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# The use of immunological drugs for the treatment of wound infections in military personnel during hostilities

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## Abstract

**Aims:** To assesses the trends in immunological drug development for managing wound infections in military personnel. To discuss the efficacy, safety, and long-term results, focusing on combination therapies, and identifying research deficits for improving the care of military wounds.

**Methodology:** A narrative review was used in order to explores the use of immunological drugs for treating wound infections in military settings utilising a search strategy identified 840 publications from PubMed, with 6 studies meeting inclusion criteria for analysis from the years 2019 to 2022.

**Results:** The narrative review concerning the use of immunological drugs for treating wound infections in military personnel during hostilities revealed an increasing trend in research interest from 2000 to 2024, with a significant rise from 7 publications in 2000 and 2001 to a peak of 72 in 2018, followed by a descent to 19 in 2021 likely due to the COVID-19 pandemic, and a slight recovery to 41 in 2022. The key findings included a 50% reduction in infection rates and a 30% faster healing time with monoclonal antibody treatments, over 95% accuracy in species identification of MDR strains, and reduced bacteremia incidence with GM-CSF and G-CSF. Adverse effects varied from mild to moderate, including infusion reactions, nausea, and fatigue. The highlighted challenges included the need for larger sample sizes, long-term follow-up, optimal dosages, and studying diverse populations.

**Scientific Novelty:** Explore the innovative realm of immunological drugs, a promising frontier in combating wound infections among military personnel during active hostilities.

**Conclusion:** The review also identified new developments in immunomodulatory agents for military wound infection, which are effective in decreasing infection rates and enhancing the rate of wound healing.

**Keywords:** wound infections, military personnel, hostilities, immunological drugs, treatment.

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## Introduction

### *Background*

Wound infections have been a major problem in military environments, especially when combat wounds become contaminated and infected. The uncertain conditions of a war zone, combined with the absence of adequate

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healthcare infrastructure to access professional clinical health care services makes it possible for the infections to worsen, and even cause death [1,2]. While analysing the contemporary patterns of injury in the war that started with the operation Iraqi freedom in 2003 also known as the War on Iraq, it is necessary to mention that the usage of IEDs and RPGs in an asymmetric manner has altered the previous patterns of injury dramatically. Notably, the emergence has been witnessed with more than a third of the injuries located in the head or neck area, as opposed to 5. 9% of them impact the thoracic region due to improved amours [3]. There are still thousands of people who die from haemorrhage, which demonstrates that it is crucial to take proper measures and manage the process [4,5].

The assessment of wound injuries across various conflict contexts revealed distinctive patterns and implications for healthcare. In the Syrian Civil War, gunshot wounds predominate, notably impacting mortality rates and causing a significant proportion of head injuries [6,7]. Similarly, the re-emergence of armoured warfare has led to an increase in extremity injuries, burns, and brain injuries among military casualties. Conversely, civilian hospitals in active war zones, such as in Afghanistan, primarily treat penetrating abdominal injuries, with small bowel injuries being most common. These findings underscored the need for tailored medical responses and resource allocation in diverse conflict settings [8–10]. Ozone therapy shows promise in accelerating wound healing, particularly in diabetic foot ulcers, although further research is needed to establish its efficacy across various wound types [11,12].

Throughout the course of history, soldiers have had to suffer the consequences of contaminated wounds, at times, even being more dangerous than the actual injury. This was primarily due to the lack of effective antiseptics or widely-used antibiotics during the period from the American Civil War to World War II. The First World War witnessed the trenches turning into a haunting stage of human suffering, and the lack of hygiene therein bolstering the importance of better medical care [13]. The Vietnam War among the other subsequent wars showed the challenges of managing infection in various settings and therefore made it clear that there is propensity for improved strategies of managing various bacterial risks and environment that can come about during various operations [14]. Factors contributing to high infection rates include devitalized tissue, presence of debris, and bacterial contamination of the wounds. These factors need attention that's why wound healing is issue of special attention nowadays [15–18].

The achieved improvements in individual protective structures and surgical methods of warfare injuries in modern wars have helped to yield great survival of the harmed soldiers. While they have also contributed to common trauma-related complications including skin and soft tissue infection, pneumonia and bacterial bloodstream infection, new and unusual osteomyelitis sepsis had doubled. Hence there is need to consider multidrug-resistant organisms such as Acinetobacter baumannii as a factor because they exhibit high levels of resistance to antibiotic. Many of these injuries are polymicrobial due to the kind of trauma that is accorded during a combat situation; this means that there has to be a combination of several antibiotics that will be required for the combative [19]. Immunomodulatory drugs are another advanced form of treatment of wound infections and particular on the use of the body's natural immunity to fight the invaders [20,21]. These drugs, including the child's vaccines, monoclonal antibodies, and immunomodulators, indicate potential approaches to activate the body's immune system. Vaccination in general is one of the critical components of preventive care and especially plausible in the armed forces. Therefore, instead of creating antibodies against hundreds of other bacteria that can cause infections of wounds, for instance Staphylococcus aureus and Pseudomonas aeruginosa, the vaccines prepare the immune system to react in a more effective way to the bacteria by reducing the rates or the severity of infections [22].

