides was not proven superior to cefazolin or clindamycin alone to prevent infection in extremity fractures in the studies reported by Tribble et al. [21] and by Lloyd and co-workers. [22]

Even the value of local application of local antibiotics, like vancomycin powder, although advocated by some authors does not seem to have sufficient scientific evidence support. [23]

In this context, generic measures are proposed to limit the occurrence of MDR pathogens and bone and joint infections in a battlefield. These include

1. Infection Control Measures:

- Implement strict infection control protocols, including hand hygiene, wound care, and environmental sanitation, to prevent the transmission of pathogens among wounded individuals and healthcare personnel.
- Use personal protective equipment (PPE), such as gloves and masks, to reduce the risk of cross-contamination and nosocomial infections in field hospitals and medical facilities.

2. Prompt Wound Management:

- Prioritize prompt and effective wound management to minimize the risk of infection following traumatic injuries sustained in combat. This includes thorough wound debridement, temporary immobilization, irrigation with antimicrobial solutions, and appropriate wound dressing to prevent bacterial colonization and biofilm formation.
- Utilize advanced wound care technologies, such as negative pressure wound therapy (NPWT) or antimicrobial dressings, to promote wound healing and reduce the risk of infection.

3. Early Detection and Diagnosis:

- Develop rapid diagnostic tests capable of detecting MDR pathogens and biofilm-associated infections in battlefield settings. Point-of-care testing devices that provide real-time results can facilitate timely initiation of targeted antimicrobial therapy and infection control measures. [24]
- Incorporate imaging modalities, such as ultrasound or portable X-ray machines, into field medical units to aid in the diagnosis of bone and joint infections and guide treatment decisions in specialized hospitals.

4. Antimicrobial Stewardship:

- Implement antimicrobial stewardship programs to optimize the use of antibiotics and minimize the development of antimicrobial resistance among bacterial pathogens. This includes judicious antibiotic prescribing, dose optimization, and de-escalation of therapy based on culture and susceptibility results.
- Utilize combination therapy or alternative antimicrobial agents when treating suspected or confirmed MDR infections to improve treatment efficacy and reduce the risk of treatment failure.

5. Surgical Intervention:

- Prioritizing surgical intervention, such as thorough debridement, meticulous removal of all non-soft tissue-bound bone fragments, extensive irrigation of wounds with antiseptics, and fracture fixation. Promotion of wound healing in cases of traumatic injuries with suspected or confirmed bone and joint involvement. Utilization of various reconstructive surgery methods for wound closure when necessary (Figure 3).
- Consider early surgical consultation and intervention for cases of implant-associated infections or complicated fractures to prevent the establishment of biofilm-associated infections and reduce the risk of treatment failure.
- Provide comprehensive education and training to military personnel, healthcare providers, and support staff on infection prevention practices, antimicrobial stewardship principles, and the recognition and management of bone and joint infections in battlefield settings.
- Foster a culture of awareness and accountability regarding the risks associated with MDR pathogens and the importance of adherence to infection control protocols and treatment guidelines.

