WILDERNESS & ENVIRONMENTAL MEDICINE 2023; 34(2): 231–42

REVIEW ARTICLE

External Hemorrhage Control Techniques for Human Space Exploration: Lessons from the Battlefield CME

Stijn J. J. Thoolen, MD[1,2]; Maybritt I. Kuypers, MD[3,4]

[1]*Neural Systems Group, Massachusetts General Hospital, Harvard Medical School, Charlestown, MA;* [2]*Centre for Human and Applied Physiological Sciences, King's College London, United Kingdom;* [3]*European Astronaut Centre, European Space Agency, Cologne, Germany;* [4]*Department of Emergency Medicine, Amsterdam UMC, University of Amsterdam, the Netherlands*

The past few decades of military experience have brought major advances in the prehospital care of patients with trauma. A focus on early hemorrhage control with aggressive use of tourniquets and hemostatic gauze is now generally accepted. This narrative literature review aims to discuss external hemorrhage control and the applicability of military concepts in space exploration. In space, environmental hazards, spacesuit removal, and limited crew training could cause significant time delays in providing initial trauma care. Cardiovascular and hematological adaptations to the microgravity environment are likely to reduce the ability to compensate, and resources for advanced resuscitation are limited. Any unscheduled emergency evacuation requires a patient to don a spacesuit, involves exposure to high G-forces upon re-entry into Earth's atmosphere, and costs a significant amount of time until a definitive care facility is reached. As a result, early hemorrhage control in space is critical. Safe implementation of hemostatic dressings and tourniquets seems feasible, but adequate training will be essential, and tourniquets are preferably converted to other methods of hemostasis in case of a prolonged medical evacuation. Other emerging approaches such as early tranexamic acid administration and more advanced techniques have shown promising results as well. For future exploration missions to the Moon and Mars, when evacuation is not possible, we look into what training or assistance tools would be helpful in managing the bleed at the point of injury.

Keywords: resuscitation, bleeding, spaceflight, advanced trauma life support, tactical combat casualty care

Introduction

Space is a remote and hazardous environment, and over the years, space exploration has led to 21 fatalities from 5 events.[1] Most mishaps that involved injuries have occurred during liftoff or re-entry, including drowning incidents, cabin decompression, and blunt trauma. However, there have also been in-flight incidents that could have required emergency management, such as fires, vehicular collisions, and loss of environmental controls.[1,2] While there have not been any evacuations for major trauma injury to this day, the possibility of a resuscitation scenario on future missions cannot be eliminated.[3-5] Recent modeling for a 923-d standard Mars mission (560 d on the surface) has provided a risk estimate of 5.209% for reaching medical evacuation criteria secondary to traumatic injury, such as burns, musculoskeletal injuries, and bleeding.[5] Among these conditions, traumatic hypovolemic shock accounted for 0.193% and ranked highest for reaching loss of crew life, with an estimated risk of 0.107%.[5] Considering the high impact of these injuries on health and mission success, resuscitation protocols informed by mission attributes and targeted toward realistic interventions will be critical.

Trauma resuscitation in space is limited because of a variety of factors, including microgravity, logistical

Corresponding author: Stijn JJ Thoolen, MD, Neural Systems Group, Department of Psychiatry, Massachusetts General Hospital/Harvard Medical School, Charlestown, MA; e-mail: sthoolen@mgh.harvard.edu.

https://doi.org/10.1016/j.wem.2023.01.006

constraints, and vehicle mass and volume limitations. In the case of life-threatening injuries, the International Space Station (ISS) medical kit currently allows for basic trauma and surgical procedures as well as Advanced Cardiac Life Support,[6,7] and astronauts are trained in resuscitation scenarios by the "treat first what kills first" principle: securing an adequate airway and managing ventilation before hemorrhage control.[8]

In recent years, however, care standards in prehospital and austere environments have seen a paradigm shift. Based on observations that extremity hemorrhage was a leading cause of preventable death in combat casualties, revision of battlefield trauma care recommendations resulted in the development of Tactical Combat Casualty Care (TCCC) guidelines by US military services.[9] By emphasizing "good medicine with good tactics," TCCC has focused on treating major external bleeding caused by penetrating injury and delaying the onset of hypovolemic shock through the application of direct pressure and aggressive use of tourniquets and hemostatic gauze—even before attempts at managing the airway and breathing.[10-12] The successful implementation of TCCC has made important contributions to the highest casualty survival rates in the history of modern warfare and reduced fatal casualties attributed to extremity hemorrhage.[13-16]

Lessons learned from the military have been translated into the civilian sector through initiatives such as the Hartford Consensus,[17,18] the White House Stop the Bleed campaign, and the development of TCCC-based courses by the National Association of Emergency Medical Technicians.[10] Evidence-based guidelines from the American College of Surgeons Committee on Trauma and the American Heart Association now encourage the use of tourniquets and hemostatic agents in controlling massive hemorrhage in prehospital trauma care.[19,20] The wilderness medicine community is adopting TCCC concepts as well, as early intervention becomes more critical with prolonged evacuation times and constrained resources.[21-24]

Space travel represents the ultimate remote medicine setting, with a lack of medical resources (equipment and personnel), unprecedented autonomy, and limited evacuation possibilities.[25] The extreme environmental conditions and physiological changes associated with microgravity[26] may increase the risk of mortality and morbidity in the case of massive external hemorrhage. With ongoing plans to set foot on the Moon and Mars and an increasing amount of flight opportunities for "space tourists," a careful re-evaluation of current emergency resuscitation guidelines is necessary. To this end, our aim was to examine massive external hemorrhage control and the applicability of TCCC principles in space.

Methods

A literature review was conducted to identify articles about the management of external bleeding and the use of tourniquets and hemostatic agents in austere environments—in particular, the spaceflight setting. PubMed was searched through June 2022 using Boolean combinations of the following key words and their Medical Subject Heading (MeSH) derivatives: "trauma," "emergency," "bleeding," "hemorrhage," "advanced trauma life support," "prehospital," "tactical combat casualty care," "tourniquets," "hemostatic dressing," "spaceflight," "weightlessness," "parabolic flight," "extreme environments," "wilderness," "arctic," "Antarctic," "submarine," and "oil platform." References obtained were cross-checked, and gray literature was searched for additional relevant publications. One hundred two articles were reviewed, representing techniques, protocols, or challenges in the civilian setting as well as extreme and austere environments, outcomes of TCCC concepts in civilian and military settings, or physiological changes in spaceflight that are relevant to initial resuscitation and external hemorrhage control.

Mechanisms of Injury

For long-duration spaceflight, risk estimates have previously been derived by studying analog populations, such as military pilots, submarine crews, and Antarctic winter-over research teams.[27-29] However, spaceflight poses unique operational and occupational risks that are different from those on Earth. Significant medical events during spaceflight have generally not been related to orthopedic or surgical trauma, which, in contrast, accounts for more than half of the evacuation events from McMurdo Station in Antarctica.[27,28] Morbidity from gravity-based events on Earth and other accidental injuries, such as falls and motor vehicle accidents, are not represented in weightlessness.

Nevertheless, minor trauma already occurs in space. A database of in-flight musculoskeletal injuries and minor trauma in the US space program has documented an incidence of 0.021 and 0.015 per flight day for men and women, respectively, with abrasions and contusions being most prevalent, followed by strains and lacerations.[30] Most of these injuries occurred from impacting structures while stowing or translating equipment, exercise, and extravehicular activity (EVA), with a rate of 0.26 injuries per EVA in microgravity alone.

People and objects still possess mass, which can generate significant force when accelerated. In low Earth

orbit (LEO), risk of major blunt and penetrating injuries that could involve life-threatening external hemorrhage would therefore be primarily related to the dynamic stages of flight—launch, landing, and docking—or EVA.[31] Potential mechanisms include impact from micrometeorites or crush-type injuries from movement of high-mass structures during space station construction, vehicle docking, and payload deliveries. Vehicular collisions and near-miss accidents have occurred in flight multiple times.[2] In addition, upcoming exploration-class missions will include surface operations in partial gravity, with increasing amount of EVA and heavy work in a highly dynamic environment.[32] For instance, astronauts may be involved in habitat construction, heavy equipment transfer, human-machine interactions, and rover vehicle operations. Increased fracture risk from osteoporosis in space may further add to risk of blood loss from blunt or penetrating injury,[33,34] and above all, with the current intensification of activity in the human spaceflight industry, one must take into account that different and unforeseen emergencies could always arise.

Environmental Challenges

In space, trauma management is not as straightforward as in the emergency department. Especially when an astronaut is exposed outside the spacecraft or space habitat, many of the previously mentioned scenarios would be challenged by prolonged time to reach initial trauma care on board. With concurrent spacesuit or spacecraft damage, for instance, protecting the crew from ongoing environmental hazards would be a priority before starting any resuscitation procedures. In case the injured astronaut reaches his crewmates, prolonged times for suit removal and deployment of stowed equipment could cause further delays, and restraining patients and supplies is complicated without gravity.[3,35] Although the performance of most Advanced Trauma Life Support procedures appears to be feasible in microgravity,[7] limited shelf lives during long-duration missions and vehicle constraints of available storage space and electrical power may compromise the availability of adequate equipment, medical supplies, and resuscitation fluids such as blood products.[25] In addition, a crew's medical expertise is generally limited. For current ISS operations, crew members receive approximately 9 h of medical training preflight that includes basic first aid procedures and cardiopulmonary resuscitation. Further hands-on training is provided to 1 or 2 specially designated crew medical officers, who are not required to be physicians, and in total receive approximately 14 to 40 h of medical training that is mostly oriented toward basic skills that enable them to interface more effectively with a flight surgeon on the ground.[6] With real-time communication interruptions and delays of up to 22 min on missions to Mars, ground-based assistance via telemedicine may not be readily available, further compromising the possibilities for adequate damage control.[36]

In case of a medical emergency evacuation from LEO, a spacecraft such as the Soyuz or Crew Dragon could technically undock and land within 3 to 4 h. Yet, even with a preferred, nonballistic landing at one of the primary landing sites, it could take anywhere between 5 and 48 h until the patient reaches a definitive healthcare facility on Earth. This may include up to several hours in the spacecraft in which patient access and the provision of any medical care is severely constrained due to the need for pressure suits and cramped conditions.[28,36] Also, crew members would be exposed to approximately 4 +Gx during the landing profile. A hemorrhagic shock model in primates undergoing centrifugation has shown that exposure to re-entry acceleration forces significantly increases shock parameters compared with a normovolemic control condition, with more adverse events when the hemorrhage is severe (class III or IV, or >30% loss of blood volume).[8,37] Importantly, because uninjured crew members typically display hypovolemic signs of a class I hemorrhage (15% loss of blood volume) due to microgravity-induced fluid shifts and cardiovascular deconditioning in space, a true class I hemorrhage in space may respond much like a class II hemorrhage (15–30% loss of blood volume) upon return to Earth.[38] In case of massive hemorrhage this could seriously compromise a casualty. The alternative of a ballistic re-entry would cause even higher (8 or 9) G stresses, and unpredictable landing sites would further delay appropriate medical monitoring and intervention.[36] Future deep space exploration missions will be even more challenging. Reaching definitive care may take anywhere from multiple days (eg, 4–5 d from the Moon) to multiple months, or, more realistically, may not even be feasible at all.

Cardiovascular Deconditioning and Hematological Changes

Various circulatory physiological changes occur in space that are likely to reduce the ability to withstand the consequences of massive hemorrhage. In the absence of gravity, fluid is redistributed toward the upper body, and the relative hypervolemia at heart level results in compensatory loss of water and electrolytes and a net decrease in plasma volume.[26,39] Astronauts have been found to lose 10 to 23% of circulating blood volume within 24 to 48 h in space to reach a new equilibrium of

central blood volume that is similar to that in the upright position on Earth.[39-41] The low variance in gravitational stimuli resets the autonomic nervous system, resulting in overall blunting of the cardiac chronotropic and baroreflex responses to hypotension.[42-44] Reductions in systemic vascular resistance do not require large contractility of the heart,[45] and cardiac atrophy of 12% has been observed after 10 d of spaceflight.[46] These adaptations may be appropriate for regular microgravity conditions but will significantly increase the impact of any blood loss and reduce the ability to compensate for hypovolemic stress (Figure 1).[47,48]

A decrease in erythrocyte volume of 10% has been found after 1 wk in space, specifically reducing oxygen-carrying capacity in blood circulation.[49] Similar results have been obtained for long-duration missions, with 11% decreases of red blood cell mass after 28, 59, and 84 d compared to preflight,[50,51] and nearly half the astronauts showed anemic hemoglobin concentrations after missions longer than 21 d.[52] The severity of this "spaceflight anemia" is likely to increase on longer exploration-class missions,[52] during which this effect may be further amplified by exposure to space radiation.[53]

Platelet number and activity have also been shown to be decreased in microgravity conditions.[34] Findings of reduced platelet aggregation and adhesion as well as other altered coagulation systems suggest that hemostasis may be more difficult to achieve in space,[54] despite recent findings of a potentially increased risk for thrombus formation.[55] Systemic vasodilation from high levels of atmospheric carbon dioxide—typically fluctuating between 2.3 and 5.3 mm Hg in spacecraft—may further increase risk of blood loss,[56,57] and venous bleeding has also been shown to increase in parabolic flights, possibly because of the lack of venous wall compression.[33]

Thus, a massive bleeding—especially as it leads to hypovolemia and coagulopathy in the case of shock—is likely to have a relatively profound impact on the overall outcome of a trauma injury compared with that in the terrestrial setting. The "golden hour"—the period immediately after significant trauma in which intervention has the greatest effect on outcome—may be shorter,[38] and with reduced fluid resuscitation possibilities on board, early hemorrhage control becomes even more critical.[25,58]

External Hemorrhage Control in Space

TOURNIQUETS

An important factor in the life-saving potential of the TCCC guidelines has been the renewed focus on tourniquet use. While a casualty could administer self-aid by applying direct pressure at the site of bleeding as an effective initial technique, it would preclude a care-providing crew member with limited time and resources from performing other procedures.[11,18] With the immediate and correct application of a tourniquet, the crew would have time for conversion to other methods of hemostasis such as hemostatic or pressure dressings.