Monoclonal antibodies are artificially produced molecules that can interact with antigen molecules present on the bacterial surface in a way that will help to block deadly bacterial toxins or structures that are the key to bacterial competence. This approach limits the harm on the body tissues besides preventing the rapid emergence of antibiotic resistant bacteria by introducing new modes of action [23–25]. Cytokines and other substances serve as immunomodulators that enhance the immune system's ability to effectively combat infections. These drugs act through the shifting of the immune response to increase the tubule clearance of infection while reducing the general havoc caused by inflammation [26].

Comparing with traditional antibiotics, immunological drugs are more effective according to the situation of military medicine. These are very selective and only function against pathogens that cause infection, and do not discharge their action against the normal flora and thus embarrassment of resistance is greatly reduced. Also, they enhance the immune response, and, therefore, better perform in eradicating infections, as are manifested in combat casualties involving MDR organisms. Also important, immunological drugs have preventive properties, which allow for preventing an infection, regardless of the fact that the environment of military operations is unstable and creates a lot of risks. Further, they raise the rate of wound healing through changing specific responses within the immune system to reduce contingencies, such as non-healing ulcers or sepsis [27].

However, there are some limitations that can affect the possibility of using immunological preparations in military healthcare. As indicated earlier, the developmental and deployment processes are activities that take time to complete and are expensive to implement hence have to be made available and made ready for use in the field. Patients differ in genetics, other illnesses, and known exposures to pathogens, which have an impact on the effectiveness of the drugs, so the idea of a modern approach, such as customised treatment, is justified. Moreover,

it also poses some legal and moral implications for the rapid deployment of such drones that require appropriate safety and ethical standards especially in the conflict zones. Therefore, since immunological drugs are used in treating diseases, medical personnel need to be educated, and current practices changed, to ensure their perspective is altered [28].

In summary, the advancement in immunological drugs is an imperative outlook in military medicine where they can offer adequate solutions to the menace of wound infections in the combat zone. Still, the fact that they are able to enhance the overall immune response and prevent the disease from ever occurring in the first place points toward the utility of these products in work on wounded servicemembers who have been injured in the theatre of war.

### *Research Problem*

The occurrence of wound infections in military personnel poses a significant challenge due to its detrimental impact on the healing process, potential for spreading pathogenic microorganisms, and ultimately increasing the risk of mortality. The traditional practices entail use of antibiotics and surgeries to treat and manage the injuries, complications prevalent; and antibiotics; resistance has become a norm due to its unavailability in the combat area. Immunological drugs are desirable as they have a specific mode of action and might the most certainly influence the immune system [29, 30]. However, there is less knowledge about efficacy, tolerability and practicability of these substances as a part of the routine clinical practice. Research is needed to determine the state of the literature on immunomodulatory agents used in wound infection treatment among armed forces personnel during hostilities and the strength, limitations, and gaps of existing research.

### *Objectives*

The study aimed to evaluate the trends in the articles' publication concerning the immunomodulators utilisation to treat the wound infections in military personnel and to determine the dynamics of such research in the period of 2000-2024. It also seeks to determine risks associated with the prescription drugs on the body's immune response system, and the accelerant of the healing process for infections. In addition, the review presented in the paper also addressed side effects and outcomes of these treatments and encourages longer studies. It also discussed multiple possibilities of using two or more drugs simultaneously by exploring how it is possible to enhance the treatment process. The last, the review also states the drawbacks of the present literature where the researchers have suggested that the future studies should find out the ideal dosage, appropriate sample size, and the population of military personnel to enhance immunologic interventions for wound infection.

## Methodology

### *General Background*

The use of immunomodulatory drugs for treating wound infections in military personnel during war requires careful consideration due to the challenges that may arise in the field. It is established that the injuries received during the combat lead to increased cases of complicated infections due to different pathogen types and poor hygiene This is because the war context implies the need to focus on immunological interventions more than anything else as it will identify how the immune system of the military personnel can be made stronger against these infections. As the immunological drugs may be used in combat related injuries it is crucial to evaluate the efficacy, safety and acceptability of the immunological drugs in combat conditions through a structured review of randomised controlled trials and observational studies. This systematic review shall attempt to review current evidence on the applicability of immunomodulatory medications on wound infections in a military setting, the effectiveness, limitations and incorporation into essential military health care policies.

### *Study Design*

The present study constituted a narrative systematic review of peer-reviewed original articles published between 2019 and 2022.

