Efficacy of Vancomycin Powder in Mitigating Infection of Open Penetrating Trauma Wounds on the Battlefield

An Evidence-Based Review

Brett R. TerBeek[1]; Paul E. Loos[2]; Timothy B. Pekari[3]; David J. Tennent, MD[4]*

ABSTRACT

Background: Open penetrating trauma wounds to the extremities remain the most common injuries encountered in combat and are frequently complicated by bacterial infections. These infections place a heavy burden on the Servicemember and the healthcare system as they often require multiple additional procedures and can frequently cause substantial debility. Previous studies have shown that vancomycin powder has demonstrated efficacy in decreasing infection risks in clean and contaminated orthopedic surgical wounds. **Methods:** This review evaluates the most prevalent organisms cultured post-trauma, the current Tactical Combat Casualty Care (TCCC) guidelines for antibiotic prophylaxis, and relevant research of vancomycin's prophylactic use. **Results:** Results from previous studies have shown a time-dependent reduction in bacterial load when vancomycin powder is introduced early post injury in traumatic orthopedic wounds. Furthermore, perioperative application affords a cost-effective method to prevent infection with minimal adverse effects. **Discussion:** The current TCCC guidelines advocate for the use of antibiotics at the point of injury. When vancomycin powder is used in synergy with these guidelines, it can contribute a timely and powerful antibiotic to prevent infection. **Conclusion:** The prophylactic use of vancomycin powder is a promising adjunctive agent to current Clinical Practice Guidelines (CPG), but it cannot be conclusively determined to be effective without further research into its application in traumatic combat wounds.

KEYWORDS: *vancomycin; trauma; combat; TCCC; prehospital; osteomyelitis; infection*

Introduction

America's wars in Iraq and Afghanistan have shown an increase in survivable open extremity trauma wounds from various mechanisms of injury. These injuries are most commonly caused by improvised explosive devices (IEDs) or gunshot wounds.[1] Extremities have historically been the most vulnerable to wounding and that still persist in today's conflicts. An issue plaguing the recovery of these Servicemembers is the occurrence of wound site infections. These infections often lead to the development of deep tissue infections and osteomyelitis resulting in morbidity and less frequent mortality. This disproportionately affects soldiers involved in dismounted blast injuries. During the initial blast, penetrating trauma wounds are always contaminated with the aerosolized mire of the environment.[2] Several types of gram-positive bacteria are commonly inoculated during this period and ultimately may lead to infection. Special Operations Combat Medics are frequently confronted with austere conditions and greater wait times for medical evacuation. This results in time for these inoculated pathogens to establish a more pervasive infection. When considering future conflicts, near-peer wars will not have the luxury of rapid evacuation times and prolonged field care may be a reality. Current antibiotic administration guidelines for TCCC advises systemic delivery of oral broad-spectrum antimicrobials or intravenous, if oral is not possible.[3] This evidence-based approach should not be changed.

Prophylactic, local, intrawound antibiotic administration has been studied and has demonstrated a reduction in infections during orthopedic surgery. In post-amputation wound closure, local application of vancomycin has demonstrated a reduction in deep tissue infections.[4] Additionally, when post-wound infections do occur, they place a massive financial burden on the Department of Defense (DoD), in both additional treatment expenses as well as in delayed return to duty.[1] Locally-applied vancomycin provides the benefit of high antibiotic concentration without the systemic toxicity found through high levels of intravenous (IV) vancomycin.[5] Extrapolating this clinical use to the battlefield could offer the exact adjunctive, prophylactic agent that combat injuries require. Clinical use has demonstrated reduced amputation revision surgeries and reduced post-operative infection.[4,6] The addition of point of injury topical antibiotics may further enhance the already reduced infection rates provided by the systemic antibiotic administration in the TCCC guidelines. Many of these wounds are associated with vascular injuries and may not have sufficient vascular flow to allow the systemic antibiotics to effectively treat bacterial wound contaminants.[7] This evidence-based review explores the efficacy of the prophylactic application of vancomycin powder in mitigating infection from open-penetrating trauma wounds on the battlefield.