Well-designed tourniquets can reliably achieve hemorrhage control and have been demonstrated to save lives when applied before the onset of shock,[59,60] also in civilian and wilderness settings.[61-63] Nevertheless, conclusive evidence remains weak.[24,64] In terms of safety, tourniquets have remained a controversial topic because of their complications, which are primarily related to ischemia and compression.[65,66] Reviews of recent combat and civilian experiences have shown minimal morbidity, but the total tourniquet time in these studies was less than 2 h in most of the casualties.[67-69] Beyond the 2-h "safe time" limit, slow release of a tourniquet is ideally done in a medical treatment facility with advanced resuscitative capability because prolonged tourniquet time can be associated with life-threatening systemic hyperkalemia and reperfusion injury.[11,70,71] If a tourniquet has been in place for more than 6 h, it should not be removed unless close monitoring and laboratory capability are available.[11]

No evidence exists of the effectiveness and safety of tourniquet use in space, and risk of complications remains unclear. Although every effort should be made to reassess and convert tourniquets in less than 2 h, prolonged time and impaired medical access in spacecraft during medical evacuation could lead to serious complications. In one military study on 297 limbs, 100% morbidity (amputation or fasciotomy) was recorded after a tourniquet duration of 3 h or more (n=8), even though the contribution of tourniquet time could not be differentiated from other factors such as injury severity or treatment indication.[67] In another study of 14 limb injuries with a tourniquet duration of 3 h or more, significant morbidity was related to compartment syndrome, and rhabdomyolysis was present in all cases.[71]

Building upon TCCC, the US military has recently published additional guidelines to prepare personnel for "what to consider next" after all TCCC interventions have been effectively performed, specifically focusing on situations in which evacuation or mission requirements call for prolonged (hours to days) care in austere settings or during long-distance movements.[72] These "prolonged casualty care" (PCC) guidelines state that on-site tourniquet conversion beyond the 2-h mark (but before 6 h) should still be considered by a trained combat medic if

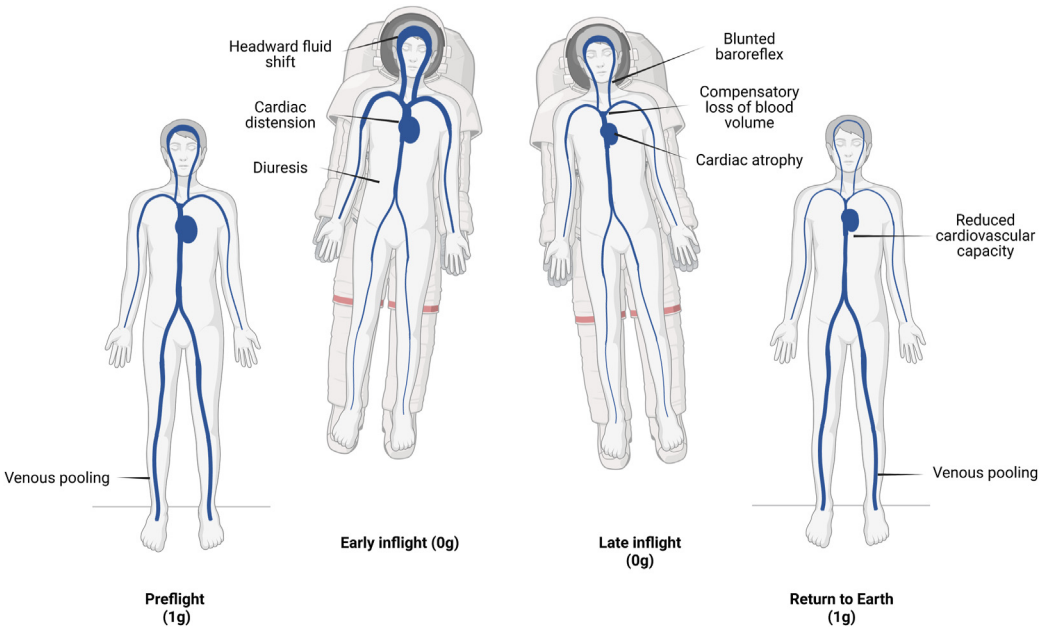

Figure 1. Cardiovascular deconditioning in space. Upon entering the microgravity environment, fluid shifts toward the upper body. After several days in flight, central blood volume is restored to preflight levels through reductions in plasma and red blood cells, and the cardiovascular system adapts to the lower systemic vascular resistance and absence of gravitational stimuli. Upon return to Earth, the normal redistribution of blood volume results in low central blood volume, reduced hematocrit, and an overall reduced cardiovascular capacity to deal with normogravity conditions. Adapted from Charles et al[47] and Gunga et al.[48] Created with BioRender.com.

needed. Eventually however, the risks from prolonged tourniquet application may need to be deemed an acceptable tradeoff in a spaceflight emergency scenario, in which the consequences of a major bleeding may well necessitate a judgment call favoring "life over limb."

Another important factor that has been shown to influence outcomes is correct tourniquet application.[73-75] It is important that any tourniquet selected for use in the space environment can be used in the right place, at the right time, and with adequate training. Ten different commercial limb tourniquets have met the criteria for approval by the Committee on TCCC (CoTCCC) (Figure 2).[76] They should be placed 2 to 3 inches above the wound and tightened until the distal pulse is absent to prevent compartment syndrome. Depending on the width of the tourniquet used, more than one tourniquet may be needed in bigger limbs.[21] Recently, 2 Combat Application Tourniquets (Gen 7) have been added to the ISS medical kit, and a brief familiarization training on their application has been implemented in the 2-y preflight training period for all crew members. In case a tourniquet is used in-flight, the crew is currently required to contact the ground for further support.

Different from bleedings at the extremities, those that are located at junctional regions where the extremities join the torso, such as the groin or the axilla, may be too proximal for limb tourniquet application.[21] Several junctional tourniquets have been developed, and TCCC guidelines suggest the use of such devices if the bleeding site is amenable.[11] However, there is still limited evidence available on their effectiveness and safety,[19,77,78] and none is specifically recommended by the CoTCCC.[76] Moreover, they add bulk and weight that limit their use in space.

HEMOSTATIC AGENTS

When external hemorrhage occurs at sites that are not amenable to tourniquet use, hemostatic dressings are currently recommended in combination with direct pressure.[11,19] The current TCCC hemostatic dressing of choice is Combat Gauze (QuickClot). Celox Gauze, ChitoGauze, or XStat can be used as alternatives (Figure 3).[76] Apart from the preference for gauze-type dressings because these are more easily packed into the depths of narrow-tract wounds and do not present ocular hazards in windy environments,[23] powders or granular agents cannot be poured into the wound in microgravity.

While many gaps still remain in high-level evidence on the effectiveness of hemostatic gauzes,[19,79] a retrospective review of 3792 military cases showed that the

Figure 2. Limb tourniquets recommended by the Committee on Tactical Combat Casualty Care (CoTCCC).[76] *RMT Civilian models are not recommended by the CoTCCC for military use; **Pneumatic tourniquets are considered primarily for tourniquet replacement, conversion, or prolonged application.

use of Combat Gauze, Celox, or ChitoGauze (n=317) improved survival by an average of 7%.[80] Combat Gauze—which was recently added to the medical pack on the ISS—has been shown to achieve hemostasis in 79 to 89% of penetrating injuries in military studies[81-83] and 73 to 95% in civilian trauma.[59,84,85] However, the function of Combat Gauze depends primarily on blood-clotting activity.[86] Even though successful hemostasis has been reported in coagulopathic models of hypothermia and hemodilution,[87,88] this dressing may be less effective in space.[54,55] Celox and ChitoGauze are chitosan-based hemostatic dressings that form a mucoadhesive barrier and work independently of the coagulation system.[86] Both have been found to be safe and more effective than Combat Gauze in preclinical studies, with a 10% failure rate to stop or minimize bleeding using ChitoGauze in a civilian setting.[22,89] To determine the effectiveness of different hemostatic dressings in space, comparative studies in microgravity conditions are required. If results are similar, the lightest, safest, and most compact choice would be favored.[90]

For deep limb or junctional wounds, XStat is preferred. It involves a syringe-like applicator that injects rapidly expanding cellulose-based sponges coated with chitosan, and the first clinical evidence from a civilian setting has shown that in 9 out of 10 penetrating trauma injuries, bleeding completely stopped on initial deployment.[91] Finally, for external hemorrhage of the head and neck, the iTClamp has been recommended as an additive or alternative. This self-locking mechanical clip applies pressure and promotes the generation of a hematoma that can tamponade bleeding and may be useful if wound edges are easily reapproximated.[11] Both XStat and iTClamp may be particularly useful in space as they are small and require minimal training to us, but for both devices, efficacy and safety in prehospital and austere environments—including space—remain to be determined.[64]

TRANEXAMIC ACID

Another advancement that has led to increased survival rates on the battlefield is the early administration of tranexamic acid (TXA) for casualties in or at high risk of hemorrhagic shock.[11,92] TXA is a lysine derivative that slows down the conversion of plasminogen to plasmin, thereby preventing clot breakdown without inducing clot formation. The US military has included TXA in TCCC and clinical practical guidelines since publication of the CRASH-2 and MATTERs studies about a decade ago, which demonstrated reduced mortality in more than 20,000 civilian and 896 patients with military trauma when TXA was given within 3 h of injury.[93,94] In the latter study, TXA was also associated with less coagulopathy.[94] For the greatest survival benefit, TXA should be given as soon as possible after injury[95] but not later than 3 h, as this has actually shown to increase mortality.[11,93]

Figure 3. Hemostatic agents recommended by the Committee on Tactical Combat Casualty Care.[76] Xstat is best suited for deep, narrow-tract junctional wounds. iTClamp may be used alone or in conjunction with hemostatic dressing or XStat.

So far, no data exist on the use of TXA in space, and despite promising initial results recent evidence suggests that TXA may increase the risk of venous thromboembolism by approximately 3-fold.[96,97] As a result, potential overuse in lower-risk trauma patients remains a concern. These observations are particularly relevant for spaceflight, when altered coagulability, higher levels of fibrinogen, endothelial dysfunction, and stagnant blood flow in the upper body already seem to increase the risk of thrombosis in otherwise healthy astronauts.[55] Further investigation into the safety and mechanisms of action of TXA will be necessary to better understand its usability for future space missions, including its application when resuscitation fluids are not available. Storage requirements, the potential impact of radiation on shelf-life stability, and a lack of resources for resupply will also have to be considered.[92,98]

Advanced Techniques and Future Perspectives

Besides the current TCCC and PCC concepts for extremity and junctional hemorrhage control, more advanced techniques may provide additional solutions for the major resuscitation challenges in space exploration, in particular for injuries of the chest and abdomen that are not amenable to compression. Examples of recent developments include the Abdominal Aortic Junctional Tourniquet (AAJT) for external pressure to the abdomen, injection of self-expanding foam (ResQFoam) or hemostatic hydrogel, resuscitative endovascular balloon occlusion of the aorta (REBOA), wound-closure through nanobridging, and portable blood salvage and autotransfusion technology to recycle spilled blood.[99-101] Although these techniques require further improvement, their life-saving potential and relative ease of administration in austere environments deserve careful consideration.

With regard to fluid resuscitation, early administration of whole blood has recently been recommended for implementation in TCCC guidelines, and the use of freeze-dried plasma is currently under investigation in special operations forces as well.[101,102] These products are particularly suited for use in austere environments, and their role in space exploration has recently been discussed in detail by Nowak and colleagues.[25]

Finally, Moon and Mars missions may require even more specialized care and definitive surgical repair when medical evacuation is not possible.[90] To this end, battlefield trauma care in the US military and other North Atlantic Treaty Organization countries has involved forward positioned (Role 2) surgical teams that can provide early damage control resuscitation and surgery as close as possible to the point of injury and without the need for transportation to a more advanced care facility.[103,104] In space, such a staged or minimalist surgical approach may

allow for temporizing measures if more advanced procedures are beyond the capabilities of the crew medical officer, so that definitive surgical reconstruction can be undertaken with better logistic planning, minimal time pressure, and additional specialty training and consultation from Earth.[90] Although a detailed discussion of advanced resuscitation and surgery procedures is beyond the scope of this review, it is worth mentioning that renewed attention to the optimal utilization and composition of such forward teams by the Committee on Surgical Combat Casualty Care (CoSCCC) could provide valuable lessons for future space missions as well.[105]

TRAINING AND MEDICAL SUPPORT

The capability of any spaceflight medical care system to handle trauma scenarios will ultimately be limited by the capability and training of the crew. Correct tourniquet application, the use of hemostatic agents, pressure dressings, and other basic hemorrhage control techniques—including practice under simulated emergency stress—are essential medical training components for maximizing trauma resuscitation outcomes.[73,74] The current training curriculum for providing emergency care in LEO, however, does not cover training in hemorrhage control techniques other than preflight tourniquet familiarization and is designed primarily to prepare a crew medical officer to interact with ground support in a meaningful fashion.[6] On a Mars mission, loss of real-time support means that this training paradigm will be inadequate.[4]

Guided by exploration-class mission parameters, additional hands-on training in trauma resuscitation—including early hemorrhage control—will be needed. Similar to TCCC training principles in the military,[10,102] this would likely also require all crew members to be involved so that each is independently capable of providing life-saving emergency care.[6] More complex procedures, however, will require more specialized training, and having a broadly trained paramedic or physician on board may greatly enhance mission safety.[106] In a study comparing air medical evacuation outcomes in 671 combat casualties, a higher level of flight medic training was shown to be associated with better survivability and physiological outcomes.[107]

Current operations in LEO require all training to be conducted during a 2-y preflight period,[6] and time and opportunities for medical training are usually limited. In combination with prolonged mission durations and constantly evolving scenarios, this means that exploration crews may have to rely on onboard refresher and just-in-time training programs to maintain and expand their skillset.[108] To this end, trauma and surgical manikins have previously been studied in microgravity conditions,[38,106] and the European Space Agency (ESA) and National Aeronautics and Space Administration (NASA) are currently investigating onboard training systems based on virtual reality. Such platforms may soon allow for virtual trauma simulations to practice resuscitation principles[109] and could potentially also be used for just-in-time rehearsals of more complex, staged procedures.

