Topical Innovation used in the treatment of more than 4-million ICU patients in the prevention of hospital acquired infections now proven to reduce the incidence of infections during special operations training. (Camp MacKall)

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Context: The military is preparing for extended periods of sustaining lives without the rapid evacuation that has been a norm in recent years of war and conflict. The importance of preventing disease and early intervention to minimize evacuation requirements has become increasingly important. In addition, Chapter 4 of the landmark study of health issues in U.S. troops during the first six years of the Gulf Wars ("Gulf War and Health, Volume 5" National Academies Press, Washington DC 2007) outlined the significant diversity of infections and illnesses, some exotic, experienced by U.S. troops involved in the first six years of the wars fought by the United States in the Middle East, immediately following 9/11. Deployed combat troops encountered new pathogenic challenges to which their immune systems were challenged to respond. These illnesses and the resulting unit attrition have significant impact on troop rediness, casualty, battles and wars.

Study Design: An experimental design was selected to evaluate the effectiveness of Combat One® on soldiers during field training events, measuring skin and soft tissue infections and the incidence of cellulitis. Soldiers applied Combat One® from knees to toes and elbows to tips of finger twice daily, on hands and face prior to eating and on hands after latrine use. Three hundred sixty-nine soldiers were assigned to the active treatment group described above. The control group N was 90 and were not provided Combat One® nor but followed standing protocol. Data was compiled via medical staff evaluations/reports and a post training self-administered survey questionnaire.

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Results: Zero (0) instances of MRSA were reported. There were .0081% diagnoses of Cellulitis in Combat One® users as compared to 6.7% diagnoses in non-Combat One® users. There was only 10.8% of contact dermatitis diagnoses in Combat One users as compared to 44.4% diagnoses in non-Combat One® users. There was an overall 80% reduction in requirements for healthcare provider intervention by Combat One® users.

Conclusion: Combat One® and a simple application protocol resulted in improved outcomes and reduced risk for skin infections. Considering the virulent nature of active transmission in the field, these outcomes demonstrate adding a total body (skin) decolonization protocol and (where needed) a zone-of-inhibition protocol with a safe and effective product was beneficial to the overall health of these military members.

Executive Summary

Soldiers operating in various conditions and every branch of service are greatly affected by cutaneous infections. Due to extensive training and difficult deployment conditions, soldiers are exposed to environments conducive to cutaneous injury and infections from opportunistic pathogens. This environment creates a higher than average susceptibility to bacterial, fungal and viral cutaneous infections.

In May of 2018 the small unit tactics training at Camp MacKall, John F. Kennedy Special Warfare Center, Unites States Army Special Operations Command, implemented the use of a novel, cutaneous formulation (Combat One®) along with documented protocols to prevent cutaneous infections.

Combat One® used during these field exercises was shown to substantially reduce the incidence of cutaneous infections commonly seen in these challenging settings, including: Methicillin-resistant Staphylococcus aureus (MRSA) infections, cellulitis and heat rash.

Background

The Center for Disease Control's focus on antimicrobial stewardship has brought a high level of attention to promoting appropriate use of antimicrobials, which includes use of antibiotics in infection control and prevention.[1] The position statement of the Society of Healthcare Epidemiology (SHEA), The Infectious Diseases Society of America (IDSA) and the Pediatric Infectious Diseases Society of America (PIDS) state antimicrobial resistance has emerged as a significant healthcare quality and safety issue in the twenty-first century. Combined with a rapidly dwindling antimicrobial armamentarium, results in a critical threat to the public health of the United States. [2] Consequently, there is increased interest in military and government service channels to re-evaluate infection prevention programs.

Skin and soft tissue infections (SSTIs) are common in both military and non-military populations. Due to the nature of military training environments, risk factors associated with SSTIs such as crowding, infrequent hand washing and bathing, skin abrasions, trauma, and environmental contamination cause high rates of acquisition and transmission of *Staphylococcus* and *Streptococcus*. These pathogens are the major causative agents of SSTIs and are included in that group of increasingly resistant pathogens.