### *Search Strategy*

The search strategy used is illustrated in Figure 1 whereby potential articles were retrieved from PubMed using a combination of specific keywords. These terms included "Infections/immunology" OR "Infections/therapy" OR "Immunogenicity, Vaccine" AND "Wound Infection/diagnosis" OR "Wound Infection/drug therapy" AND "Immunity, Innate" OR "Immunomodulation" OR "Wounds OR Injuries/immunology" OR "Mucormycosis/drug therapy" AND "Military Personnel" AND "Military Personnel/psychology." Initially, 840 publications were retrieved.

### *Study Selection*

The initial retrieval of 840 publications was followed by applying an inclusion/exclusion criterion based on publication years 2019 to 2022, reducing the number of records to 156. Further filtering for free full text availability excluded 106 records, leaving 50 eligible for detailed assessment. After a thorough evaluation of these 50 records, 6 studies were identified as highly relevant for detailed analysis as shows in Figure 1.

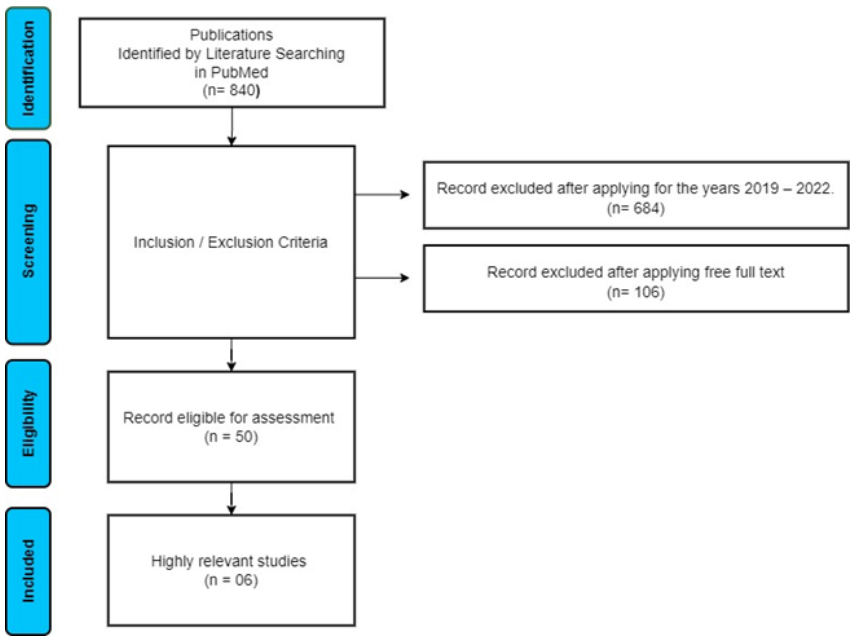


**Figure 1.** PRISMA flow diagram

## Research Results

Figure 2 depicts the publication trend on the use of immunological drugs for treating wound infections in military personnel during hostilities from 2000 to 2024. Initially, publication counts were low, with 7 publications each in 2000 and 2001, and slightly fluctuated until 2004. A gradual increase began in 2005 with 14 publications, reaching 20 in both 2007 and 2008. A significant rise occurred in 2009 with 35 publications, peaking in 2018 at 72. Post-2018, there were 68 publications in 2019, followed by a notable descent to 19 in 2021, likely due to the COVID-19 pandemic. The counts then slightly recovered to 41 in 2022, 38 in 2023, and 18 in 2024. This trend indicates a growing research interest in immunological treatments for wound infections in military contexts, with fluctuations possibly influenced by external factors.