Still, it will be unlikely that a crew medical officer will possess the skills to cover all medical conditions and emergency scenarios that may occur. The Autonomous Medical Operations group at NASA and the Space Medicine Team at ESA are putting significant work into the development of an onboard support system, including software and hardware that can assist in medical operations when greater independence from Earth is required.[110] By using systems engineering practices, such a system can integrate complex data and functions from various spacecraft systems into autonomous operations to support crew health and performance.[111] For trauma care, this could include diagnostics and monitoring using machine learning models based on physiological data from advanced monitoring technology. For instance, continuous arterial waveform analysis has shown promising results for early hemorrhage detection.[112] Other examples include medical database management to support clinical decision making and the incorporation of augmented reality for step-by-step procedural guidance.[110]

Conclusion

The spaceflight environment poses unique challenges to prehospital trauma care. The limited resources and training, physiological changes due to microgravity exposure, and complicated nature of an emergency evacuation are all changing parameters as missions move farther from Earth. The potential benefits of medical care capabilities focused on the point of injury—versus a return to definitive care—should be carefully weighed for different mission types. Effective early hemorrhage control will be a crucial component of such an approach to preserve cardiovascular reserve, even more so in upcoming exploration-class missions during which an emergency return to Earth is simply not possible. The implementation of basic techniques such as hemostatic dressings and tourniquets will require additional training but could play an important role in delaying the onset of hypovolemic shock. Future research focusing on their efficacy in space is desired. Other techniques—including early TXA administration and devices for junctional or noncompressible wounds—show promise too but will need further characterization first. Looking forward, the

ongoing advancement and approaches emerging from the battlefield suggest that tactical and surgical combat casualty care will continue to provide valuable lessons in the years to come and can help to further improve hemorrhage control and trauma care for future space exploration.

Acknowledgments: This work is the result of a library project by ST as part of the Space Physiology and Health MSc at King's College, London, UK. We would further like to acknowledge Christopher Schubert, medical training lead at the NASA Johnson Space Center, for his insightful comments and input on the manuscript.

Author Contributions: study concept and design (ST, MK); acquisition of data (ST); drafting of manuscript (ST); critical revision of the manuscript (MK); approval of final manuscript (ST, MK).

Financial/Material Support: None.

Disclosures: None.

References

1. Summers RL, Johnston SL, Marshburn TH, Williams DR. Emergencies in space. *Ann Emerg Med*. 2005;46(2):177–84.
2. Bloomberg JJ, Reschke MF, Clément GR, Mulavara AP, Taylor LC. *NASA Evidence Report: Risk of Impaired Control of Spacecraft/Associated Systems and Decreased Mobility Due to Vestibular/Sensorimotor Alterations Associated with Space flight*. Houston, TX: National Aeronautics and Space Administration, Lyndon B. Johnson Space Center; 2016. Available at: https://humanresearchroadmap.nasa.gov/Evidence/reports/SM.pdf. Accessed October 25, 2022.
3. Kirkpatrick AW, Ball CG, Campbell M, Williams DR, Parazynski SE, Mattox KL, et al. Severe traumatic injury during long duration spaceflight: light years beyond ATLS. *J Trauma Manag Outcomes*. 2009;3:4.
4. Antonsen EL, Myers JG, Boley L, Arellano J, Kerstman E, Kadwa B, et al. Estimating medical risk in human spaceflight. *NPJ Microgravity*. 2022;8(1):8.
5. Antonsen EL, Van Baalen M, Kadwa B, Boley L, Arellano J, Kerstman E, et al. *NASA TM-20210009779: Comparison of Health and Performance Risk for Accelerated Mars Mission Scenarios*. Houston, TX: National Aeronautics and Space Administration, Lyndon B. Johnson Space Center; 2021. Available at: https://ntrs.nasa.gov/api/citations/20210009779/downloads/NASA-TM-20210009779.pdf. Accessed October 25, 2022.
6. Blue RS, Bridge LM, Chough NG, Cushman J, Khpal M, Watkins S. *NASA/TM–2014-217384: Identification of Medical Training Methods for Exploration Missions*. Houston, TX: National Aeronautics and Space Administration, Lyndon B. Johnson Space Center; 2014. Available at: https://ntrs.nasa.gov/api/citations/20130013532/downloads/20130013532_Final.pdf. Accessed November 10, 2022.
7. Campbell MR, Billica RD, Johnston 3rd SL, Muller MS. Performance of advanced trauma life support procedures in microgravity. *Aviat Space Environ Med*. 2002;73(9):907–12.
8. American College of Surgeons' Committee on Trauma. *ATLS: Advanced Trauma Life Support*. 10th ed. Chicago, IL: American College of Surgeons; 2018.
9. Butler Jr FK, Hagmann J, Butler EG. Tactical combat casualty care in special operations. *Mil Med*. 1996;161(suppl):3–16.
10. Butler FK. Two decades of saving lives on the battlefield: tactical combat casualty care turns 20. *Mil Med*. 2017;182(3):e1563–8.
11. Montgomery HR, Drew B, Torrisi J, Adams MG, Remley MA, Rich TA, et al. TCCC guidelines comprehensive review and edits 2020: TCCC guidelines change 20-05 01 November 2020. *J Spec Oper Med*. 2021;21(2):122–7.
12. Butler Jr FK. Introduction to tactical combat casualty care (Ch. 23). In: *National Association of Emergency Medical Technicians*. PHTLS: Prehospital Trauma Life Support: Military Edition. 9th ed. Burlington, MA: Jones & Bartlett Learning; 2021.
13. Eastridge BJ, Mabry RL, Seguin P, Cantrell J, Tops T, Uribe P, et al. Death on the battlefield (2001-2011): implications for the future of combat casualty care. *J Trauma Acute Care Surg*. 2012;73(6)(suppl 5):S431-7.
14. Kotwal RS, Montgomery HR, Kotwal BM, Champion HR, Butler Jr FK, Mabry RL, et al. Eliminating preventable death on the battlefield. *Arch Surg*. 2011;146(12):1350–8.
15. Butler Jr FK, Blackbourne LH. Battlefield trauma care then and now: a decade of tactical combat casualty care. *J Trauma Acute Care Surg*. 2012;73(6)(suppl 5):S395-402.
16. Savage E, Forestier C, Withers N, Tien H, Pannell D. Tactical combat casualty care in the Canadian Forces: lessons learned from the Afghan war. *Can J Surg*. 2011;54(6):S118–23.
17. Callaway DW. Translating tactical combat casualty care lessons learned to the high-threat civilian setting: tactical emergency casualty care and the Hartford consensus. *Wilderness Environ Med*. 2017;28(2S):S140–5.
18. Jacobs LM, Wade D, McSwain NE, Butler FK, Fabbri W, Eastman A, et al. Hartford Consensus: a call to action for THREAT, a medical disaster preparedness concept. *J Am Coll Surg*. 2014;218(3):467–75.
19. Bulger EM, Snyder D, Schoelles K, Gotschall C, Dawson D, Lang E, et al. An evidence-based prehospital guideline for external hemorrhage control: American College of Surgeons Committee on Trauma. *Prehosp Emerg Care*. 2014;18(2):163–73.
20. Charlton NP, Pellegrino JL, Kule A, Slater TM, Epstein JL, Flores GE, et al. 2019 American Heart Association and American Red Cross focused update for first aid: presyncope: an update to the American Heart Association and American Red Cross guidelines for first aid. *Circulation*. 2019;140(24):e931–8.
21. Drew B, Bennett BL, Littlejohn L. Application of current hemorrhage control techniques for backcountry care: part one, tourniquets and hemorrhage control adjuncts. *Wilderness Environ Med*. 2015;26(2):236–45.
22. Littlejohn L, Bennett BL, Drew B. Application of current hemorrhage control techniques for backcountry care: part two, hemostatic dressings and other adjuncts. *Wilderness Environ Med*. 2015;26(2):246–54.
23. Butler FK, Bennett B, Wedmore CI. Tactical combat casualty care and wilderness medicine: advancing trauma care in austere environments. *Emerg Med Clin North Am*. 2017;35(2):391–407.
24. Kragh Jr JF, Dubick MA. Bleeding control with limb tourniquet use in the wilderness setting: review of science. *Wilderness Environ Med*. 2017;28(2S):S25–32.
25. Nowak ES, Reyes DP, Bryant BJ, Cap AP, Kerstman EL, Antonsen EL. Blood transfusion for deep space exploration. *Transfusion*. 2019;59(10):3077–83.
26. Hamilton DR. Cardiovascular disorders (Ch. 16). In: Barratt MR, Pool SL, eds. *Principles of Clinical Medicine for Space Flight*. New York, NY: Springer; 2008:317–59.

27. Billica RD, Simmons SC, Mathes KL, McKinley BA, Chuang CC, Wear ML, et al. Perception of the medical risk of spaceflight. *Aviat Space Environ Med*. 1996;67(5):467–73.
28. Johnston SL, Arenare BA, Smart KT. Medical evacuation and vehicles for transport (Ch. 7). In: Barratt MR, Pool SL, eds. *Principles of Clinical Medicine for Space Flight*. New York, NY: Springer; 2008:139–61.
29. Stewart LH, Trunkey D, Rebagliati GS. Emergency medicine in space. *J Emerg Med*. 2007;32(1):45–54.
30. Scheuring RA, Mathers CH, Jones JA, Wear ML. Musculoskeletal injuries and minor trauma in space: incidence and injury mechanisms in U.S. astronauts. *Aviat Space Environ Med*. 2009;80 (2):117–24.
31. Caldwell E, Gernhardt M, Somers JT, Younker D, Newby N. *NASA Evidence Report: Risk of Injury Due to Dynamic Loads. Houston, TX*. National Aeronautics and Space Administration, Lyndon B. Johnson Space Center; 2012. Available at: https://humanresearchroadmap.nasa.gov/Evidence/reports/Occupant%20Protection.pdf. Accessed October 25, 2022.
32. Chappell SP, Norcross JR, Abercromby AFJ, Bekdash OS, Benson EA, Jarvis SL. *NASA Evidence Report: Risk of Injury and Compromised Performance Due to EVA Operations*. Houston, TX: National Aeronautics and Space Administration, Lyndon B. Johnson Space Center; 2017. Available at: https://humanresearchroadmap.nasa.gov/Evidence/reports/EVA.pdf. Accessed October 25, 2022.
33. Campbell MR. A review of surgical care in space. *J Am Coll Surg*. 2002;194(6):802–12.
34. Locatelli L, Colciago A, Castiglioni S, Maier JA. Platelets in wound healing: what happens in space? *Front Bioeng Biotechnol*. 2021;9, 716184.
35. Garbino A, Nusbaum DM, Buckland DM, Menon AS, Clark JB, Antonsen EL. Emergency medical considerations in a space-suited patient. *Aerosp Med Hum Perform*. 2016;87(11):958–62.
36. Bacal K, Beck G, McSwain Jr NE. A concept of operations for contingency medical care on the International Space Station. *Mil Med*. 2004;169(8):631–41.
37. Stepaniak PC, Hamilton GC, Olson JE, Gilmore SM, Stizza DM, Beck B. Physiologic effects of simulated + Gx orbital reentry in primate models of hemorrhagic shock. *Aviat Space Environ Med*. 2007;78(4)(suppl):A14.
38. Campbell MR, Billica RD. Surgical capabilities (Ch. 6). In: Barratt MR, Pool SL, eds. *Principles of Clinical Medicine for Space Flight*. New York, NY: Springer; 2008:123–37.
39. Leach CS, Alfrey CP, Suki WN, Leonard JI, Rambaut PC, Inners LD, et al. Regulation of body fluid compartments during short-term spaceflight. *J Appl Physiol (1985)*. 1996;81(1): 105–16.
40. Udden MM, Driscoll TB, Pickett MH, Leach-Huntoon CS, Alfrey CP. Decreased production of red blood cells in human subjects exposed to microgravity. *J Lab Clin Med*. 1995;125 (4):442–9.
41. Convertino VA. Clinical aspects of the control of plasma volume at microgravity and during return to one gravity. *Med Sci Sports Exerc*. 1996;28(10)(suppl):S45-52.
42. Robertson D, Convertino VA, Vernikos J. The sympathetic nervous system and the physiologic consequences of spaceflight: a hypothesis. *Am J Med Sci*. 1994;308(2):126–32.
43. Fritsch-Yelle JM, Charles JB, Jones MM, Wood ML. Microgravity decreases heart rate and arterial pressure in humans. *J Appl Physiol (1985)*. 1996;80(3):910–4.
44. Herault S, Fomina G, Alferova I, Kotovskaya A, Poliakov V, Arbeille P. Cardiac, arterial and venous adaptation to weightlessness during 6-month MIR spaceflights with and without thigh cuffs (bracelets). *Eur J Appl Physiol*. 2000;81(5):384–90.
45. Norsk P, Asmar A, Damgaard M, Christensen NJ. Fluid shifts, vasodilatation and ambulatory blood pressure reduction during long duration spaceflight. *J Physiol*. 2015;593(3):573–84.
46. Perhonen MA, Franco F, Lane LD, Buckey JC, Blomqvist CG, Zerwekh JE, et al. Cardiac atrophy after bed rest and spaceflight. *J Appl Physiol (1985)*. 2001;91(2):645–53.
47. Charles JB, Bungo MW, Fortner GW. Cardiopulmonary function (Ch. 14). In: Nicogossian AE, Leach-Huntoon C, Pool SL, eds. *Space Physiology and Medicine*. 3rd ed. Philadelphia, PA: Lea & Febiger; 1994.
48. Gunga HC, Weller von Ahlefeld V, Appell Coriolano HJ, Werner A, Hoffmann U. The cardiovascular system in space. In: *Cardiovascular System, Red Blood Cells, and Oxygen Transport in Microgravity*. Cham: Springer International Publishing; 2016: 11–34.
49. Alfrey CP, Udden MM, Leach-Huntoon C, Driscoll T, Pickett MH. Control of red blood cell mass in spaceflight. *J Appl Physiol (1985)*. 1996;81(1):98–104.
50. Johnson PC, Driscoll TB, Leblanc AD. Blood volume changes. In: Johnson R, Dietlein LF, eds. *Biomedical Results of Skylab*. Washington, DC: Scientific and Technical Information Office, NASA; 1977:235–41.
51. Alfrey CP, Rice L, Udden MM, Driscoll TB. Neocytolysis: physiological down-regulator of red-cell mass. *Lancet*. 1997;349(9062):1389–90.
52. Trudel G, Shafer J, Laneuville O, Ramsay T. Characterizing the effect of exposure to microgravity on anemia: more space is worse. *Am J Hematol*. 2020;95(3):267–73.
53. Paul AM, Overbey EG, da Silveira WA, Szewczyk N, Nishiyama NC, Pecaut MJ, et al. Immunological and hematological outcomes following protracted low dose/low dose rate ionizing radiation and simulated microgravity. *Sci Rep*. 2021;11(1):11452.
54. Dai K, Wang Y, Yan R, Shi Q, Wang Z, Yuan Y, et al. Effects of microgravity and hypergravity on platelet functions. *Thromb Haemost*. 2009;101(5):902–10.
55. Kim DS, Vaquer S, Mazzolai L, Roberts LN, Pavela J, Watanabe M, et al. The effect of microgravity on the human venous system and blood coagulation: a systematic review. *Exp Physiol*. 2021;106(5):1149–58.
56. Kim KJ, Bekdash OS, Norcross JR, Conkin J, Garbino A, Fricker J, et al. The partial pressure of inspired carbon dioxide exposure levels in the extravehicular mobility unit. *Aerosp Med Hum Perform*. 2020;91(12):923–31.
57. Law J, Van Baalen M, Foy M, Mason SS, Mendez C, Wear ML, et al. Relationship between carbon dioxide levels and reported headaches on the international space station. *J Occup Environ Med*. 2014;56(5):477–83.
58. Kirkpatrick AW, Dulchavsky SA, Boulanger BR, Campbell MR, Hamilton DR, Dawson DL, et al. Extraterrestrial resuscitation of hemorrhagic shock: fluids. *J Trauma*. 2001;50(1):162–8.
59. Kragh Jr JF, Walters TJ, Baer DG, Fox CJ, Wade CE, Salinas J, et al. Survival with emergency tourniquet use to stop bleeding in major limb trauma. *Ann Surg*. 2009;249(1):1–7.
60. Kragh Jr JF, Littrel ML, Jones JA, Walters TJ, Baer DG, Wade CE, et al. Battle casualty survival with emergency tourniquet use to stop limb bleeding. *J Emerg Med*. 2011;41(6):590–7.
61. Zietlow JM, Zietlow SP, Morris DS, Berns KS, Jenkins DH. Prehospital use of hemostatic bandages and tourniquets: translation from military experience to implementation in civilian trauma care. *J Spec Oper Med*. 2015;15(2):48–53.