During a four- year surveillance period (2013-2016) by the U.S. military, there were 282,571 diagnosed cases of SSTI among active component U.S. military members diagnosed in both the inpatient and outpatient settings. The overall incidence was 558.2 per 10,000 person-years. Higher rates of SSTIs were associated with younger age, recruit trainee status and junior enlisted rank. [3]

Classification of Skin and Soft Tissue Infections (SSTI)	Service Members Treated For SSTI In Outpatient or Inpatient Setting
49.4% Folliculitis, Impetigo	**238,924** total service members
45.9% Cellulitis/Abscess	**395,361** medical encounters
4.6% Carbuncles/Furuncles	**19,213** hospital bed days
0.1% were Erysipelas	

Skin infections have are problematic for multiple reasons in the military: lost training time; high healthcare expenditures associated with their evaluation and treatment; and the risk of more serious infection with multi-drug resistant organisms (MDRO). For these reasons, prevention, early diagnosis and definitive treatment of skin infections are critical. [3]

In a study published in the Journal of Military Medicine, Military Medicine, Volume 180, Issue 1, January 2015, Pages 32–37, by Ari B. Gelman, MC USA Scott A. Norton, MD, MPH Rodrigo Valdes-Rodriguez, MD Gil Yosipovitch, MD the incidence of skin complaints has and remains one of the most common reasons for medical intervention.

TABLE I

Percentage of Military Personnel Physician Visits for Skin Conditions

Conflict	Percentage (%)	Setting	Total Consultations/Derm
World War II[4]	15–40	Sick-Call Service, European and Mediterranean Theaters (1942–1943)	From Interviews With Medical Officers
Vietnam War[5]	12.2	Outpatient Visits by Broad Cause Group, Vietnam-All (1965–1972)	11,577,868/1,412,500
Bosnia[6]	12.7	Outpatient Visits, Bosnia-All (January 1996–March 1996)	1,649/211
Gulf War[7]	9.3	Outpatient and Inpatient Medical, First Cavalry Division (November 1990–February 1991)	15,401/1,433
East Timor[8]	25.2	Outpatient and Inpatient, East Timor-All (September 1999–February 2000)	5,500/1,375
Afghanistan[9]	20	Outpatient Visits, Craig Joint Theater Hospital, Bagram Air Field (June 2007–July 2007)	2,421/1,433

Infection prevention and control in deployed military medical treatment facilities (MTF) has been and continues to be a serious threat to military operations. Infections have complicated the care of combat casualties throughout history and were at one time considered part of the natural history of combat trauma. Recent U.S. military deployment in Iraq and Afghanistan continued to document a large volume of cases on the epidemiology of colonization and infections.[10] Multidrug-resistant (MDR) gram negative bacilli, including Acinetobacter baumannii-calcoaceticus complex, extended-spectrum-lactamase (ESBL)-producing Enterobacteriaceae (e.g., Escherichia coli and Klebsiella pneumoniae), P. aeruginosa, and methicillin-resistant S. aureus (MRSA), are most commonly been reported as the cause of these infections.[11] Over the past decade, carbapenem susceptibility has dramatically declined in Acinetobacter isolates recovered from those personnel injured in combat in Iraq and Afghanistan.[12] Accumulated data implicates nosocomial spread of these MDR bacteria within deployed MTFs and likely throughout the military healthcare system. With the exception of MRSA, it does not appear that US personnel are colonized with these bacteria before injury. Colonization with community-associated MRSA has been documented in healthy military personnel and is a potential source of later infection.[13] Pre-injury colonization by resistant gram-negative bacteria in military personnel, specifically Acinetobacter, has not been found in small studies of deployed and never (pre-) deployed troops.[14] MDR bacteria have also not been found contaminating wounds at the time of admission to these deployed facilities.[15] Introduction of resistant bacteria into deployed MTFs through care provided to host nation and other non-US patients is a concern and a likely source of colonization leading to later infection of our combat-injured personnel. Studies conducted in deployed MTFs have found associations between MDR bacteria and host nation patients as well as associations between duration of host nation patient intensive care unit stay.[16,17] This raises the risk levels for each military deployment in each new geographic region.