Methods

PubMed was reviewed for clinical literature, using the following search terms, "vancomycin powder," "combat trauma," "infection," "TCCC AND antibiotics," "vancomycin AND orthopaedic AND surgery," "bacteria AND combat AND trauma," and "osteomyelitis." This research also examined literature identifying the microbiology of trauma wounds

*Correspondence to brett.terbeek@gmail.com
[1]**Brett R. TerBeek** is a physician assistant and former Special Forces Operations and intelligence sergeant affiliated with 1/25 SBCT, Fort Wainwright, AK. [2]**Paul E. Loos** is a Special Forces medical sergeant affiliated with 1st SFC(A), Fort Bragg, NC. [3]**Timothy B. Pekari** is a physician assistant and [4]**Dr David J. Tennent** is an orthopedic surgeon affiliated with Evans Army Community Hospital, Fort Carson, CO.

sustained in Iraq and Afghanistan, as well as the current TCCC guidelines. Studies that explored the prophylactic antibiotic use of powdered vancomycin in orthopedic extremity surgeries were included. Additionally, the Defense Technical Information Center's PubDefense was queried to explore ongoing clinical trials as well as research that has been conducted on this topic. Lastly, primary research on animal trials, and retrospective and prospective studies exploring the efficacy of prophylactic vancomycin powder, use have also been incorporated in this work.

Results

Blast Injuries and Osteomyelitis

Throughout the duration of the recent conflicts in Afghanistan and Iraq, substantial research has been conducted regarding the infectious pathogens found post-injury. Casualties that suffered blast injuries were at a higher risk for infection.[8] Blast injuries were also associated with the development of osteomyelitis (p = .001) as demonstrated by Tribble et al. in a case-control analysis of 215 patients with combat-related open tibia fractures.[9] Of these 215 patients that were evaluated, 130 cases of osteomyelitis were identified.[9] Osteomyelitis has been identified as the primary complication associated with combat-related extremity wounds, with 15% of patients developing this infection and 17% of patients having recurrent osteomyelitis.[1] A retrospective cohort study conducted by Yun et al. identified 110 patients with orthopedic injuries from early (2003–2006) in the Iraq and Afghanistan wars.[10] These 110 patients underwent hospitalization 139 times for osteomyelitis. The most common pathogens identified at the first level of higher care include *Acinetobacter* spp., *Klebsiella pneumoniae*, and *Pseudomonas aeruginosa*.[10] The recurrent infections were primarily gram-positive organisms: *Staphylococcus aureus*, methicillin-susceptible *S. aureus*, and methicillin-resistant *S. aureus* (MRSA).[10]

An additional variable is the virulence of *S. aureus*, *P. aeruginosa*, and *E. coli* and their biofilm formation. When given enough time, these organisms adhere to one another and to their environment when they begin to produce an extracellular polymeric substance (EPS).[11–15] This EPS formation confers defenses to each bacterium contained therein, providing recalcitrance to host defenses and antimicrobial treatment.[5] Biofilm formation is of particular importance in the destructiveness of osteomyelitis and the threat it poses to further limb loss.[14] While the recognition of biofilms and their role in chronic infections is becoming more evident, a clear picture of their function in combat trauma is not yet known.[1]

TCCC Guidelines for Antibiotic Administration and Antibiotic Use in Civilian Trauma Care

Prompt use of antibiotics at the point of injury is a part of the standard operating procedure for combat medics on the battlefield. Point of injury antimicrobial treatment by the combat medic provider is advised in the case of all open penetrating trauma wounds on the battlefield. The medic may administer antibiotics, but it is the wounded soldier's responsibility to take their personally issued Combat Wound Medication Pack (CWMP). The current standard of care is moxifloxacin, 400mg by mouth if the patient can swallow or ertapenem, or 1g IV / intramuscular (IM) if the patient is unconscious or in shock.[3] These guidelines have been reached through a decade of evolution with the last major updates in 2012. The change in CPG arose from evidence highlighting the need to remove expanded gram-negative coverage.[16]