62. Pons PT, Jerome J, McMullen J, Manson J, Robinson J, Chapleau W. The Hartford consensus on active shooters: implementing the continuum of prehospital trauma response. *J Emerg Med*. 2015;49(6):878–85.
63. Eilertsen KA, Winberg M, Jeppesen E, Hval G, Wisborg T. Prehospital tourniquets in civilians: a systematic review. *Prehosp Disaster Med*. 2021;36(1):86–94.
64. Strauss R, Menchetti I, Perrier L, Blondal E, Peng H, Sullivan-Kwantes W, et al. Evaluating the tactical combat casualty care principles in civilian and military settings: systematic review, knowledge gap analysis and recommendations for future research. *Trauma Surg Acute Care Open*. 2021;6(1):e000773.
65. Dayan L, Zinmann C, Stahl S, Norman D. Complications associated with prolonged tourniquet application on the battlefield. *Mil Med*. 2008;173(1):63–6.
66. Fitzgibbons PG, Digiovanni C, Hares S, Akelman E. Safe tourniquet use: a review of the evidence. *J Am Acad Orthop Surg*. 2012;20(5):310–9.
67. Kragh Jr JF, Walters TJ, Baer DG, Fox CJ, Wade CE, Salinas J, et al. Practical use of emergency tourniquets to stop bleeding in major limb trauma. *J Trauma*. 2008;64(2)(suppl):S38-49; discussion S49-50.
68. Kragh Jr JF, O'Neill ML, Walters TJ, Jones JA, Baer DG, Gershman LK, et al. Minor morbidity with emergency tourniquet use to stop bleeding in severe limb trauma: research, history, and reconciling advocates and abolitionists. *Mil Med*. 2011;176(7):817–23.
69. Scerbo MH, Mumm JP, Gates K, Love JD, Wade CE, Holcomb JB, et al. Safety and appropriateness of tourniquets in 105 civilians. *Prehosp Emerg Care*. 2016;20(6):712–22.
70. Drew B, Bird D, Matteucci M, Keenan S. Tourniquet conversion: a recommended approach in the prolonged field care setting. *J Spec Oper Med*. 2015;15(3):81–5.
71. Sabate-Ferris A, Pfister G, Boddaert G, Daban JL, de Rudnicki S, Caubere A, et al. Prolonged tactical tourniquet application for extremity combat injuries during war against terrorism in the Sahelian strip. *Eur J Trauma Emerg Surg*. 2022;48(5):3847–54.
72. Remley M, Loos P, Riesberg J, Montgomery H, Drew B, Keenan S, et al. Joint trauma system prolonged casualty care guidelines (CPG ID:91); 2021. Available at: https://jts.amedd.army.mil/assets/docs/cpgs/Prolonged_Casualty_Care_Guidelines_21_Dec_2021_ID91.pdf. Accessed October 25, 2022.
73. Unlu A, Kaya E, Guvenc I, Kaymak S, Cetinkaya RA, Lapsekili EO, et al. An evaluation of combat application tourniquets on training military personnel: changes in application times and success rates in three successive phases. *J R Army Med Corps*. 2015;161(4):332–5.
74. Schreckengaust R, Littlejohn L, Zarow GJ. Effects of training and simulated combat stress on leg tourniquet application accuracy, time, and effectiveness. *Mil Med*. 2014;179(2):114–20.
75. Beekley AC, Sebesta JA, Blackbourne LH, Herbert GS, Kauvar DS, Baer DG, et al. Prehospital tourniquet use in Operation Iraqi Freedom: effect on hemorrhage control and outcomes. *J Trauma*. 2008;64(2)(suppl):S28-37; discussion S37.
76. Joint Trauma System, Committee on Tactical Combat Casualty Care. CoTCCC Recommended Deviced and Adjuncts. December 15, 2021. Available at: https://books.allogy.com/web/tenant/8/books/f94aad5b-78f3-42be-b3de-8e8d63343866/. Accessed July 20, 2022.
77. Kotwal RS, Butler Jr FK. Junctional hemorrhage control for tactical combat casualty care. *Wilderness Environ Med*. 2017;28(2S):S33–8.
78. Gaspary MJ, Zarow GJ, Barry MJ, Walchak AC, Conley SP, Roszko PJD. Comparison of three junctional tourniquets using a randomized trial design. *Prehosp Emerg Care*. 2019;23(2):187–94.
79. Bennett BL. Bleeding control using hemostatic dressings: lessons learned. *Wilderness Environ Med*. 2017;28(2S):S39–49.
80. Winstanley M, Smith JE, Wright C. Catastrophic haemorrhage in military major trauma patients: a retrospective database analysis of haemostatic agents used on the battlefield. *J R Army Med Corps*. 2019;165(6):405–9.
81. Ran Y, Hadad E, Daher S, Ganor O, Kohn J, Yegorov Y, et al. QuikClot Combat Gauze use for hemorrhage control in military trauma: January 2009 Israel Defense Force experience in the Gaza Strip—a preliminary report of 14 cases. *Prehosp Disaster Med*. 2010;25(6):584–8.
82. Shina A, Lipsky AM, Nadler R, Levi M, Benov A, Ran Y, et al. Prehospital use of hemostatic dressings by the Israel Defense Forces Medical Corps: a case series of 122 patients. *J Trauma Acute Care Surg*. 2015;79(4)(suppl 2):S204-9.
83. Schauer SG, April MD, Naylor JF, Fisher AD, Cunningham CW, Ryan KL, et al. QuikClot Combat Gauze use by ground forces in Afghanistan the Prehospital Trauma Registry experience. *J Spec Oper Med*. 2017;17(2):101–6.
84. Leonard J, Zietlow J, Morris D, Berns K, Eyer S, Martinson K, et al. A multi-institutional study of hemostatic gauze and tourniquets in rural civilian trauma. *J Trauma Acute Care Surg*. 2016;81(3):441–4.
85. Travers S, Lefort H, Ramdani E, Lemoine S, Jost D, Bignand M, et al. Hemostatic dressings in civil prehospital practice: 30 uses of QuikClot Combat Gauze. *Eur J Emerg Med*. 2016;23(5):391–4.
86. Bennett BL, Littlejohn L. Review of new topical hemostatic dressings for combat casualty care. *Mil Med*. 2014;179(5):497–514.
87. Johnson D, Bates S, Nukalo S, Staub A, Hines A, Leishman T, et al. The effects of QuikClot Combat Gauze on hemorrhage control in the presence of hemodilution and hypothermia. *Ann Med Surg (Lond)*. 2014;3(2):21–5.
88. Causey MW, McVay DP, Miller S, Beekley A, Martin M. The efficacy of Combat Gauze in extreme physiologic conditions. *J Surg Res*. 2012;177(2):301–5.
89. Te Grotenhuis R, van Grunsven PM, Heutz WM, Tan EC. Prehospital use of hemostatic dressings in emergency medical services in the Netherlands: a prospective study of 66 cases. *Injury*. 2016;47(5):1007–11.
90. Kirkpatrick AW, Campbell MR, Jones JA, Broderick TJ, Ball CG, McBeth PB, et al. Extraterrestrial hemorrhage control: terrestrial developments in technique, technology, and philosophy with applicability to traumatic hemorrhage control in long-duration spaceflight. *J Am Coll Surg*. 2005;200(1):64–76.
91. Warriner Z, Lam L, Matsushima K, Benjamin E, Strumwasser A, Demetriades D, et al. Initial evaluation of the efficacy and safety of in-hospital expandable hemostatic minisponge use in penetrating trauma. *J Trauma Acute Care Surg*. 2019;86(3):424–30.
92. Drew B, Auten JD, Cap AP, Deaton TG, Donham B, Dorlac WC, et al. The use of tranexamic acid in tactical combat casualty care: TCCC proposed change 20-02. *J Spec Oper Med*. 2020;20(3):36–43.
93. CRASH-2 trial collaborators, Shakur H, Roberts I, Bautista R, Caballero J, Coats T, et al. Effects of tranexamic acid on death, vascular occlusive events, and blood transfusion in trauma patients with significant haemorrhage (CRASH-2): a randomised, placebo-controlled trial. *Lancet*. 2010;376(9734):23–32.

94. Morrison JJ, Dubose JJ, Rasmussen TE, Midwinter MJ. Military application of tranexamic acid in trauma emergency resuscitation (MATTERs) study. *Arch Surg*. 2012;147(2):113–9.
95. Gayet-Ageron A, Prieto-Merino D, Ker K, Shakur H, Ageron FX, Roberts I. Effect of treatment delay on the effectiveness and safety of antifibrinolytics in acute severe haemorrhage: a meta-analysis of individual patient-level data from 40 138 bleeding patients. *Lancet*. 2018;391(10116):125–32.
96. Johnston LR, Rodriguez CJ, Elster EA, Bradley MJ. Evaluation of military use of tranexamic acid and associated thromboembolic events. *JAMA Surg*. 2018;153(2):169–75.
97. Myers SP, Kutcher ME, Rosengart MR, Sperry JL, Peitzman AB, Brown JB, et al. Tranexamic acid administration is associated with an increased risk of posttraumatic venous thromboembolism. *J Trauma Acute Care Surg*. 2019;86(1):20–7.
98. Blue RS, Bayuse TM, Daniels VR, Wotring VE, Suresh R, Mulcahy RA, et al. Supplying a pharmacy for NASA exploration spaceflight: challenges and current understanding. *NPJ Microgravity*. 2019;5:14.
99. Jamal L, Saini A, Quencer K, Altun I, Albadawi H, Khurana A, et al. Emerging approaches to pre-hospital hemorrhage control: a narrative review. *Ann Transl Med*. 2021;9(14):1192.
100. Gourlay T, Simpson C, Robertson CA. Development of a portable blood salvage and autotransfusion technology to enhance survivability of personnel requiring major medical interventions in austere or military environments. *J R Army Med Corps*. 2018;164(2):96–102.
101. Butler Jr FK, Holcomb JB, Shackelford SA, Barbabella S, Bailey JA, Baker JB, et al. Advanced resuscitative care in tactical combat casualty care: TCCC guidelines change 18-01:14 October 2018. *J Spec Oper Med*. 2018;18(4):37–55.
102. Deaton TG, Auten JD, Betzold R, Butler Jr FK, Byrne T, Cap AP, et al. Fluid Resuscitation in tactical combat casualty care; TCCC Guidelines Change 21-01. 4 November 2021. *J Spec Oper Med*. 2021;21(4):126–37.
103. Kotwal RS, Staudt AM, Mazuchowski EL, Gurney JM, Shackelford SA, Butler FK, et al. A US military role 2 forward surgical team database study of combat mortality in Afghanistan. *J Trauma Acute Care Surg*. 2018;85(3):603–12.
104. Luft A, Pasquier P, Soucanye de Landevoisin E, Morel-Stum N, Baillon A, Louis S, et al. The damage control resuscitation and surgical team: the new French paradigm for management of combat casualties. *Mil Med*. 2022;187(3–4):e275–81.
105. Gurney JM, Jensen SD, Gavitt BJ, Edson TD, Brown SR, Cunningham CW, et al. Committee on Surgical Combat Casualty Care position statement on the use of single surgeon teams and invited commentaries. *J Trauma Acute Care Surg*. 2022;93(2S)(suppl 1):S6-11.
106. Kuypers MI. Emergency and wilderness medicine training for physician astronauts on exploration class missions. *Wilderness Environ Med*. 2013;24(4):445–9.
107. Holland SR, Apodaca A, Mabry RL. MEDEVAC: survival and physiological parameters improved with higher level of flight medic training. *Mil Med*. 2013;178(5):529–36.
108. Barshi I, Dempsey DL. *NASA Evidence Report: Risk of Performance Errors Due to Training Deficiencies*. Houston, TX: National Aeronautics and Space Administration, Lyndon B. Johnson Space Center; 2016. Available at: https://humanresearchroadmap.nasa.gov/Evidence/other/TRAIN.pdf. Accessed October 25, 2022.
109. Colonna AL, Robbins R, Stefanucci J, Creem-Regeh S, Patterson B, Engel BT, et al. Trauma bay virtual reality – a game changer for ATLS instruction and assessment. *J Trauma Acute Care Surg*. 2022;93(3):353–9.
110. Colombano S, Lindsey T, Mansouri-Samani M, Lee R, Marker N. Medics: Medical decision support system for long-duration space exploration. Human Research Program Investigators' Workshop (HRP IWS 2020) conference paper. Available at: https://ntrs.nasa.gov/citations/20200000615. Accessed February 24, 2023.
111. Hanson A, Mindock J, Okon S, Hailey M, McGuire K, Bardina J, et al. A model-based systems engineering approach to exploration medical system development. 2019 IEEE Aerospace Conference. Available at: https://ieeexplore.ieee.org/document/8741864. Accessed February 24, 2023.
112. Convertino VA, Cardin S. Advanced medical monitoring for the battlefield: a review on clinical applicability of compensatory reserve measurements for early and accurate hemorrhage detection. *J Trauma Acute Care Surg*. 2022;93(2S)(suppl 1):S147-54.