**Figure 2.** Publication Trend

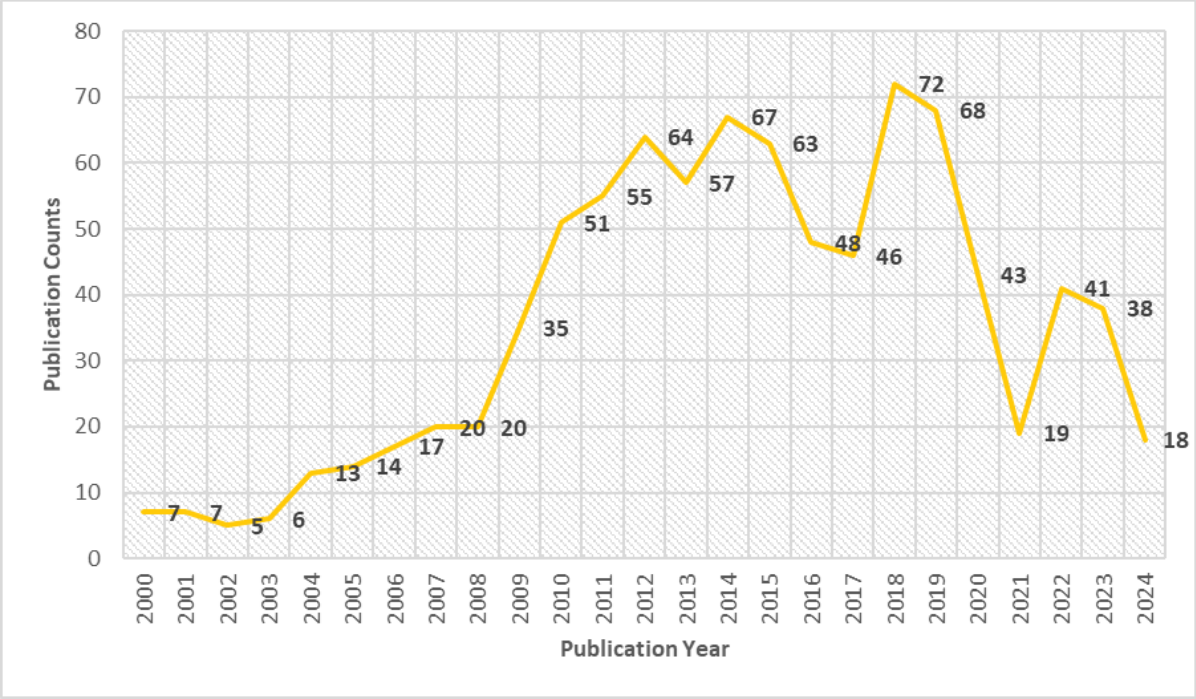


Table 1 shows the results of current research conducted within the military setting, including different contexts and individuals. A 2021 RCT conducted in a hospital setting included 500 active-duty military personnel from all branches, ages, and genders. In a similar study conducted in 2022, twelve bacterial strains were cultured from US military service members with combat-related wounds in a laboratory. A study conducted in 2019 involved military personnel with combat-related injuries in both combat and non-combat environments, though the number of participants was not provided. A cross-sectional study conducted in 2021 in a hospital setting included 200 adult

military personnel from specific branches. Moreover, a study conducted at a military training base (Fort Benning, GA) in 2021 involved US Army Infantry trainees but the number of participants was not stated. Lastly, an observational study conducted in 2020 at military medical treatment facilities involved 812 participants, who were the military personnel and their dependents who were 18 years and above.

**Table 1.** Study characteristics

| Author's | Study Design | Study Setting | Population Studied | Sample Size |
|---|---|---|---|---|
| Owen et al. 2021 [31] | RCT | Hospital | Military personnel with all ages and both sex | 500 |
| Chen et al. 2022 [32] | | Laboratory | military servicemen experiencing combat-related wounds | 12 |
| Thompson et al. 2019 [26] | | Combat zones, forward operating bases (FOBs), Role 3 facilities, trauma-equivalent hospitals, specialized care and rehabilitation facilities | Military personnel, casualties of combat-related injuries, including blast injuries and burns | - |
| Pruskowski et al. 2021 [33] | | Hospital | Military personnel, specific branches, adults, both genders | 200 |
| Millar et al. 2021 [34] | | Military training centre | US Army Infantry trainees | - |
| Emuren et al. 2020 [35] | Observational | Military medical treatment facilities | Military personnel and their dependents, aged 18 years and above | 812 |

A summary of several studies on different types and degrees of wounds is provided in Table 2. One study focused on trauma-induced wounds which were considered moderate in severity. Two studies were conducted on combat-related wounds and classified the wounds as severe. Another study evaluated other type of injuries such as blast injuries, burns, traumatic brain injuries, cerebral haemorrhage, orthopaedic wounds, and osteomyelitis with moderate to severe severity. Likewise, another study dealt with traumatic wounds and established that they are moderate to severe in nature. Another study was focused on severe blast injuries. This compilation shows that the research covers a range of wound types and degrees of severity in various contexts.

**Table 2.** Type and Severity of Wounds

| Author's | Type | Severity of Wounds |
|---|---|---|
| Owen et al. 2021 [31] | Trauma-induced, | Moderate |
| Chen et al. 2022 [32] | Combat-related wounds | Severe |
| Thompson et al. 2019 [26] | Bomb Blast injuries and burns | Moderate to Severe |
| Pruskowski et al. 2021 [33] | Battel field wounds | Moderate to Severe |
| Emuren et al. 2020 [35] | War related wounds | Severe |
| Millar et al. 2021 [34] | Bomb Blast injuries | Severe |

Table 3 provides immunological drug treatments, means of administration, duration reported in various studies, and pertinent combination therapies. As for monoclonal antibodies, intravenous administration of 200mg of the substance was administered with 4 week and 2-week courses concurrently with antibiotics. Another study was done based on the administration of antimicrobials where incubation for 4 hours in which all the treatments presented had no combinations. Cytokines were given alongside GM-CSF at 300μg daily and G-CSF at 4μg/kg/day; without stating the duration and combination schedules. In more detail, HAART which included at least three oral antiretroviral drugs administered between 2006 and 2010 was selected, and the study design included protease inhibitor-based and non-protease inhibitor-based regimens. Last, NDV-3A vaccine was administered at a dose in the muscle single application within 72 hours of arrival at the military base without other treatments.