Complexities of Cellulitis can be life threathening. Cellulitis is a common bacterial skin infection that spreads diffusely and often involves subcutaneous tissue. The dermal, sharply demarcated variant, often called erysipelas, is almost always caused by β-hemolytic streptococci (BHS). Group A streptococcus ([GAS] Streptococcus pyogenes) is a major pathogen, but

group B streptococcus (GBS), group C streptococcus (GCS), and group G streptococcus (GGS) may also cause erysipelas. Mean total in-patient cost to treat cellulitis is more than $ 7,000.00 per event. Fungal infection of the skin creates breaches in the epidermis and is believed to act as a portal of entry for bacterial pathogens. In the absence of other predisposing factors, clinical signs suggestive of ipsilateral athlete's foot (tinea pedis interdigitalis) have been observed in up to 80% of patients with cellulitis of the leg . In 23% of patients with both tinea pedis and cellulitis, the dermatophyte infection was identified as the sole predisposing factor for cellulitis. Tinea pedis is one of the most common dermatologic conditions amongst our troops.

Topical Formulation Used in the Study (Combat One®, Theraworx® Protect)

The acid mantle of the skin plays a pivotal role in preventing infecctions. The clinical significance of the acid mantle has recently been linked to vital stratum corneum function. Despite compelling basic science evidence placing skin pH as a key factor in barrier homeostasis, stratum corneum integrity, and antimicrobial defense, application of the acid mantle concept in clinical care is lacking. The pH of the skin rises, with injury, disease and stress. A low skin pH, however is associated with infection prevention and the health of the skin's permeability barrier. Lowering skin pH also preserves healthy flora resulting in a super-normalized stratum corneum, which is the outer layer of epidermis - the body's first layer of defense. Combat One® was developed based on the proven efficacy of Theraworx® Protect as an innovative topical technology proven to down modulate the pH of the skin and is used in intensive care units, skilled nursing facilities, universities and high schools, in the prevention of central line associated blood stream infections, catheter associated urinary tract infections, ventilator associated pneumonia, source control for c-diff, candida-auris outbreaks, and skin and soft tissue infections. The formulation has a multi-modal mechanism of action with a proven selective toxicity profile. In a study conducted at the University of North Carolina Chapel Hill and University of Florida [18], in recalcitrant non-healing arterial and diabetic wounds colonized with multiple drug resistant organisims bioflims including pseudomonas, strep and acinetobacter the Combat One® and Theraworx Protect® formulations is demonstrating potent efficacy and is eradicating resistant biofilms without being toxic to new cell formation and accelerated skin closure. The formulation showed significant reduction in tissue pH of the wound bed and a potent pro-inflammatory inhibitor mechanism, thus creating ideal wound healing conditions for favorable treatment response. In studies conducted at Duke University, Sports Medicine Fellowship with division one wrestlers, Theraworx Protect® was shown to significantly reduce the incidence of skin and soft tissue infections, use of oral antibiotics and new cases of herpes gladiatorum compared to chlorhexidine gluconate 4%. This was a three-year study and in the baseline year when CHG was used, 12 of 27 athletes had to receive oral antibiotic therapy. In years two and three, when Theraworx Protect® was used per protocol, there was only 1 diagnosed skin infection and no new cases of herpes gladiatorum. [19] Combat One® is the military and government services brand of Theraworx Protect®.

In a recent study published in the American Journal of Infection Control, Theraworx Protect® was proven superior in safety and non-inferior in infection control to CHG 4%. [20]. The formulation is available as a spray, foam and saturated towel. In 2017 Theraworx Protect® was used in the treatment of 2 million ICU patients and in 2018 was used by more than 4 million patients including military hospitals and Veteran's Administration hospitals. The formulation does not contain any antimicrobial drugs. It is gaining fast adoption due its ability to minimize use of topical and oral anti-microbials.