WILDERNESS & ENVIRONMENTAL MEDICINE 2023; 34(2): 201–10

CONCEPTS

First-Trimester Pregnancy: Considerations for Wilderness and Remote Travel CME

Christanne H. Coffey, MD[1]; Leslie M. Casper, MD[2]; Elaine M. Reno, MD[3]; Sierra J. Casper, W-EMT[4]; Erin Hillis, PA-S2[5]; David A. Klein, MD, MS[6]; Sarah M. Schlein, MD[7]; Linda E. Keyes, MD[3]

[1]Department of Emergency Medicine, University of California, San Diego, San Diego, CA; [2]Mammoth Lakes, CA; [3]Department of Emergency Medicine, University of Colorado, Aurora, CO; [4]Mammoth Hospital, San Diego Fire-Rescue Department, San Diego, CA; [5]Yale School of Medicine, New Haven, CT; [6]Department of Obstetrics, Gynecology, and Reproductive Sciences, University of California, San Diego, San Diego, CA; [7]Larner College of Medicine, University of Vermont, Burlington, VT

Women increasingly participate in outdoor activities in wilderness and remote environments. We performed a literature review to address diagnostic and therapeutic considerations during first-trimester pregnancy for remote multiday travel. Pretrip planning for pregnant patients traveling outside access to advanced medical care should include performing a transvaginal ultrasound to confirm pregnancy location and checking D rhesus status. We discuss the risk of potential travel-related infections and recommended vaccinations prior to departure based on destination. Immediate evacuation to definitive medical care is required for patients with a pregnancy of unknown location and vaginal bleeding. We propose algorithms for determining the need for evacuation and present therapeutic options for nausea and vomiting, urinary tract infections, and candidiasis in the field.

Keywords: pregnant, vaginal bleeding, traveler, nausea and vomiting, women, remote medicine

Introduction

Women participate in extreme activities in remote and wilderness locations. They comprised 41% of trekkers in the Everest region in 2014[1] and, according to a US outdoor industry survey, made up 46% of outdoor activity participants in 2019.[2] Between 2014 and 2017, 41% of rescues by Seattle Mountain Rescue were for women.[3] Pregnant individuals partake in many outdoor activities, including hiking, mountain biking, rock climbing, skiing, snowboarding, sailing, diving, kayaking, surfing, stand-up paddling, and others, but may receive little advice from their healthcare advisers regarding these activities.[4]

It has been reported that 45% of pregnancies in the United States are unintended[5]; consequently, a person may not be aware of a current pregnancy when embarking on a wilderness trip. Wilderness providers and trip leaders need to be prepared to address medical concerns in travelers with a known or newly discovered early pregnancy. This literature review addresses common potential emergencies for pregnant travelers on multiday trips in the wilderness and other remote environments prior to 14 wk of gestation. Although women constitute most individuals who become pregnant and give birth, our aim is to provide helpful information pertaining to all pregnant persons.

Methods

We identified medical considerations in the first trimester of pregnancy and performed a literature review using PubMed and Cochrane Library, along with a targeted search for wilderness and travel-specific references. We identified original research where the evidence was directly applicable or could be extrapolated to practice in remote settings. Abstracts and non-English manuscripts were excluded.

Corresponding author: Christanne H. Coffey, MD, Department of Emergency Medicine, University of California, San Diego Health, San Diego, California; e-mail: chcoffey@health.ucsd.edu.

Submitted for publication March 2022.

Accepted for publication December 2022.

https://doi.org/10.1016/j.wem.2022.12.001

Pretrip Recommendations

Pretravel planning for expeditions, specifically extended travel into remote areas, must consider the needs of individual travelers, including issues around pregnancy. If a sexually active premenopausal traveler is embarking on a multiday wilderness trip, they should consider performing a pregnancy test before departure. A negative test, however, does not eliminate the risk of first-trimester pregnancy during travel. Early during pregnancy, urine human chorionic gonadotropin (hCG) testing may be negative before hormone levels rise adequately. A previous study reported a urine hCG test maximum sensitivity rate of 90% on the first day vs 97% 1 wk after a missed period.[6] For those taking oral contraceptives, travel disruptions, including illness, lost or missing medication in luggage, and changes in time zones, may impair adherence, increasing the risk of unintended pregnancy. Rapid urine hCG tests are essential in medical travel kits. If an individual is unable to provide a urine sample, several drops of blood can serve as a substitute for these tests.[7]

PRETRIP PLANNING IN PREGNANT TRAVELERS

Pretrip travel planning is important for pregnant patients, especially for those engaging in remote and more physically demanding travel. We recommend that travelers with a known pregnancy seek medical care prior to departure for any extended travel or travel to remote locations. Participants should investigate local resources at their destination and have an evacuation plan to reach definitive medical care. We recommend evacuation insurance for all pregnant travelers. The safety of remote travel during pregnancy may vary with individual risk factors such as age, medical history, conception method (in vitro fertilization or intrauterine insemination), and individual risk tolerance.

We recommend a first-trimester transvaginal ultrasound to determine the location of the pregnancy prior to departure for any remote or multiday travel. If an intrauterine pregnancy (IUP) is confirmed, the risk of complications occurring during travel decreases. Individuals with early pregnancy of unknown location with bleeding or pain should not travel and should be referred immediately for definitive medical care. Low risk, asymptomatic pregnant participants may consider delaying travel to remote locations with poor access to medical care until an IUP can be confirmed at approximately 6 wk of estimated gestational age. We recommend that those at high risk of ectopic pregnancy (Table 1) do not travel to remote locales until an IUP is confirmed. Practitioners should advise against travel and address ectopic pregnancies immediately when suspected.

Table 1. Risk factors for ectopic pregnancy

Previous ectopic pregnancy	Assisted reproductive technology pregnancy
Previous fallopian tube surgery	Endometriosis
Previous pelvic or abdominal surgery	Smoking
History of pelvic inflammatory disease	Age > 35 y
History of infertility	Intrauterine device

All patients, especially those at high risk of fetal genetic disorders, such as advanced maternal age or a personal or family history of genetic diseases, may want to arrange the travel timing to accommodate fetal genetic testing, typically performed between 10 and 14 wk.

Blood type and D rhesus (RhD) status should be determined if not already documented. RhD-negative pregnant individuals should be counseled on the increased risk of RhD alloimmunization if they do not receive RhD immune globulin within 72 h of vaginal bleeding during pregnancy. During alloimmunization, anti-RhD antibodies develop, which may cause severe fetal anemia or death in subsequent pregnancies.[8] If RhD-negative pregnant travelers have vaginal bleeding, they should seek care at a facility with RhD immune globulin within 72 h.

NONGENITOURINARY INFECTIONS DURING TRAVEL

Travelers early in pregnancy should be counseled about the risks of mosquito-borne diseases. Zika is a teratogenic infection initially reported in a large epidemic throughout French Polynesia in 2013 and spread extensively during 2015. Zika infection during pregnancy can result in developmental abnormalities in the fetus, including microcephaly and central nervous system lesions.[9] This risk decreases as pregnancy progresses, with the reported highest risk (8%) in the first trimester, which gradually decreases to 4% in the third trimester.[9] Although most pregnant patients infected with Zika will have a mild or asymptomatic clinical course, the developing fetus can still be affected.[10] The risk of contracting Zika depends on multiple factors, including the local prevalence of Zika and the patient's exposure risk. Prevention primarily involves mosquito control measures,[11] which include wearing protective clothing, using mosquito repellants, staying indoors during heavy biting times, and sleeping

under bed netting. The US Centers for Disease Control and Prevention (CDC) recommends Environmental Protection Agency–registered insect repellents (N,N-diethyl-meta-toluamide (DEET), picaridin, insect repellent 3535, oil of lemon eucalyptus, or paramenthanediol) that are safe during pregnancy. Permethrin-treated clothing is also recommended. No adverse effects have been noted with topical permethrin use in pregnant patients.[12] Pregnant individuals or those desiring pregnancy should avoid travel to areas where Zika is prevalent.[13]

Malaria is a parasitic infection transmitted by the *Anopheles* mosquito, infecting millions of people worldwide annually. Pregnant individuals infected with malaria have increased morbidity and mortality and experience high risks of intrauterine demise, miscarriage, low-birth-weight neonates, premature delivery, and neonatal death.[14] Malaria is the leading infectious cause of fetal growth restriction worldwide.[15] Patients should be counseled about the risks of malaria during pregnancy and encouraged to take appropriate protection measures, including deferring travel if possible. If they are unable to defer travel, chemoprophylaxis and mosquito avoidance are recommended. The optimal antimalarial agent for prevention depends on regional transmission, drug resistance patterns, and patients' characteristics. For travel to chloroquine-sensitive areas, the agent of choice during pregnancy is chloroquine, and for travel to areas with chloroquine-resistant malaria, mefloquine is commonly used.[16] Doxycycline carries a risk of skeletal or dental malformation, and primaquine has a risk of severe hemolysis in glucose-6-phosphate dehydrogenase–deficient individuals, so both drugs should be avoided during pregnancy.[17] The mosquito avoidance measures previously mentioned should be taken.

Travelers' diarrhea is common during international travel, with the most common bacterial agents being *Escherichia coli*, *Campylobacter*, *Salmonella*, and *Shigella*. Norovirus and rotavirus dominate the viral landscape, whereas exposure to contaminated water can result in *Giardia intestinalis* and *Cryptosporidium* infections.[18] We recommend prompt oral hydration and use of azithromycin over fluoroquinolones during pregnancy because of an improved safety profile.[19,20] Rifamycin is used as an alternative treatment for noninvasive travelers' diarrhea. There is evidence demonstrating a decrease in systemic exposure of oral contraceptives with rifamycin use, but its safety in pregnancy is unknown,[21] and therefore, it is not recommended. The US Food and Drug Administration recommends avoiding bismuth subsalicylate during pregnancy but considers loperamide safe.

Nausea during pregnancy, combined with gastrointestinal losses due to travelers' diarrhea, places pregnant patients at a high risk of dehydration. Hydration status should be closely monitored. Management of nausea and vomiting is discussed below. Travelers and expedition leaders should ensure that they carry appropriate antimicrobials that are safe during pregnancy in their medical kit (Table 2).

VACCINATIONS DURING PREGNANCY

Many pregnant patients worry about the safety of vaccinations during pregnancy. Individuals who are planning a pregnancy should complete all age-based CDC-recommended vaccinations before becoming pregnant. Vaccinations during pregnancy should be considered when there is a high possibility of exposure to an infection that could harm the traveler or fetus and the vaccine is unlikely to cause adverse effects.[22] Regardless of destination, pregnant people should be encouraged to get an annual influenza vaccine and complete their coronavirus disease 2019 vaccine series and boosters based on current CDC guidance. Live attenuated virus vaccines, such as typhoid (oral) and yellow fever, are traditionally contraindicated during

Table 2. Antimicrobials for pregnant adventurers

Infection	*Medication*	*Dose (mg)*	*Frequency*	*Avoid*
Malaria prophylaxis	Chloroquine	300 base (500 salt)	Weekly	Doxycycline
	Mefloquine[a]	228 base (250 salt)	Weekly	Primaquine
Travelers' diarrhea	Azithromycin	1000	Once	Fluoroquinolones
Urinary tract infection	Amoxicillin	500 or	8 h	Fluoroquinolones
		875	12 h	
	Cephalexin	250 to 500	6 h	Sulfamethoxazole
	Nitrofurantoin[b]	100	12 h	Trimethoprim
Candidiasis	Clotrimazole	100	Daily	Fluconazole
	Miconazole (Vag supp)	200	Daily	

Vag supp, vaginal suppository.
[a]In chloroquine-resistant areas.
[b]In patients with anaphylaxis to penicillin.

pregnancy because of a theoretical risk of crossing the placenta and causing a viral infection in the fetus.[23] Pregnant people can receive a typhoid (injectable) polysaccharide vaccine when needed, but safety and efficacy studies have not been performed in pregnant individuals.[22] There are no large, prospective trials evaluating the risks of yellow fever vaccination in pregnancy; however, retrospective[24] and observational[25] studies support no association between vaccination during pregnancy and adverse outcomes. The World Health Organization recommends yellow fever vaccination when the risks of yellow fever infection outweigh the risks of vaccination, including unavoidable travel to an endemic area.[26] We recommend that patients seek counsel from a travel medicine specialist to discuss the need for other vaccines during pregnancy (Table 3).

Table 3. Travel vaccinations during pregnancy

Vaccine	*Type*	*Recommendation*
COVID-19	Messenger RNA Viral vector	Messenger RNA preferred over viral vector vaccines
Hepatitis A	Killed	If traveling to highly endemic areas
Influenza (injection)	Killed	Recommended annually
Influenza (nasal)	Live attenuated	Contraindicated
Japanese encephalitis	Killed	Consider when traveling to highly endemic areas. Discuss with travel physician
Meningococcal (MenACWY)	Conjugated	Recommended
(MenB)	Recombinant	Postponed until after pregnancy unless outbreak reported
Rabies	Killed	If high risk of rabies exposure Pre-exposure and postexposure prophylaxis safe
Typhoid (injection)	Killed	Avoid unless high risk of exposure
Typhoid (oral)	Live	Contraindicated
Yellow fever	Live attenuated	Consider if benefits outweigh risks

COVID-19, coronavirus disease 2019; MenACWY, Meningococcal serogroups A, C, W, and Y; MenB, Meningococcal serogroup B; RNA, ribonucleic acid.