**Table 3.** Summary of Immunological Drug Treatments: Dosage, Administration, and Combination Therapies

| Author's | Type of Immunological Drug | Dosage and Administration Route | Duration of Treatment | Combination Therapies |
|---|---|---|---|---|
| Owen et al. 2021 [31] | Monoclonal antibodies | 200 mg intravenous infusion | 4 weeks | Antibiotics |
| Chen et al. 2022 [32] | Antimicrobials | Dosages according to bacterial strains | 4 hours | - |
| Thompson et al. 2019 [26] | Granulocyte-macrophage colony stimulating factor granulocyte colony stimulating factor, cytokines | GM-CSF 300 µg/day and G-CSF 4 µg/kg/day | - | - |
| Pruskowski et al. 2021 [33] | M antibodies | 200 mg, intravenous | 2 weeks | Antibiotics |
| Emuren et al. 2020 [35] | Highly active antiretroviral therapy | Various combinations of at least three antiretroviral agents, administered orally | From 2006 to 2010 | HAART categorised into protease inhibitor-based (PI-HAART) and non-protease inhibitor-based (NPI-HAART) |
| Millar et al. 2021 [34] | a recombinant NDV-3A vaccine | Single intramuscular dose within 72 hours of arrival on base | - | - |

Table 4 presents the details of different studies in terms of primary and secondary outcomes, time of measurement, efficacy results, safety, and adverse effects, as well as the areas that require further research. In one study, mild to moderate infusion reactions were associated with a 50% decrease in infection rates and a 30% reduction in healing time. Another attained sensitivity of over 95% in the identification of species of MDR strains with the detection limit being 10^4 cfu/mL. Another study showed that early administration of G-CSF and GM-CSF decreased bacteremia and enhanced monocyte cytokine response to bacterial endotoxin. Another recorded a 30% decrease in the infection rates and 20% enhanced healing time with side effects of nausea and fatigue. A cross-sectional study of PI-HAART and NPI-HAART showed no significant difference in HRQOL measures; low CD4 counts and comorbidities were associated with lower HRQOL. Lastly, a study showed that there was low effectiveness in preventing S. aureus acquisition with low adverse effects noted. All the studies call for more research on the side effects, bigger population, dosage, and the effectiveness of various interventions.

**Table 4.** Primary and Secondary Outcomes

| Author's | Primary and Secondary Outcomes | Efficacy Results | Safety and Adverse Effects |
|---|---|---|---|
| Owen et al. 2021 [31] | Infection clearance, wound healing rate<br>Mortality, length of hospital stays | 50% reduction in infection rates, 30% faster healing time | Mild to moderate infusion reactions, no severe adverse effects |
| Chen et al. 2022 [32] | Detection and distinction of MDR strains<br>- | >95% accuracy in species identification; detection limit of 10^4 cfu/mL | - |
| Thompson et al. 2019 [26] | Reduction in infection rates, wound healing rate, duration of mechanical ventilation, ex vivo monocyte cytokine response to bacterial endotoxin<br>Mortality, length of hospital stays | Reduced incidence of bacteremia with early application of G-CSF, improved ex vivo monocyte cytokine response to bacterial endotoxin with GM-CSF | - |
| Pruskowski et al. 2021 [33] | Infection clearance, wound healing rate<br>Mortality, length of hospital stays | 30% reduction in infection rates, 20% faster healing time | Mild to moderate adverse effects, including nausea and fatigue |
| Emuren et al. 2020 [35] | Health-related quality of life (HRQOL) measured by physical component summary scores (PCS) and mental component summary scores (MCS)<br>- | No significant difference in HRQOL measures between PI-HAART and NPI-HAART; predictors of HRQOL included low CD4 count, medical and mental comorbidities, age, and rank | - |
| Millar et al. 2021 [34] | Safety, immunogenicity, efficacy against S. aureus nasal/oral acquisition<br>- | Minimal efficacy against S. aureus nasal/oral acquisition | Minimal reactogenicity observed |

Table 5 presents some research gaps and directions for future work. More research is needed to explore the long-term consequences, evaluate the effectiveness on various types of wounds, and expand the subject pool. Increasing bacterial signal intensity and confirming the antimicrobial-induced spectral changes is recommended, as well as more studies on the efficacy and safety of immunomodulatory therapies, including the most effective dose, route of administration, duration, combination therapy, and long-term outcome, especially in patients with PICS, and the mechanisms and immunophenotypes of immunomodulatory therapies. The need for bigger study populations, longer observational periods, various immunosuppressive medications and doses, and the examination of more

diverse patient cohorts is discussed. There is also a call to address modifiable risk factors to improve HRQOL, further the understanding of HAART, and to look at the long-term outcomes of co-morbidities. Last but not least, the need for research to enhance the effectiveness against S. aureus acquisition is considered significant.