To extrapolate and supplement from civilian trauma care, Lack et al. identified a time greater than 66 minutes from injury to the administration of antibiotics as a predictor of infection in type III open tibia fractures with an odds ratio of 3.78 (95% CI, 1.16–12.31; p = .03).[17] This retrospective study examined patients (n = 137) who had type III open tibia fractures. The outcome measured was the presence of deep infection within 90 days of the fracture. The variables of age, smoking, diabetes, and injury severity score were shown to have minimal influence upon infection rates. They further assessed that outcomes for these types of fractures would be improved with antibiotic prophylaxis occurring within one hour of the incident. This continues to support the notion that time is a critical variable in the avoidance of infection.[17]

Intrawound Vancomycin Powder Use in Orthopedic Wound Models

Using orthopedic wound models, Tennent et al. analyzed debridement and irrigation (D&I) as the sole treatment in trauma wounds, in contrast with vancomycin powder as an adjunct to debridement and irrigation.[5] An essential variable to this study was time, with the treatments being performed at either 6 hours or 24 hours. This study examined 54 rat femurs contaminated with *S. aureus* (an osteomyelitis isolate). The research demonstrated statistically significant results (p < .001) with the bacterial load being reduced in the bone when vancomycin was applied 6 hours after contamination as an adjunct to D&I. This was in contrast to solely D & I. When the powder was administered at 24 hours following the bacterial contamination, the infection was not reduced. This was most likely due to the formation of the bacterial biofilm. A significant residual amount of vancomycin powder remained present in the animal's musculature for up to 14 days following the inoculation.[5]

Likewise, Caroom et al. examined 45 rats with simulated open femur fractures that were inoculated with *S. aureus*.[19] This study was different than the Tennent et al. study, in that time was not the variable.[5] The variables in this study were the three treatment modalities, all of which were conducted at 6 hours post-wound. These included D&I alone (control group), D&I plus vancomycin and tobramycin beads, or D&I plus 10mg of intrawound vancomycin powder. The results for this study showed that the placement of intrawound vancomycin powder significantly reduced bacterial growth (p < .0001) when compared with the control group.[19]

An unexpected benefit of prophylactic vancomycin powder administration was researched by Seavey et al. in 2017.[16] Heterotopic ossification (HO) commonly occurs following blast injuries in up to 65% of patients. The early use of this powder in the rat models lead to a statistically significant reduction in HO. Time was again the critical variable. The earlier the vancomycin powder was applied, the higher likelihood both infection and HO would be prevented.[16]

Results of Vancomycin Administration During Surgery

The orthopedic realm has been prophylactically applying vancomycin powder before closing surgical wounds for over a decade. From 2009–2015, in a Pavey et al. study, one surgeon conducted 223 (n = 223) lower limb amputations.[4] This

population included both primary closures and revision amputation surgeries. Of that, 141 patients did not receive vancomycin, and 82 patients' amputations were closed with the prophylactic application of vancomycin powder. The overall absolute risk reduction (ARR) was 13% (p = .034), while the ARR for revision amputations was 16% (p = .037). To prevent one infection of deep tissue in amputation surgery, the number needed to treat (NNT) was eight, while the NNT for revision amputations was seven. The greatest benefit was seen in the patients who underwent revision amputation surgery with a history of infection, with an ARR of 25% and NNT of four (p = .01). Initially, in 2009, the surgeon began applying the vancomycin powder to patients who had previous infections or had been difficult to treat. However, after the clinical evidence suggested improved outcomes, he began treating all patients with it by 2013.[4]