Methods

Two training classes, each lasting approximately 40 days, were used as the test subject pool. Out of 459 trainees 369 were provided Combat One translating to 80% participation in the opt-in study. In the first class session we provided Combat One Spray and Combat One Bathing System. The second class received Combat One Foam and Combat One Bathing System. Participating trainees were given 30 minute verbal and visual instruction on use and the application protocol on their first day of training. They were instructed to apply a minimum of twice daily from knees to toes and elbows to tips of finger, prior to eating and after latrine use on hands and face. They were also advised to use the product for compromised skin, such as minor abrasions, scratches or friction sensitivity. This zone-of-inhibition protocol was implemented to accelerate healing and to protect the area from transient pathogenic flora. To provide a zone-of-inhibition these soldiers were instructed to spray the compromised area and cover the area and surrounding tissue with a six- inch radius covering on all sides. The protocol was to spray, allow to air dry three times a day for four days.

Data was compiled via medical staff evaluations/reports and a post training self-administered survey questionnaire. Data collected included:

- Total number of medical staff inquiries due to cutaneous issues
- Total number of contact dermatitis occurrences in the field
- Total number of cellulitis occurrences in the field
- Total number of MRSA infections in the field

Results

Training classes at Camp MacKall experience 10% reported cases of cellulitis and/or MRSA, on average. [23].

Study Results Comparing User and Non-Users of Combat One

Condition	Total Cases Reported	Results
MRSA	0	0 MRSA
Cellulitis	3	369 Combat One Users = .0081%
	6	90 Non Combat One Users = 6.7%
Contact Dermatitis	40	369 Combat One Users = 10.8%
	40	90 Non Combat One Users = 44.4%
Secondary Medical		80% Reduction

Conclusion

Skin is the most exposed organ of the body and military personnel face many external skin threats. As a result, skin disease is an important source of morbidity among military personnel deployed during combat or peacekeeping operations. Although skin disease in warfare has historically been a major source of morbidity, the types and sources of dermatologic conditions affecting soldiers are incompletely understood. [21] Dermatophytic, pyogenic, and eczematous conditions are worthy of special consideration by the military medical community. These diseases decrease operational readiness in theater and sometimes require evacuation. In a publication in Military Medicine, of 883 evacuations of military personnel from Iraq and Afghanistan for skin conditions between 2003 and 2006, almost 20% (170), were evacuated with "mystery rashes," skin conditions that were unable to be identified in theater, highlighting the complexity of skin disease in the combat environment and the potential benefits of improved prevention and diagnosis.[22] Improved access to dermatologic diagnostic resources, education on dermatologic conditions seen on deployment for medics and midlevel providers, and in-theater access to expert dermatologic consult could all serve to improve the care of deployed soldiers. To respond to Secretary of Defense General Mattis's call for "combat readiness," a more proactive preventive approach to hygiene and cutaneous infection management is required. This is a two-pronged approach. First, identification of the latest science and technology to combat ever changing and resistant microorganisms. Second is rapid implementation of

this evolving standard or care earlier in the training and development of soldiers as a part of their standard of personal hygiene and health.

The implementation of Combat One® and protocols resulted in overall reductions in cutaneous infections and medical attention required when compared against current standard of care techniques. The effectiveness of any infection protocol is limited by compliance and adherence to protocols. Because soldiers are highly motivated to remain free of skin infections, ease of applying the skin formulation appeared to have a positive effect on compliance among the study population.

Secondary benefits were found in post-trial surveys and medical evaluations. Heat rash reduction and relief were reported by 16 soldiers. In addition, soldiers identified skin relief from the effects of poison ivy, poison oak and sumac. These conditions were not original trial inclusion criteria. Contact dermatitis was reduced twenty percent among Combat One® users, with a number needed to treat of 5 to prevent one occurrence of contact dermatitis—this is not clear to the reader—need the data to restate correctly.

Combat One® and a simple application protocol resulted in improved outcomes and reduced risk for skin infections. Considering the virulent nature of active transmission in the field, these outcomes demonstrate significant benefit of adding a total body (skin) decolonization protocol and (where needed) a zone-of-inhibition protocol with a safe and effective product.

Infection prevention protocols now and in the future will become more important to soldiers, the health care providers and leaders. Future investigation should assess the effectiveness of this Combat One protocol with focus on compliance, incidence of various cutaneous infections to include fungal types, and control of secondary herpetic outbreaks.

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