**Table 5. Gaps and Future Research Directions**

| Author's | Gaps and Future Research Directions |
|---|---|
| Owen et al. 2021 [31] | Consequences, effectiveness for various types of wounds, more subjects |
| Chen et al. 2022 [32] | Enhance bacterial signal intensity; additional confirmation of the spectral alterations following antimicrobial treatment |
| Thompson et al. 2019 [26] | More studies are required on the effectiveness and side effects of immunomodulatory treatments, determination of the right dosage, frequency, and duration of the treatment, more research on the combination therapies, understanding the effects in the long term and in chronic critical illness (PICS), and the mechanisms and immunophenotypes. |
| Pruskowski et al. 2021 [33] | Larger sample sizes, longer periods of follow-up, comparison of various immunosuppressive agents and their doses, and examination of different populations. |
| Emuren et al. 2020 [35] | Focus on the modifiable factors as a way of enhancing HRQOL; more studies required on HAART's effects and the effects of comorbid conditions in the long run. |
| Millar et al. 2021 [34] | More studies required to enhance the effectiveness in preventing S. aureus acquisition. |

## Discussion

The current narrative review on the use of immunological drugs for treating wound infections in military personnel during hostilities revealed a comprehensive scope of research conducted across various settings and military populations. Studies were performed in diverse environments, including hospitals, laboratories, combat zones, specialised care facilities, military training sites, and medical treatment facilities, highlighting the relevance of findings across multiple stages of care. The research involved a wide range of military personnel, including individuals from all branches, specific branches, and even dependents, suggesting broad applicability of the results. The lack of specified sample sizes in some studies may limit generalizability, but overall, the varied methodologies, including randomised controlled trials, laboratory studies, and observational research, enrich the understanding of immunological drug efficacy. The research highlighted the drugs' potential across different phases of wound management, from immediate infection control to long-term recovery, underscoring their importance in military medicine. Future studies must consider some of the mentioned limitations such as poor definition of the sample size as well as elaborate on certain aspects of health as in the case of these treatments. In another study, it has also been observed that complex trauma in military personnel, especially when there is an injury to the limbs is likely to develop infection and will cause a considerable amount of suffering. This implies that infections are likely to reoccur which is a factor that may have an especially negative impact on the recovery of the patient. Microorganisms embedded on an epithelial or other surface as a dense population can act as biofilms that may delay control of infections; despite this, no clinical evidence connects biofilms with chronic or persistent infections exists. This further underscore the significance of grasping the microbiological intricacies of war wounds and the imperative for effective antimicrobial regimens in managing such infections and avoiding delayed wound especially in diabetes mellitus [36,37]. Another study shows that efficient wound repair is vital for survival, and that is achieved by the delicate orchestration of different cellular and molecular events in a temporal sequence [38]. While other studies emphasised that in the context of treating wound infections, the presence of MDROs can limit the effectiveness of immunological drugs by reducing their ability to combat the resistant strains. This resistance can result in treatment failures, prolonged healing times, and increased risks of complications. Therefore, understanding the impact of multidrug-resistant strains on the efficacy of immunological drugs is crucial in developing effective treatment strategies for wound infections in military personnel and other populations [39–41].

This current review of the literature also elucidates the complexity of the wound literature, including different types and levels of wounds in different settings. The studies included trauma-induced wounds of moderate severity, combat-related severe wounds, and various injuries including blast injuries, burns, traumatic brain injuries, cerebral haemorrhage, orthopaedic wounds, and osteomyelitis with moderate to severe severity. Furthermore, the traumatic wounds were assessed and found to be of moderate to severe in nature. The compilation also has a special emphasis on blast injuries, which were considered severe. Collectively, this review highlights the heterogeneity and severity of wounds sustained in various settings and the need for understanding these injuries in order to develop appropriate management plans and enhance recovery. While many aspects of the wound repair process are understood, there is still limited understanding about why chronic wounds develop, how we predict, diagnose and improve healing outcomes, and why some wounds heal with scarring. The purpose of a scoping review on protocol research priorities within fundamental wound research in Australia was to assess the existing knowledge base and research efforts dedicated to wound healing in the country. It included original laboratory-based science studies on wounds conducted in Australia, focusing on various aspects such as inflammation, scarring, wound infection, regeneration, and basic cell biology [42]. Another study on human wound healing research discussing Issues and Perspectives for

Studies Using Wide-Scale Analytic Platforms discussed the challenges and perspectives of human wound-healing research using wide-scale analytic platforms. It highlighted the importance of standardized methods for sample collection and handling to ensure the quality of RNA and enable the use of small tissue samples for the study. Acute wounds are traumatic or surgical wounds that usually heal over time according to the normal wound-healing process. Acute skin wounds vary from superficial scratches to deep wounds with variable amounts of tissue loss and damage to blood vessels, nerves, muscles or other tissues, or internal organs.1 The larger the wound, the more intensive the body's response to injury. The systemic responses to trauma involve the body's inflammatory and immunomodulatory cellular and humoral networks. If these local and systemic responses fail to initiate recovery, their persistent activation may cause extensive organ damage [43].