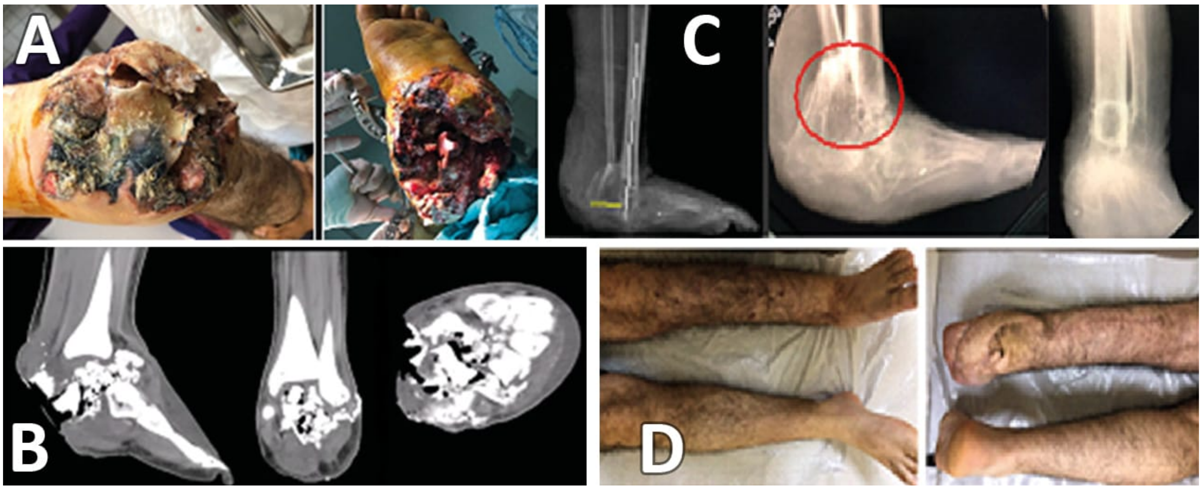

Figure 3: Patient M, 21 years old. A. Mine blast injury, soft tissue defects of right foot, extensive necrotic wound in the area of the left heel, comminuted fractures of the left calcaneus, talus, navicularis and cuboid bones. Admitted one month after the injury. Appearance of the wound at admission. B. CT scan of the foot at admission: comminuted fractures of the calcaneus, talus, navicularis and cuboid bones are visible. C. X-rays of the foot and ankle joint after completing treatment - 6 reconstructive surgeries (including 2 limb-lengthening by 4 cm each time). D. Clinical aspect at the end of treatments. [courtesy Prof. C. Alizadeh]

By implementing a multidisciplinary approach that integrates infection control measures, early detection and diagnosis, antimicrobial stewardship, surgical intervention, and education, it is possible to limit the prevalence of MDR pathogens and bone and joint infections in a battlefield setting. Collaboration among military medical personnel, public health agencies, and research institutions is essential for developing and implementing effective strategies to mitigate the impact of infectious diseases in conflict zones.

CONCLUSIONS

In spite of the technological progress in all human fields and unprecedented direct communication means currently available between people and individuals, armed conflicts are still a widespread plague throughout the world and even increasing in number and intensity.In this context, the escalation of antimicrobial resistance threatens to undermine decades of medical progress, posing a significant risk to both civilian and military populations.

Nowhere is this threat more acutely felt than in the realm of war-related musculoskeletal infections, where the intersection of trauma, microbial colonization, and environmental factors creates a fertile breeding ground for resistance.

This narrative review provides further evidence of the extent and the severity of MDR bacteria in musculoskeletal infections and points out the need for further studies and large scale solutions. While several risk factors of W-MSIs have been identified, the majority of them appear unmodifiable; on the other hand, there is a lack of studies specifically addressing the etiopathogenesis of MDR infections after battlefield injuries. In fact, the most commonly reported genesis of MDR bacteria is the selective pressures exerted by the indiscriminate use of antibiotics, both on the battlefield and in civilian healthcare settings, even if a scientific demonstration of this assumption in battlefield injuries has never been produced and other mechanisms, like for example the cross-resistance to heavy metals and antibiotics are still insufficiently understood.

The evolution of resistance mechanisms, facilitated by genetic mutations and horizontal gene transfer, has endowed pathogens with an alarming repertoire of strategies to evade the lethal effects of antimicrobial agents. Compounding this challenge is the ability of bacteria to modulate their physiological state within biofilms, exhibiting altered metabolic activity and gene expression profiles that confer enhanced resistance to antibiotics. Consequently, the efficacy of traditional treatment regimens is severely compromised, necessitating a paradigm shift in therapeutic approaches towards more targeted and multifaceted interventions.

In war-related musculoskeletal infections, the clinical implications of MDR bacteria and biofilm-mediated resistance are profound. Traumatic injuries sustained in combat frequently involve extensive soft tissue damage and bone fractures, providing an ideal substrate for microbial colonization and biofilm formation. Moreover, the exigencies of military operations often preclude timely access to definitive surgical care and comprehensive infection control measures, exacerbating the risk of treatment failure and disease recurrence. The intense psycho-emotional stress of military personnel during combat and high-energy traumatic injuries sustained in battle often involve extensive soft tissue damage and comminuted bone fractures. All of this increases the area of secondary necrosis in tissues due to lipid peroxidation, creating an ideal environment for microbial colonization and biofilm formation. Additionally, urgent military operations often hinder the stages of medical evacuation and prolong the time from injury to the provision of highly skilled medical care and a full range of infection control measures to the injured, increasing the risk of treatment failure and disease recurrence.

As such, the management of musculoskeletal infections in military personnel demands a holistic approach encompassing early diagnosis, aggressive surgical debridement, and adjunctive therapies targeting biofilm eradication and antimicrobial stewardship. Suggested preventive measure then include early transport and treatment in specialized centers and antibiotic use restrictions, but a deeper understanding and more effective measures to mitigate the occurrence of MDR W-MSIs appear urgently needed.

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