First-Trimester Bleeding

Early pregnancy bleeding has been reported to affect approximately 27% of pregnancies.[27] There are many causes of vaginal bleeding and pelvic discomfort during the first trimester, including normal gestation, early pregnancy loss, ectopic pregnancy, threatened miscarriage, and molar pregnancy.[28] Evacuation may not be required for all pregnant individuals who develop bleeding in the wilderness, but assessing risk is mandatory (Figure 1). A pretrip ultrasound that confirms an IUP provides reassurance against ectopic pregnancy. Assessment is more challenging for those without a prior confirmatory ultrasound or who are unaware that they are pregnant. Bleeding in these cases may represent an emergency requiring evacuation. Anyone with the potential to be pregnant who develops abdominal pain in the wilderness should have a urine hCG test performed and confirm the last menstrual period (LMP), defined as the first day of bleeding from the most recent period.

The severity of bleeding should be determined. Heavy bleeding is often defined as soaking through 1 to 2 large pad(s) or tampon(s) every hour for 2 h in a row.[28] A full menstrual cup is approximately equivalent to 2 saturated tampons. Menstrual cups often have measurements allowing for quantification of volume. Individuals with significant bleeding should be evacuated to mitigate risk of hemorrhage, which could lead to anemia, hypovolemia, shock, or death.

Early pregnancy ultrasound helps rule out ectopic pregnancy and should be performed in the field when available. Transabdominal ultrasound has lower sensitivity during early pregnancy than transvaginal ultrasound, which is often not available in remote settings. Identification of an intrauterine gestational sac with either a yolk sac or an embryo is required to diagnose an IUP. Fetal heart activity (FHA) confirms viability, but if assessed using transabdominal ultrasound, failure to detect FHA does not necessarily indicate a nonviable pregnancy.

Although mild cramping in the first trimester can be normal, ectopic pregnancy must be excluded for anyone with abdominal pain or pelvic pain and a positive pregnancy test result without confirmed IUP. If ultrasound is not available at the time of early pregnancy diagnosis in the field, any vaginal bleeding or pain should prompt evacuation to a medical facility with these capabilities as soon as possible. Quantitative β-hCG and other laboratory diagnostic tools used in clinical settings are unlikely to be available in most remote environments.

ECTOPIC PREGNANCY

An ectopic pregnancy is at risk of rupture within the abdomen, which can lead to severe occult bleeding that may not be recognized in the field until the patient has

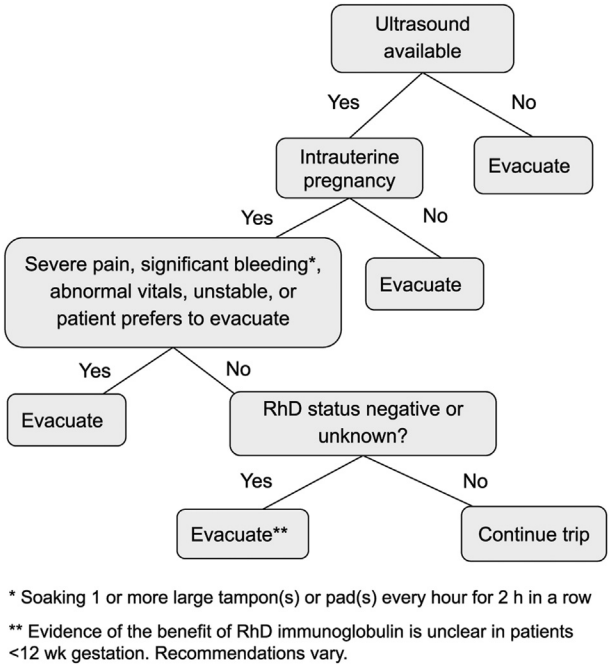

Figure 1. Evaluation of pregnant patients with abdominal pain or vaginal bleeding during the first trimester in a remote setting. RhD, D rhesus.

already experienced substantial, life-threatening blood loss. An ectopic pregnancy occurs when a fertilized egg implants in a structure outside of the uterine cavity. Patients with an ectopic pregnancy may report pelvic or abdominal pain, missed menses, or vaginal bleeding. Syncope, lightheadedness, referred shoulder pain, urinary symptoms, rectal pressure, or other gastrointestinal symptoms may be present. On examination, abdominal, pelvic, adnexal, or cervical motion tenderness may be present. Peritoneal signs, tachycardia, hypotension, pallor, or abdominal distention are also concerning findings.[29,30]

Ultrasound findings that may indicate an ectopic pregnancy include empty uterus, fluid collection within the uterine cavity (pseudosac), or free fluid. The absence of a mass does not rule out ectopic pregnancy.[31] Although heterotopic pregnancy is rare, the adnexa should also be evaluated, even when an IUP is identified. Given the limitation of diagnostics in the wilderness environment, one should err on the side of caution and evacuate any pregnant person with a suspected ectopic pregnancy. Patients with an intrauterine device who discover that they are pregnant should be evacuated immediately regardless of symptoms because there is a high likelihood of an ectopic pregnancy.[32,33]

EARLY PREGNANCY LOSS

Early pregnancy loss (EPL), also referred to as miscarriage or spontaneous abortion, is defined as a nonviable IUP with either an empty gestational sac or a gestational sac containing an embryo or fetus without FHA prior to 13 completed weeks of gestation.[29] Pregnancy loss is most common during the first trimester.[34] Prior EPL and advanced maternal age are risk factors for EPL, and rates of EPL rise with increasing maternal age.[35]

Diagnosing EPL in remote environments may be appropriate if there was a previously confirmed viable IUP on ultrasound, followed by vaginal bleeding, and subsequent ultrasound imaging revealing an empty uterus (complete miscarriage) or an IUP without FHA (missed or incomplete miscarriage) (Figure 2). Transvaginal ultrasound confirmation is the most reliable imaging method but is unlikely to be available in the wilderness setting. The LMP may not accurately represent gestational age because of variation in menstrual cycle length; therefore, LMP alone should not be used to determine whether FHA is expected.[29] Wilderness providers should be cautious to diagnose EPL based on an initial field transabdominal ultrasound without a prior confirmed viable IUP, because they could misdiagnose an ectopic pregnancy or an early viable pregnancy that does not yet meet radiographic criteria. This is particularly relevant when the equipment quality or sonographer's experience are limited. When available, remote telemedicine consultation should be considered to review images. If ultrasound is not available to confirm EPL, the patient should be evacuated.

A patient who has passed products of conception, has an empty uterus on subsequent ultrasound (complete miscarriage), and has minimal to no bleeding does not require medical evacuation and may desire to remain in the wilderness environment. Providers should recognize the need for grief management and the potential desire to be evacuated even if a physical complication is unlikely following a complete miscarriage. A person with a complete miscarriage, with significant bleeding, should be evacuated.

In the clinical environment, missed or incomplete miscarriages can be treated with expectant, medical, or surgical management. It is difficult to predict when and if significant bleeding and pain will occur in these cases. Expectant management has the potential to pose risks to the patient and group in remote environments, and other options are unlikely to be available. We recommend evacuation for all missed or incomplete miscarriages.

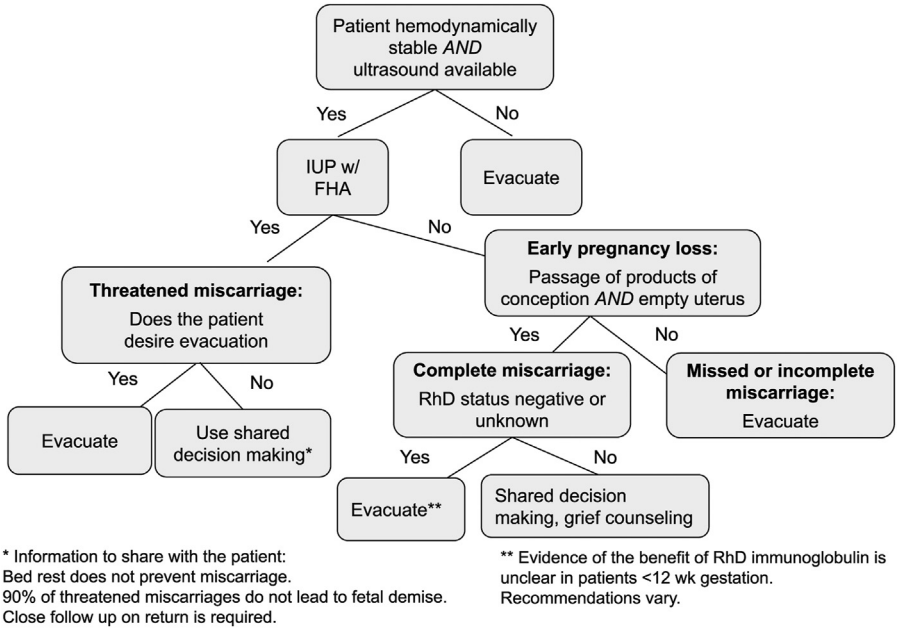

Figure 2. Evaluation of pregnant patients with a previously confirmed intrauterine pregnancy and bleeding during the first trimester in a remote setting. IUP, intrauterine pregnancy; FHA, fetal heart activity; RhD, D rhesus.

THREATENED MISCARRIAGE

A threatened miscarriage is diagnosed in a patient with a confirmed IUP with FHA and vaginal bleeding. It has been reported that over 90% of threatened miscarriages result in viable pregnancies.[36] Light bleeding is not a significant marker of risk of miscarriage, although heavy bleeding is concerning.[28] If bleeding stops, it may be appropriate to continue the current wilderness activity based on the patient's level of comfort and ability to access healthcare facilities if needed. The patient should be evacuated promptly if bleeding worsens. Bed rest does not prevent miscarriages.[37] Proposed strategies for preventing or reducing risk of miscarriage, such as progestogen supplementation, have little supporting data[38] and are not applicable to remote settings.

MEDICATIONS

Ideally, RhD status is known before travel to identify those at risk of alloimmunization. Pregnant patients with vaginal bleeding who are not confident that they are RhD positive should consider evacuation for confirmation of RhD status and potential need for Rho(D) immunoglobulin.[8]

Tranexamic acid is indicated for many severe bleeding scenarios and is often included in expedition medical kits. There are limited case reports on its successful use for hemorrhage in ectopic pregnancies.[39,40] The safety of tranexamic acid regarding birth defects and obstetric complications, including venous thromboembolism, is unclear. Therefore, tranexamic acid should only be used to mitigate severe, life-threatening hemorrhage during early pregnancy when immediate evacuation is not possible or in unstable patients during evacuation. Dosing options include 1 g of tranexamic acid intravenously once (may repeat in 30 min to 1 h if severe bleeding persists) or 1300 mg orally 3 times daily up to 5 d.

Nausea and Vomiting during Pregnancy

When travelers of reproductive age present with nausea and vomiting in a remote environment, pregnancy should be considered. A careful history, including LMP (if known) and use of contraception, should be taken and a pregnancy test performed. Nausea and vomiting may occur in 50% of pregnancies, and typical onset is prior to 9 wk gestational age.[41] Persistent vomiting may represent a condition known as hyperemesis gravidarum, which can present with ≥ 5% body weight loss, abnormalities of electrolytes, liver function tests, and thyroid function tests.[41]

Other causes of nausea and vomiting should still be ruled out (Figure 3). Associated fever, headache, and moderate-to-severe abdominal pain raise concerns for an alternative etiology.[41] Abdominal pain could suggest

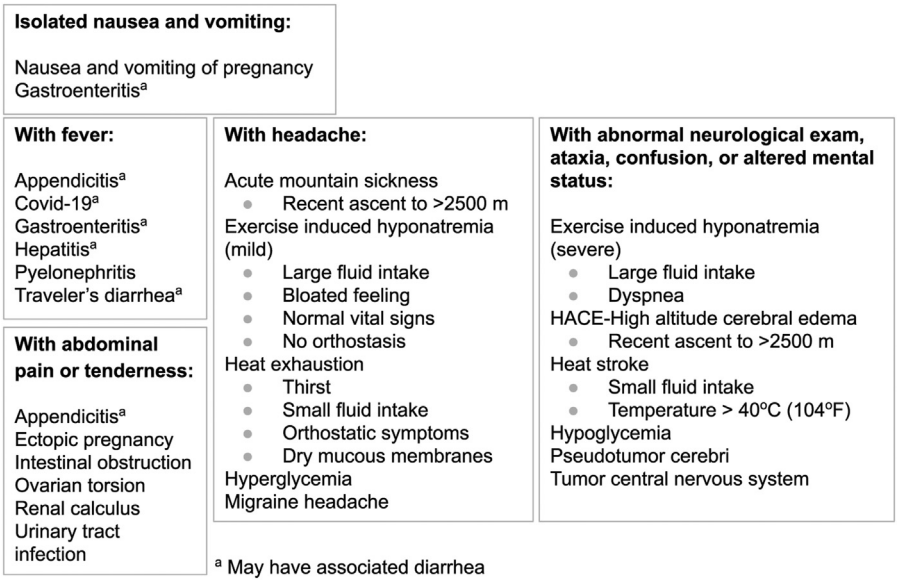

Figure 3. Differential diagnosis of nausea and vomiting during pregnancy.[41-44]

appendicitis, ectopic pregnancy, ovarian torsion, renal calculi, urinary tract infection, or intestinal obstruction.[41] Diarrhea does not usually accompany nausea and vomiting of pregnancy (NVP) and suggests an alternative diagnosis. In individuals who have recently ascended to altitudes >2500 m, nausea and vomiting, accompanied by headache, suggest acute mountain sickness; or if severe and associated with altered mental status or gait abnormalities, suggest high altitude cerebral edema.[42] An abnormal neurological exam does not occur with NVP.[41] Fever may accompany gastroenteritis, appendicitis, hepatitis, or pyelonephritis.[41] Exercise-associated hyponatremia should be considered in those aggressively hydrating with water who develop nausea and vomiting.[43] Activity in high ambient temperatures may lead to heat exhaustion or heat stroke, accompanied by nausea and vomiting.[44] Evaluation of NVP in a remote environment includes assessment of the differential diagnosis, available treatments, and ability of the patient to continue with the trip vs evacuation. Adequate hydration is critical in pregnant patients with nausea and vomiting, regardless of the underlying cause.