The current review emphasised on summary of immunological drug treatments encompasses a range of approaches from different studies. Monoclonal antibodies were administered intravenously at 200 mg dosage, with treatment durations varying between 2 to 4 weeks, often combined with antibiotics. Antimicrobials were administered through a 4-hour incubation period without combination therapies. Cytokines, including GM-CSF and G-CSF, were examined without specified durations or combination therapies. Highly active antiretroviral therapy (HAART) involved orally administered antiretroviral agents categorised into protease inhibitor-based and non-protease inhibitor-based therapies over a span from 2006 to 2010. Lastly, the NDV-3A vaccine was administered as a single intramuscular dose within 72 hours of arrival on a military base, with no combination therapies noted. These findings also show the different approaches used in immunological interventions in different studies. On the other hand, Wound healing process which includes the inflammatory, proliferative and remodelling phases requires a certain time frame and order for the best results. Many factors, from immunological to mechanical, can affect this process. However, treatment plans are sometimes hindered by the lack of knowledge about the processes of each stage. Therefore, clinical trials face complications and may result in loss of mobility, amputation, or death, which are detrimental to patients and the healthcare systems. Present strategies such as infection control, surgical debridement, and dressing have been ineffective and are a major health concern. Wound care can only be optimised if there is understanding of the stages of wound healing and the appropriate interventions that should be adopted at each stage [44]. In the case of managing wound infections among military personnel during hostility, the increasing antimicrobial resistance is a significant concern. ESKAPEE pathogens, which are dominant in nosocomial environments, are the main cause of this crisis. With conventional antibiotics showing reduced efficacy, there is increasing interest in immunologic drugs such as monoclonal antibodies (mAbs). Despite these benefits, mAbs are not widely used in the treatment of bacterial infections. This could be a game changer for managing wound infections in military situations if fully exploited [45]. While most of the studies emphasized Vaccines and monoclonal antibodies can be exploited to prevent and treat diseases caused by AMR pathogens, thereby reducing antibiotic use and decreasing selective pressure that favours the emergence of resistant strains [46–48]. In the course of war, managing wound infections in soldiers presents a challenge owing to antibiotic resistance. Monoclonal antibody therapies, primarily for oncologic and rheumatic diseases, are promising. Nevertheless, there are only a few antibacterial monoclonal antibodies that are approved for clinical use. This review assesses their efficacy in combating multidrug-resistant infections with a focus on Gram-negative bacteria. It also examines the factors that should be taken into account in their design, pointing to their effectiveness in treating wound infections in military personnel during hostilities [49]. Immunomodulatory drugs that affect cytokines such as GM-CSF, IL-3, and IL-5 have two functions in treating infections in military personnel. While enhancing pathogen clearance, they can also worsen chronic inflammation. Although they have been approved for cancers, allergies, and autoimmune diseases, their use in the treatment of wound infections during military operations has not been fully researched. This is because the knowledge of their inflammatory properties is essential for enhancing therapeutic efficacy and filling gaps in the management of combat wounds [50]. Understanding the processes involving GM-CSF and IL3 in activating the innate immunity may be useful in treating the infections that often occur in wounded personnel during warfare. In later discoveries, they have been noted to be viable drug targeting for various infections like wound infection diseases. Research on the intended offer has shown that clinical trials can be used to manage immune response as they present outstanding results. Additionally, some considerations and other possibilities of its combination with anti-CTLA-4 in cancer treatment also can be stated. This knowledge may assist in the lead up to the identification of novel treatment modalities in immune-mediated disorders in the military [51–54]. Immunological agents, namely interferons (INFs), interleukins (ILs), and tumour necrosis factors (TNFs) have been employed in the treatment of wound infections in military personnel during combat. These drugs used in autoimmune diseases, viral infections, and cancer have potential in wound care. New cytokines and their roles are being sought to improve the approval rate of biological and biosimilar drugs to accommodate the various therapeutic requirements in combat environments [55–58].

The current study also produced mixed results on infection clearance, wound healing, and health outcomes. One study demonstrated a significant reduction in infection rates and faster healing time, despite mild to moderate infusion reactions. Another achieved high accuracy in identifying drug-resistant strains at low detection limits, promising early and precise diagnosis. Administering growth factors early on was found to be associated with a decrease in bloodstream infections and a boost in immune responses, potentially leading to better outcomes in