Intrawound vancomycin powder is also being applied prophylactically in total joint arthroplasty. A retrospective investigation conducted by Patel et al. explored 460 primary total hip and knee arthroplasties conducted by one surgeon.[6] Two groups were formed including the vancomycin powder group (n = 348) and the control group without prophylactic antibiotics (n = 112). The vancomycin group's infection rate was 0.57%, while the control group maintained an infection rate of 2.7% (p = .031). Another focus of this study was the cost of the use of antibiotic powder on every patient compared to the cost of one infection. The NNT for this research was 47.5. If each patient has $17 of vancomycin powder applied, it would cost $816 to prevent one infection. When a single hip or knee joint infection is averaging over $25,000, this cost/benefit analysis shows vancomycin powder is a low-cost option with immediate value.[6]

While many studies establish vancomycin's prophylactic efficacy, the Gande et al. meta-analysis demonstrates the increased risk of developing gram-negative and polymicrobial skin and soft tissue infections (SSIs).[20] In this meta-analysis, the control group (n = 10,846) had 412 cases of SSI, in comparison with the vancomycin powder group (n = 8,456), which had 197 SSIs. In contrast, gram-positive SSIs were much higher in the control group (70% versus 45.1%, p < .05). However, gram-negative and polymicrobial SSIs were significantly more prevalent in the vancomycin group (35.8% versus 18.5%, p < .05). The rate of infection in the control group remained higher (3.8%) than that of the treatment group (2.3%). Another contribution that was demonstrated by this analysis was the lack of development of vancomycin-resistant *S. aureus* infections in any of these surgeries.[20]

Discussion

Blast Injuries and Osteomyelitis

Multiple organisms have been cultured from combat wound infections.[8] While a wide variety of both gram-positive and gram-negative microorganisms contaminate wounds, *S. aureus*, a gram-positive cocci, is the most commonly isolated pathogen in recurrent osteomyelitis infections.[21] It has been demonstrated to be a particularly virulent organism and is responsible for the recurring osteomyelitis infections requiring revisional surgeries. Several variables have been found to contribute to the likelihood of infection in combat trauma. Both a higher initial severity score and the mechanism of injury have a direct correlation to infection as established by Mende et al. and Tribble et al.[8,9] More specifically, blast injuries and injuries with concomitant muscle necrosis were most associated with the development of osteomyelitis.[9]

Treatment for osteomyelitis is particularly challenging due to the pathogenic organism's biofilm formation and limited bioavailability of the antibiotics in the dense bone tissue in an area already subjected to vascular insult.[22, 23] This is where vancomycin powder finds its niche. When vancomycin is used at the point of injury, the pathogens will not be afforded the time required for biofilm formation.[5, 12, 13] Additionally, this prophylaxis offers penetration into tissue that has been devascularized from the trauma.[12]

TCCC Guidelines for Antibiotic Administration and Antibiotic Use in Civilian Trauma Care

The current TCCC guidelines, when adhered to, have antibiotic administration as the eleventh step, following necessary stabilization of the patient.[3] This DoD guideline takes into account time, which is a critical component in getting ahead of an imminent infection. A Schauer et al. study from 2007–2016 highlights that while it is the wounded soldier's responsibility to take their own CWMP, that was done < 1% of the time in combat.[24] This infers that a more medic driven solution, such as topical application of vancomycin powder, should be pursued.

As demonstrated by the Lack et al. study, when antibiotics were applied in a time greater than one hour after a type III open tibia fracture, there was a significantly higher likelihood of infection.[17] The local vascular injury complicates the delivery and bioavailability of these antibiotics in the event of amputations or other open-penetrating trauma wounds. Near immediate and locally administered vancomycin powder mitigates the variables of time and lack of diffuse local penetration.[12,13]