If evaluation is consistent with NVP, dietary changes may help, including eating frequent, small meals, avoiding fatty and spicy foods, and eating bland or dry foods (Table 4).[41] Ginger may help with nausea (tea or capsules) but not with vomiting.[45] Acupressure on the inside of the wrist (wrist bands) may be beneficial.[41] Various medications are used, although evidence of their effectiveness is limited.[46] Vitamin B6 with doxylamine is safe and considered first-line therapy for NVP.[47] Diphenhydramine has also been shown to be effective in controlling NVP.[48] Metoclopramide and phenothiazines (promethazine and prochlorperazine) are effective and, in most studies, have not been associated with increased congenital malformations.[48,49] Ondansetron has been used successfully to treat NVP, with insufficient data on fetal safety; however, the absolute risk is believed to be low.[50-52] Ondansetron should not be combined with phenothiazine because of cardiac risk of QT interval prolongation.[41]

Patients with isolated nausea and vomiting may respond to conservative measures or treatment. Mild NVP does not have an adverse effect on the fetus, and some data support an association with a lower risk of miscarriage compared with controls.[53] We recommend evacuation if the patient is unable to tolerate fluids for 24 h or has coffee ground or bloody emesis.

Genitourinary Infections

URINARY TRACT INFECTIONS

Urinary tract infections (UTIs) in pregnant people risk progressing to pyelonephritis because of multiple different physiologic changes during pregnancy and may be associated with preterm birth, low birth weight, and perinatal mortality,[54] as well as a risk of sepsis and maternal death if left untreated. The most common pathogens are *Klebsiella*, *E coli*, and group B streptococcus.[54]

Table 4. Therapeutic options for management of nausea and vomiting during pregnancy[41]

Dietary changes:				
Frequent, small meals *Eat bland and dry foods (toast, dry cereal, crackers)*				
Avoid fatty or spicy foods				
Over-the-counter options:				
Medication	*Dosage (mg)*	*Frequency*	*Route*	*Special notes*
Folic acid alone rather than full prenatal vitamin	0.6	Daily	Oral	Standard 600-microgram dose
Ginger capsules	250	Every 6 h	Oral	
Vitamin B6 (pyridoxine) and/or	10 to 25	Every 6 to 8 h	Oral	
Doxylamine	12.5	Every 6 to 8 h	Oral	
Dimenhydrinate or	25 to 50	Every 4 to 6 h	Oral	WARNING: Do not exceed 200 mg daily if patient also taking doxylamine
Diphenhydramine	25 to 50	Every 4 to 6 h	Oral	
Wrist bands for nausea	-	As needed	Wrist	Ex: Sea-Band, ReliefBand
Prescription medications:				
Medication	*Dosage (mg)*	*Frequency*	*Route*	*Special notes*
Doxylamine or Pyridoxine	10/10 DR (2 tablets) or	At bedtime	Oral	More frequent dosing per pharmaceutical guideline
	20/20 ER	At bedtime	Oral	
Prochlorperazine or	25	Every 12 h	Rectal	Long-term or excess use may cause dystonic reactions
Promethazine	12.5 to 25	Every 4 to 6 h	Oral or rectal	
If symptoms persist:				
Metoclopramide or	5 to 10	Every 6 to 8 h	Oral	WARNING: Do not combine ondansetron with use of prochlorperazine or promethazine
Ondansetron	4	Every 8 h	Oral	

DR, delayed release (Diclegis); ER, extended release (Bonjesta).

UTI symptoms may include burning or pain with urination, urinary frequency, and change in urine smell or color. Urine dipsticks can easily be carried in medication kits to test for infection. If a pregnant individual has symptoms consistent with a UTI, oral antibiotics should be initiated, such as penicillins or first- and second-generation cephalosporins. Amoxicillin and cephalexin are safe during pregnancy.[55] In the case of severe anaphylaxis to penicillins, nitrofurantoin can be used. Patients with symptoms that include fever, flank pain, vomiting, and/or costovertebral angle tenderness[56] require evacuation to a medical center that can evaluate and manage pyelonephritis and sepsis. Pregnant patients with symptoms of a UTI that do not improve in 48 h should be reevaluated and evacuation considered.[57]

CANDIDAL INFECTIONS

Candida vulvovaginitis is a vaginal yeast infection caused by *Candida*. Normally, *Candida* is not pathogenic, but loss of chemical balance, especially hormonal changes during pregnancy, can cause *Candida* to multiply.[58,59] Common symptoms include thick, white vaginal discharge; vaginal itching or soreness; swelling; painful urination; and painful intercourse.[60]

Pregnant patients with symptoms of vulvovaginal candidiasis can use clotrimazole or miconazole creams or suppositories. Common medication side effects include burning, redness, and irritation. While oral azole treatment is commonly used for uncomplicated infections outside of pregnancy, oral treatment during the first trimester is not recommended because of a potential increased risk of miscarriage or birth defects, although data are conflicting.[61,62] Vulvovaginal candidiasis does not require evacuation.

Conclusions

With proper preparation and precaution, remote travel can be safe and appropriate during early pregnancy. We offer considerations for pretrip planning and a practical approach to vaginal bleeding, nausea and vomiting, and

genitourinary infections for pregnant individuals participating in wilderness and remote travel. Research is lacking on pregnancy outcomes and first-trimester exposure to remote and extreme environments. Future investigations are needed to address this important health issue.

Acknowledgments: The authors acknowledge the Wilderness Medical Society Women in Wilderness Medicine Research Committee for creating the space for collaboration on women's health in wilderness environments. The authors thank Hillary E. Davis, MD, PhD, and Jonathan Steller, MD, for their critical revision of the manuscript.

Author Contributions: All authors participated in the concept and design, drafting, critical revision, and final approval of the manuscript.

Financial/Material Support: None

Disclosures: None.

References

1. Keyes LE, Mather L, Duke C, Regmi N, Phelan B, Pant S, et al. Older age, chronic medical conditions and polypharmacy in Himalayan trekkers in Nepal: an epidemiologic survey and case series. *J Travel Med*. 2016;23(6):taw052.
2. Outdoor Foundation. 2021 outdoor participation trends report. Available at: https://outdoorindustry.org/wp-content/uploads/2015/03/2021-Outdoor-Participation-Trends-Report.pdf. PDF download. Accessed March 03, 2022.
3. McDonough MJ, Feinstein BA, Webster GE, Condino AE. Medical care during mountain rescue in King County, Washington, from 2004 to 2017. *Wilderness Environ Med*. 2020;31(4):431–6.
4. Keyes LE, Hackett PH, Luks AM. Outdoor activity and high altitude exposure during pregnancy: a survey of 459 pregnancies. *Wilderness Environ Med*. 2016;27(2):227–35.
5. Finer LB, Zolna MR. Declines in unintended pregnancy in the United States, 2008-2011. *N Engl J Med*. 2016;374(9):843–52.
6. Wilcox AJ, Baird DD, Dunson D, McChesney R, Weinberg CR. Natural limits of pregnancy testing in relation to the expected menstrual period. *JAMA*. 2001;286(14):1759–61.
7. Fromm C, Likourezos A, Haines L, Khan AN, Williams J, Berezow J. Substituting whole blood for urine in a bedside pregnancy test. *J Emerg Med*. 2012;43(3):478–82.
8. American College of Obstetricians and Gynecologists. Practice bulletin no. 181: prevention of Rh D alloimmunization. *Obstet Gynecol*. 2017;130(2):e57–70.
9. Roth NM, Reynolds MR, Lewis EL, Woodworth KR, Godfred-Cato S, Delaney A, et al. Zika-associated birth defects reported in pregnancies with laboratory evidence of confirmed or possible Zika virus infection—US Zika pregnancy and infant registry, December 1, 2015-March 31, 2018. *MMWR Morb Mortal Wkly Rep*. 2022;71(3):73–9.
10. Pacheco O, Beltrán M, Nelson CA, Valencia D, Tolosa N, Farr SL, et al. Zika virus disease in Colombia—preliminary report. *N Engl J Med*. 2020;6(6):e44, 383.
11. Faria NR, Azevedo RD, Kraemer MU, Souza R, Cunha MS, Hill SC, et al. Zika virus in the Americas: early epidemiological and genetic findings. *Science*. 2016;352(6283):345–9.
12. Kennedy D, Hurst V, Konradsdottir E, Einarson A. Pregnancy outcome following exposure to permethrin and use of teratogen information. *Am J Perinatol*. 2005;22(2):87–90.
13. Vouga M, Chiu YC, Pomar L, de Meyer SV, Masmejan S, Genton B, et al. Dengue, Zika and chikungunya during pregnancy: pre- and post-travel advice and clinical management. *J Travel Med*. 2019;26(8):taz077.
14. Schantz-Dunn J, Nour NM. Malaria and pregnancy: a global health perspective. *Rev Obstet Gynecol*. 2009;2(3):186–92.
15. Chua CL, Khoo SK, Ong JL, Ramireddi GK, Yeo TW, Teo A. Malaria in pregnancy: from placental infection to its abnormal development and damage. *Front Microbiol*. 2021;12:777343.
16. Irvine MH, Einarson A, Bozzo P. Prophylactic use of antimalarials during pregnancy. *Can Fam Physician*. 2011;57(11):1279–81.
17. Nosten F, McGready R, d'Alessandro U, Bonell A, Verhoeff F, Menendez C, et al. Antimalarial drugs in pregnancy: a review. *Curr Drug Saf*. 2006;1(1):1–15.
18. Kanhutu K, Torda A. Travel and pregnancy: an infectious diseases perspective. *Obstet Med*. 2011;4(2):53–8.
19. Sarkar M, Woodland C, Koren G, Einarson AR. Pregnancy outcome following gestational exposure to azithromycin. *BMC Pregnancy Childbirth*. 2006;6(1):1–5.
20. Yefet E, Schwartz N, Chazan B, Salim R, Romano S, Nachum Z. The safety of quinolones and fluoroquinolones in pregnancy: a meta-analysis. *BJOG*. 2018;125(9):1069–76.
21. Simmons KB, Haddad LB, Nanda K, Curtis KM. Drug interactions between rifamycin antibiotics and hormonal contraception: a systematic review. *BJOG*. 2018;125(7):804–11.
22. Kroger AT, Atkinson WL, Sumaya CV, Pickering LK. General recommendations on immunization; recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep*. 2011;60(2):1–64.
23. Sur DK, Wallis DH, O'Connell TX. Vaccinations in pregnancy. *Am Fam Physician*. 2003;68(2):299–304.
24. Hall C, Khodr ZG, Chang RN, Bukowinski AT, Gumbs GR, Conlin AM. Safety of yellow fever vaccination in pregnancy: findings from a cohort of active duty US military women. *J Travel Med*. 2020;27(6):taaa138.
25. Suzano CE, Amaral E, Sato HK, Papaiordanou PM. Campinas group on yellow fever immunization during pregnancy. The effects of yellow fever immunization (17DD) inadvertently used in early pregnancy during a mass campaign in Brazil. *Vaccine*. 2006;24(9):1421–6.
26. World Health Organization. Safety of immunization during pregnancy: a review of the evidence: Global Advisory Committee on Vaccine Safety. Available at: https://apps.who.int/iris/bitstream/handle/10665/340577/WHO-HIS-2014.07-eng.pdf. Accessed March 10, 2022.
27. Hasan R, Baird DD, Herring AH, Olshan AF, Funk ML, Hartmann KE. Association between first-trimester vaginal bleeding and miscarriage. *Obstet Gynecol*. 2009;114(4):860–7.
28. American College of Obstetricians and Gynecologists. Practice bulletin no. 200: early pregnancy loss. *Obstet Gynecol*. 2018;132(5):e197–207.
29. National Guideline Alliance (UK). *Ectopic pregnancy and miscarriage: diagnosis and initial management*. London: National Institute for Health and Care Excellence (UK); 2019. Available at: https://www.nice.org.uk/guidance/ng126/resources/ectopic-pregnancy-and-miscarriage-diagnosis-and-initial-management-pdf-66141662244037. Accessed February 22, 2022.
30. American College of Obstetricians and Gynecologists. Practice bulletin no. 193: tubal ectopic pregnancy. *Obstet Gynecol*. 2018;131(3):e91–103.
31. Barnhart KT. Clinical practice. Ectopic pregnancy. *N Engl J Med*. 2009;361(4):379–87.
32. Li C, Zhao WH, Meng CX, Ping H, Qin GJ, Cao SJ, et al. Contraceptive use and the risk of ectopic pregnancy: a multi-center case-control study. *PLoS One*. 2014;9(12):e115031.