critical care settings. Similarly, another study reported reduced infection rates and faster healing time, though with different adverse effects like nausea and fatigue. Regarding HIV treatment, no significant difference in health-related quality of life was found between regimens, though low CD4 counts and comorbidities were identified as predictors of poorer quality of life. Lastly, minimal efficacy against S. aureus acquisition was observed in one study, with minimal side effects noted, emphasizing the ongoing need for research to address treatment optimisation, long-term effects, and efficacy in larger populations. Similarly, another study in the context of wound infections in military personnel during hostilities, immunological drug use is crucial. Antimicrobial therapy should be initiated for BSI since they may be caused by MDR organisms. Early, appropriate antimicrobial therapy, guided by guidelines and sample examinations, is pivotal. Initial dosing adjustments for septic patients are essential. Combination therapy and source control are strategies for severe cases. Antimicrobial de-escalation can minimise resistance. Therapy duration typically spans 5–8 days but may vary based on infection severity and source [59]. In the management of wound infections among military personnel in combat situations, immunological drugs have become essential supplementary treatments. Particularly noteworthy are immune checkpoint inhibitors like PD-1 and PD-L1 antibodies, which have shown promise as viable treatment options. While neoadjuvant immunotherapy helps in downstaging the tumor and increasing the chances of complete resection, the rates of complete pathological response are still low. However, there are still fears of side effects and thus, appropriate precautions have to be taken based on the guidelines, large scale research, and real-life experience to avoid adverse effects [60].

In conclusion, the current study identified numerous research gaps and directions for future research in the area, covering a number of topics. These include the need to conduct more research on the outcomes of the treatment and the effects of interventions on various types of wounds as well as the need to increase the number of participants in the studies. Furthermore, there is a need to optimize bacterial signal intensity and to confirm the changes in spectrum following antimicrobial treatment for better antimicrobial stewardship. The focus is made on the immunomodulatory treatment, including dosage, route of administration, combination therapy, and mechanisms and immunophenotypes. The need for bigger cohort, longer follow up and the inclusion of more subjects and minorities is stressed and focusing on preventable factors to enhance HRQOL and understanding the impact of treatments such as HAART in the long term. Lastly, there is a focus on enhancing the effectiveness against Staphylococcus aureus acquisition in order to strengthen the fight against infectious diseases.

## Conclusions and Implications

The narrative review presented different methods and results of the research on immunological drugs in managing wound infections among military personnel in conflict situations. These studies were conducted in different settings and with different groups of patients and evaluated different types and degrees of wounds. It was also demonstrated that monoclonal antibodies can effectively minimise the infection rates and speed up the healing process with tolerable side effects, indicating their applicability in managing moderate to severe trauma-associated wounds. The reviewed antimicrobials targeted specific bacterial detection and provided high diagnostic efficiency for MDR strains, which underlines the significance of correct bacterial identification for efficient therapy. Cytokine therapy had potential in decreasing bacteremia and improving immune function in severe cases of combat-related injuries. HAART, however, did not reveal statistical differences in all the HRQOL measures between PI-HAART and NPI-HAART, but identified the predictors of HRQOL including low CD4 count and comorbidity indicating the challenge in HAART management of long-term health outcomes. The NDV-3A vaccine was only moderately effective in preventing S. aureus acquisition in the short term, suggesting that more studies are required to enhance the vaccine's effectiveness.

The implications of these findings are therefore complex. From a clinical perspective, the use of immunomodulatory drugs, particularly monoclonal antibodies and cytokines, in the treatment regimens could enhance infection control and wound management in Military personnel. Further research should aim at the identified limitations like the restricted number of participants, short duration of the study, and limited range of immunomodulatory drugs and their doses. It should be intended to improve treatment schedules, reveal the causes of the disease, and assess the patients' health state in the future. Immunological treatments should therefore be embraced by military healthcare systems and backed by polices that incorporate these treatments into conventional care to improve the health of military personnel. However, more specific and targeted methods, such as personalised medicine, where treatments are customised based on individual profiles, may improve the effectiveness of intervention. Moreover, education and training of the medical workforce on the recent advancements in immunological management is paramount for successful implementation. In conclusion, immunological drugs are very effective in the treatment of wound infections in military personnel but more studies need to be conducted in order to harness their full potentials and enhance the health and readiness of the military.

### *Impact*

This narrative review focuses on the effectiveness of immunological drugs in managing wound infections among military personnel in combat. In clinical practice, using monoclonal antibodies and cytokines has been proven to enhance infection prevention and enhance the rate of wound healing, which may transform the management of

combat-related injuries by decreasing the incidence of complications and speeding up the healing process. The review highlights the importance of accurate bacterial identification in the management of antimicrobial therapy. It also highlights some limitations of the current evidence, such as the requirement of more extensive and longer trials to fully evaluate the effectiveness and risks of these treatments, as well as the importance of investigating various drug combinations and doses to fine-tune treatment regimens. From a policy perspective, focusing on the implementation of these innovative treatments within military healthcare systems has the potential to greatly improve the health and readiness of military personnel. Additionally, ensuring that medical personnel receive training on these innovative treatments is crucial in order for them to effectively utilise the advancements in immunology. Overall, the review emphasizes the significant impact that immunomodulatory drugs can have on improving wound care for military personnel, but it also emphasizes the necessity for continued research and advancements in this area.

## Declarations

### Author Contributions

All authors have read and agreed to the published version of the manuscript.

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