Intrawound Vancomycin Powder Use in Orthopedic Wound Models

Vancomycin is a cell wall synthesis inhibitor and has bactericidal and time-dependent properties that give it an advantage when applied early in the process, as demonstrated by Tennent et al.[5, 18] Time was one of the variables confirmed to be crucial to the elimination of the biofilm formation and establishment of infection. Vancomycin powder that was delivered to the wound at 6 hours was shown to be much more effective in reducing the *S. aureus* bacterial load than waiting until 24 hours before application. The Caroom et al. study removed the variable of time and showed that application of vancomycin powder was more effective in reducing bacterial growth than the vancomycin/tobramycin beads.[19] The advantage that is offered in using vancomycin powder versus antibiotic beads is that the vancomycin/tobramycin beads lack the diffuse wound coverage and some types may have to be later removed, reintroducing more opportunities for infection.

Results of Vancomycin Administration During Surgery

The evidence for the efficacy of vancomycin powder's perioperative use following orthopedic injuries has accumulated over the past decade. The primary reasons surgeons have used local prophylactic antibiotic is that it significantly reduced infection rates post surgery, reduced financial burden and healthcare costs, and improved outcomes.[5,6] These reasons would be potentially appealing for the DoD in the reduction of costs and healthcare burden, as well as improved outcomes and return to duty for their Servicemembers.

Pavey et al. sought to determine if the use of inexpensive vancomycin powder would reduce the risk of costly infections and revisional surgeries.[4] The remarkable success in limiting post-amputation infection and post-revisional amputation infection led the surgeon to apply vancomycin powder during all surgeries. This retrospective study exemplifies a surgical administration of vancomycin powder that most closely represents the battlefield application.

A concern that was not discussed in these studies was the higher rates of gram-negative infections. While indeed, overall infection rates were reduced, the Gande, et al. meta-analysis showed that using vancomycin led to a higher incidence of polymicrobial and gram-negative infections.[20] This finding should not be surprising as vancomycin solely targets aerobic and anaerobic gram-positive bacteria. With this selectivity for gram-positive bacteria, it is to be expected that gram-negative infections would increase. An increase in gram-negative *E. coli* infections could be expected, with this being another common cause of osteomyelitis. Increased gram-negative infections can be prevented with the current TCCC antibiotic algorithm. Moxifloxacin targets gram-negative organisms and is effective against *E. coli.*[23] This is why the current TCCC guidelines must not be changed and vancomycin powder should be an adjunct.

Battlefield Application

Taking vancomycin powder from the operating room to the battlefield is a great leap. Recently published research by Burbank et al. and ongoing clinical trials demonstrate that vancomycin powder's transition from the operating room to the emergency room has already begun.[12, 25] While a multitude of research exists for the treatment's efficacy in surgical scenarios, a wide variety of new variables are introduced in war. The purpose of the current TCCC antibiotic guidelines is to provide the most broad-spectrum antibiotics to assist the innate immune response in responding to the overwhelming insult. As soon as the patient can reach higher levels of care, the physicians are then able to make an assessment and adjust antibiotic treatment as necessary. While this method is both easy to train and employ, a shortfall still exists. This prophylaxis is limited in the diffuse penetration to the area of vascular insult.[5] It penetrates only as far as the intact vasculature can transport it. This research suggests that a change in the current antibiotic protocol is not needed, but using vancomycin as an adjunct therapy may potentiate effects on the inoculated pathogens.

The most effective field that this prophylaxis can be researched is in the Special Operations Forces (SOF) community. The clinical and surgical expertise at the tactical level of these Servicemembers is exceptional and their training is unmatched. There are many different types of operations across the globe, which could expose this treatment to a variety of environments. These highly specialized and trained units are deployed in numerous countries, hundreds of miles from higher levels of care. In the event a Servicemember or local national is wounded in the conduct of operations, this antibiotic prophylaxis may provide an additional tool to prevent morbidity in the extremity by applying it to the wound within 6 hours. Another benefit of using this antibiotic powder is there have been no adverse effects noted with its topical use.[26,27] Additionally topical vancomycin was safe and effective when used with intra-articular tranexamic acid (TXA) in total joint replacements and the anti-fibrinolytic effect of TXA was not affected.[28] It is important to note however that TXA is not given intra-articularly in combat; it is usually applied IV, IO, or IM. If prophylactic vancomycin powder is demonstrated to be efficacious in its SOF application, this could later be applied across the spectrum of the DoD, to be used by combat medics and corpsmen.

Limitations

Though efficacy has been shown in various arenas, what this research does not expound upon is the gram-negative bacterial infection concern. *S. aureus* is one of the causative agents of combat trauma infection and later osteomyelitis, but so is the gram-negative *E. coli*, among others. With 57% of initial infections classified as gram-negative, what is unknown is the effect intrawound vancomycin powder will have on increasing gram-negative infections.[8] The only insight offered into this knowledge gap was the Gande et al. study, which researched the selection pressures for gram-negative bacteria.[20] Gram-negative infections were increased in the vancomycin powder treatment group. However, the rate of infection in the control group remained higher (3.8%) than that of the treatment group (2.3%). This finding appears to demonstrate that while gram-negative infection incidence increases when treated with prophylactic vancomycin powder, the overall infection rate is still reduced.

With a minimal amount of research on the battlefield application, there is a great deal of work that still must be done to deem this application of vancomycin efficacious. There is a vast amount of systematic reviews about its peri-operative use, but the transition to other niches is just beginning. A challenge in this research is the breadth of organisms that are cultured in battlefield wounds. The heterogeneity of microorganisms may be a representation of the various mechanisms of injury, or the lack of adherence to antibiotic CPGs, among other factors.[29] *S. aureus* is the most likely causative organism of recurrent osteomyelitis, but there remains significant biodiversity in the cultured pathogenic microorganisms.[22]

Of great concern in the prophylactic utilization of vancomycin powder is antibiotic stewardship. In an age of rapidly developing resistance, using one of the best weapons against MRSA and other multidrug–resistant organisms in a prophylactic fashion could be dangerous. This additional selection pressure could favor the formation of further resistant microorganisms. With this in mind, the Gande, et al. study demonstrates that in nearly 20,000 surgeries with vancomycin powder applied, *S. aureus* never developed resistance.[20]

Conclusion

Near-peer wars will lack the expeditious evacuation times currently in place in Afghanistan and Iraq, which have reduced casualty fatality rates.[29] This reality is indeed an area that the DoD must have effort and synergistic research to prepare for the future. Vancomycin powder certainly is not the antibiotic to stop all post-wound infections. However, vancomycin can be a tremendous adjunctive and cost-effective asset in the fight to save limbs and prevent recurrent osteomyelitis. With the potential for decreasing cases of infection following combat trauma and the low cost of application of vancomycin powder, there are few reasons not to explore this approach when the risk of infection is tremendous.

Further research must be done to demonstrate vancomycin's efficacy in open penetrating trauma wounds. The research has begun at various levels and will continue as long as successes in the realm of surgical prophylaxis continues. The Placement of Antibiotic Powder in Wounds during the Emergency Room (POWDER) study is a prospective controlled study that recently began in October 2020.[24] Open fracture injuries encountered in the Emergency Room will have 2g of topical vancomycin powder applied to evaluate effectiveness of early topical antibiotic intervention. Additionally, a prospective randomized controlled trial known as the VANCO study is currently underway.[30] The intent of the VANCO study is to evaluate efficacy of prophylactic vancomycin powder use in orthopedic trauma patients. Future research should include a prospective study of the application of vancomycin powder at the point of injury on the battlefield, applied by SOF combat medics. The current guidelines for TCCC are critically important to adhere to, and this research does not intend to subtract from the CPGs. The corroboration of this data has shown that vancomycin powder could be a promising adjunctive agent for preventing infection and morbidity in open penetrating trauma wounds across the DoD.

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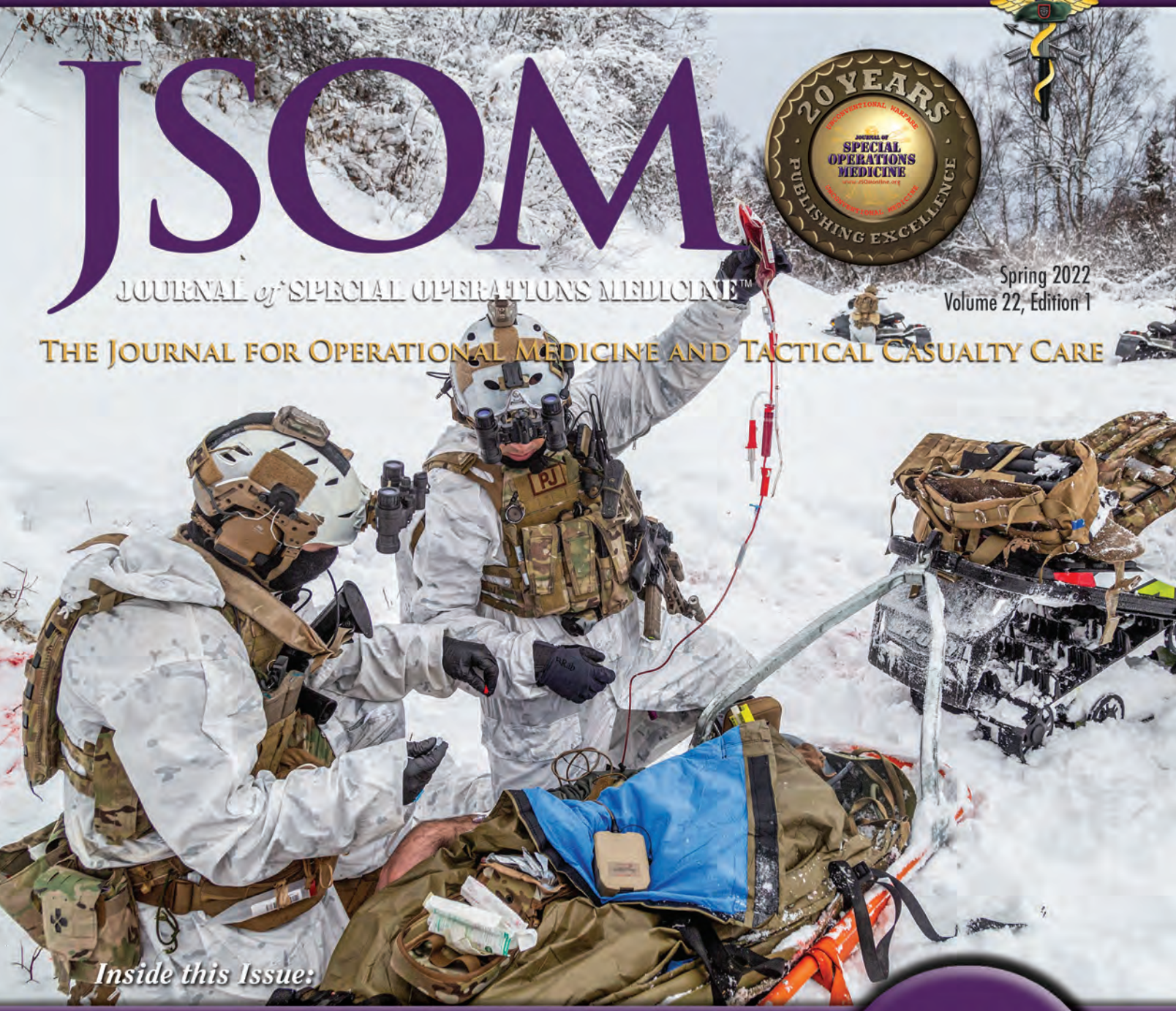

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