33. American College of Obstetricians and Gynecologists. Practice bulletin no. 121: long-acting reversible contraception: implants and intrauterine devices. *Obstet Gynecol*. 2011;118(1):184–96.
34. Wang X, Chen C, Wang L, Chen D, Guang W, French J. Conception, early pregnancy loss, and time to clinical pregnancy: a population-based prospective study. *Fertil Steril*. 2003;79(3):577–84.
35. Practice Committee of the American Society for Reproductive Medicine. Evaluation and treatment of recurrent pregnancy loss: a committee opinion. *Fertil Steril*. 2012;98(5):1103–11.
36. Tannirandorn Y, Sangsawang S, Manotaya S, Uerpairojkit B, Samritpradit P, Charoenvidhya D. Fetal loss in threatened abortion after embryonic/fetal heart activity. *Int J Gynaecol Obstet*. 2003;81(3):263–6.
37. Aleman A, Althabe F, Belizán J, Bergel E. Bed rest during pregnancy for preventing miscarriage. *Cochrane Database Syst Rev*. 2005;2:CD003576.
38. Haas DM, Hathaway TJ, Ramsey PS. Progestogen for preventing miscarriage in women with recurrent miscarriage of unclear etiology. *Cochrane Database Syst Rev*. 2019;11:CD003511.
39. Grassetto A, Fullin G, Cerri G, Simioni P, Spiezia L, Maggiolo C. Management of severe bleeding in a ruptured extrauterine pregnancy: a theragnostic approach. *Blood Coagul Fibrinolysis*. 2014;25(2):176–9.
40. Murphy NC, Hayes NE, Ainle FB, Flood KM. Jehovah's Witness patients presenting with ruptured ectopic pregnancies: two case reports. *J Med Case Rep*. 2014;8(1):1–3.
41. American College of Obstetricians and Gynecologists. Practice bulletin no. 189: nausea and vomiting of pregnancy. *Obstet Gynecol*. 2018;131(1):e15–30.
42. Luks AM, Auerbach PS, Freer L, Grissom CK, Keyes LE, McIntosh SE, et al. Wilderness Medical Society clinical practice guidelines for prevention and treatment of acute altitude illness: 2019 update. *Wilderness Environ Med*. 2019;30(4):S3–18.
43. Bennett BL, Hew-Butler T, Hoffman MD, Rogers IR, Rosner MH. Wilderness Medical Society guidelines for treatment of exercise-associated hyponatremia: 2014 update. *Wilderness Environ Med*. 2014;25(4):S30–42.
44. Lipman GS, Gaudio FG, Eifling KP, Ellis MA, Otten EM, Grissom CK. Wilderness Medical Society clinical practice guidelines for the prevention and treatment of heat illness. *Wilderness Environ Med*. 2019;30(4):S33–46.
45. Viljoen E, Visser J, Koen N, Musekiwa A. A systematic review and meta-analysis of the effect and safety of ginger in the treatment of pregnancy-associated nausea and vomiting. *Nutr J*. 2014;13(1):1–14.
46. Matthews A, Haas DM, O'Mathúna DP, Dowswell T, Doyle M. Interventions for nausea and vomiting in early pregnancy. *Cochrane Database of Syst Rev*. 2015;9:CD007575.
47. Koren G, Clark S, Hankins GD, Caritis SN, Miodovnik M, Umans JG, et al. Effectiveness of delayed release doxylamine and pyridoxine for nausea and vomiting of pregnancy: a randomized placebo controlled trial. *Am J Obstet Gynecol*. 2010;203(6):571. e1–7.
48. Magee LA, Mazzota P, Koren G. Evidence-based view of safety and effectiveness of pharmacologic therapy for nausea and vomiting of pregnancy (NVP). *Am J Obstet Gynecol*. 2002;186(5):S256–61.
49. Tan PC, Khine PP, Vallikkannu N, Omar SZ. Promethazine compared with metoclopramide for hyperemesis gravidarum: a randomized controlled trial. *Obstet Gynecol*. 2010;115(5):975–81.
50. Abas MN, Tan PC, Azmi N, Omar SZ. Ondansetron compared with metoclopramide for hyperemesis gravidarum: a randomized controlled trial. *Obstet Gynecol*. 2014;123(6):1272–9.
51. Kashifard M, Basirat Z, Golsorkhtabar-Amiri M, Moghaddamnia A. Ondansetron or metoclopramide? Which is more effective in severe nausea and vomiting of pregnancy? A randomized trial double-blind study. *Clin Exp Obstet Gynecol*. 2013;40(1):127–30.
52. Carstairs SD. Ondansetron use in pregnancy and birth defects: a systematic review. *Obstet Gynecol*. 2016;127(5):878–83.
53. Hinkle SN, Mumford SL, Grantz KL, Silver RM, Mitchell EM, Sjaarda LA, et al. Association of nausea and vomiting during pregnancy with pregnancy loss: a secondary analysis of a randomized clinical trial. *JAMA Internal Med*. 2016;176(11):1621–7.
54. Hill JB, Sheffield JS, McIntire DD, Wendel Jr GD. Acute pyelonephritis in pregnancy. *Obstet Gynecol*. 2005;105(1):18–23.
55. Bookstaver PB, Bland CM, Griffin B, Stover KR, Eiland LS, McLaughlin M. A review of antibiotic use in pregnancy. *Pharmacotherapy*. 2015;35(11):1052–62.
56. Jolley JA, Wing DA. Pyelonephritis in pregnancy: an update on treatment options for optimal outcomes. *Drugs*. 2010;70(13):1643–55.
57. Schimelpfenig T. *National Outdoor Leadership School Wilderness Medicine*. 6th ed. Guilford, CT: Stackpole Books; 2016.
58. Ramos-E-Silva M, Martins NR, Kroumpouzos G. Oral and vulvovaginal changes in pregnancy. *Clin Dermatol*. 2016;34(3):353–8.
59. Sobel JD. Vulvovaginal candidosis. *Lancet*. 2007;369(9577):1961–71.
60. Eckert LO, Hawes SE, Stevens CE, Koutsky LA, Eschenbach DA, Holmes KK. Vulvovaginal candidiasis: clinical manifestations, risk factors, management algorithm. *Obstet Gynecol*. 1998;92(5):757–65.
61. Mølgaard-Nielsen D, Svanström H, Melbye M, Hviid A, Pasternak B. Association between use of oral fluconazole during pregnancy and risk of spontaneous abortion and stillbirth. *JAMA*. 2016;315(1):58–67.
62. Bérard A, Sheehy O, Zhao JP, Gorgui J, Bernatsky S, de Moura CS, et al. Associations between low- and high-dose oral fluconazole and pregnancy outcomes: 3 nested case-control studies. *CMAJ*. 2019;191(7):E179–87.

WILDERNESS & ENVIRONMENTAL MEDICINE 2023; 34(2): 218–21

CASE REPORT

Four Cases of Acute Kidney Injury Requiring Dialysis in Ultramarathoners

Andrew V. Pasternak IV, MD, MS[1]; Cristin Newkirk-Thompson, MD[2]; John H. Howard III, MD[3]; John C. Onate, MD[4]; Tamara Hew-Butler, DPM, PhD[5]

[1]Silver Sage Center for Family Medicine, Reno School of Medicine, University of Nevada, Reno, NV; [2]Renown Primary Care, Reno, NV; [3]Capital Nephrology Medical Group, Sacramento, CA; [4]University of California Davis School of Medicine, Sacramento, CA; [5]Division of Kinesiology, Health and Sport Studies, Wayne State University, Detroit, MI

Transient acute kidney injury (AKI) following ultraendurance footraces is a common biochemical diagnosis. However, severe AKI requiring renal replacement therapy is uncommon in ultramarathoners. We report 4 runners (3 men; mean age, 44 ± 3 y) who required prolonged (10–42 d) dialysis following the Western States 100 Mile Endurance Run over a 3-y span (0.38% of starters). The maximum ambient temperatures on the race day ranged from 36.6° to 38.3°C. The runners presented to local hospitals 17 to 32 h after running, with laboratories confirming rhabdomyolysis, hyponatremia (mean serum sodium concentration, 127±2 mmol·L^{-1}), and AKI (mean serum creatinine concentration, 8.5±2 mg·dL^{-1}). The case-cluster report highlights the potential synergistic effects of high ambient temperatures, muscle damage, and electrolyte imbalance on protracted renal dysfunction in ultramarathoners competing in a warming world.

Keywords: ultramarathon, rhabdomyolysis, acute renal failure, heat nephropathy

Introduction

Although mild-to-moderate acute kidney injury (AKI) and exertional rhabdomyolysis (ER) are common following ultramarathons, severe AKI with prolonged hospitalization and dialysis is rare.[1,2] A 2022 systematic review of 1113 ultrarunners over the last 15 y reported an overall incidence of mild AKI of 42%, with only 1 case (0.01%) meeting the criteria for severe renal failure but not requiring dialysis.[3] In addition, a systematic review of case reports identified only 27 runners who developed severe AKI following marathon or ultramarathon running.[2] Of the 27 runners, only 15 required dialysis.

Given the low historical risk of developing severe renal injury because of running ultramarathons, it is concerning that over the last 3 y of the Western States 100 Mile Endurance Run (WS100), 4 runners out of 1053 starters (0.38%) required prolonged dialysis treatment for AKI with ER. It remains unclear which features of the WS100, including extreme heat and a considerable net downhill course, exacerbate risk factors for AKI necessitating dialysis. This case cluster highlights the emerging potential for heat stress nephropathy to impact ultramarathoners competing in extreme environments hypothetically as an athletic variant of Mesoamerican nephropathy, as suggested elsewhere.[4]

Case Report

The WS100 is a 100-mile (161 km) trail running race which traverses the Sierra Nevada mountains and includes 5486 m of ascent and 7010 m of descent. Roughly 315 to 400 annual starters have 30 h to complete the race distance. Ambient temperatures typically range between 4 and 37°C.

Table 1 summarizes the demographics, training history, medical history, and select laboratory values of the 4

Corresponding author: Andrew Pasternak, MD, MS, Silver Sage Center for Family Medicine, University of Nevada, Reno School of Medicine, Reno, NV; e-mail: avpiv711@sbcglobal.net.

Submitted for publication June 2022.

Accepted for publication December 2022.

https://doi.org/10.1016/j.wem.2022.12.004

Table 1. Summary of 4 runners requiring dialysis after WS100

Variable	*Runner A*	*Runner B*	*Runner C*	*Runner D*
Age at time of race (y)	47	47	43	41
Year running WS100	2018	2018	2021	2021
Sex	M	F	M	M
Number of ultramarathons run prior to race	14	4	54	36
Number of 100-mile races run prior to race	8	1	8	7
Finished WS100	Y	Y	N (dropped mile 85)	Y
Previous medical issues	Hypertension	Hydronephrosis but no renal damage	None	None
Time from stopping running to presentation in ED	19.5 h	32 h	28 h	17 h
BUN ($mg \cdot dL^{-1}$)	101	109	108	92
Serum creatinine ($mg \cdot dL^{-1}$)	8.94	5.19	10.3	9.39
Sodium levels ($mmol \cdot L^{-1}$)	125	128	126	128
Potassium ($mmol \cdot L^{-1}$)	7.7	4.6	5.2	7.5
Calcium ($mg \cdot dL^{-1}$)	5.8	7.3	6.1	6.4
Magnesium ($mg \cdot dL^{-1}$)	3.3	n/a	n/a	4.2
AST ($U \cdot L^{-1}$)	5365	780	1040	5956
ALT ($U \cdot L^{-1}$)	1526	450	4098	962
CPK ($U \cdot L^{-1}$)	292,500	>16,000	153,900	>37,580
Time on dialysis	10 d	4 wk	4 wk	6 wk
Hospital complications	Atrial fibrillation, complete heart block	None	None	Respiratory failure, jugular venous thrombosis
Back running	Y	Y	Y	Y
Completed ultramarathon since being on dialysis	Y	Y	N	N

WS100, Western States 100 Mile Endurance Run; M, male; F, female; Y, yes; N, no; ED, emergency department; BUN, blood urea nitrogen; n/a, not available; AST, aspartate transaminase; ALT, alanine transaminase; CPK, creatine phosphokinase.

runners who required dialysis after the race during 2 "hot" years (2018 and 2021, with the 2020 race canceled because of COVID-19). In 2018, the maximum temperature was 36.6°C, and in 2021, the maximum temperature was 38.3°C. All 4 runners reported nausea and vomiting, dark urine, and muscle cramping during the race. One runner ingested 2 doses of 200 mg of ibuprofen, whereas the other runners did not ingest nonsteroidal anti-inflammatory (NSAID) or other medications during the race. Two runners reported consuming salt tablets. Because of the elevated risk of developing hyponatremia during ultradistance running, we promote the "drink to thirst" guidelines outlined by the Wilderness Medical Society.[5] All 4 runners reported drinking fluids according to the dictates of thirst, ingesting a combination of water, Coca-Cola, Sprite, and sports drinks.

All 4 runners reported feeling "worse" after the race than after similar events. However, none of the runners required acute care or immediate hospitalization. Three runners traveled back to the race start or their hometowns before seeking medical care for persistent fatigue, severe myalgias, nausea, and vomiting. Hematemesis occurred in 1 of the runners. The time to seek medical care ranged from 17 to 32 h after they stopped running. All 4 runners required dialysis for a minimum of 10 d to a maximum of 6 wk. All the runners have subsequently returned to training, without lingering medical issues.

Discussion

The pathophysiologic combination of ER, hyponatremia, and AKI requiring hospitalization has been reported after ultramarathons, including a previous WS100, but is rare.[1] Only 15 similar cases have been reported in the literature.[2] Exertional rhabdomyolysis with mild AKI is a recognized, transient phenomenon following ultramarathon footraces and typically does not require dialysis.[6] Research on the prevalence of severe AKI after endurance running has been limited to case reports and data from research studies focusing on changes in renal function due to endurance running. As a result, there is no

accurate estimate of the incidence of severe AKI after distance running. Nevertheless, our incidence of 0.38% is concerning. This group of runners who required protracted (2−6 wk) dialysis raises concerns about a potential new medical challenge, ultramarathon running in an era of global warming.[4]

High ambient temperatures, during the 2018 and 2021 WS100 races, are a known risk factor for AKI and ER and likely contributed to renal injury. Muscle-damaging exercise before running in the heat exacerbates both the inflammatory response and renal stress.[7] Of potential concern for ultramarathon runners, especially those who live and train at high temperatures, are the results of an indirectly related study performed on otherwise young (median age, 34 y), healthy sugarcane workers who developed chronic kidney disease (CKD) after 12 mo of repeated hard, physical labor.[8] Thus, correct identification of interventions that help preserve renal function while training and racing in the heat requires further investigation.

One common strategy directed at preserving renal function during ultramarathon running is hydration. However, the relationship between hydration, ER, and AKI remains complex and underappreciated. Although dehydration is classically associated with heat stress, runners with nephropathy were hyponatremic at their initial hospital presentation.[8] It remains unclear whether or not hyponatremia on admission preceded AKI because of hypervolemia or was a renal consequence of AKI, as similarly described.[1,9]

Another risk factor for AKI and rhabdomyolysis may be the elevation profile, specifically the net descent of the WS100, which portends a more significant mechanical load. In 1 study, volunteers running in the heat for 60 min at a grade of −10% had more inflammation and renal stress than runners running on a flat surface.[7] Although other ultramarathons take place in severe heat, a race such as the Badwater 135 is a net uphill race with a notably lower total descent of 1433 m.[10] The marked downhill profile of the WS100 likely leads to more eccentric muscle damage and higher levels of rhabdomyolysis. Combined with extreme temperatures, WS100 runners are at a significantly higher risk of ER.

We have been educating runners about the potential harms of NSAIDs during ultramarathons. Compared with previous studies in which two thirds of runners presenting with AKI had used NSAIDs, only 1 of our runners had ingested an NSAID and took a relatively low dose.[2]

Another challenging aspect for the medical team is runners' clinical presentation at the finish line. All 4 runners complained of gastrointestinal distress and myalgias, but these were not severe enough to require care in medical tents. Furthermore, these signs and symptoms are common during and after ultramarathons.[11] Previous studies have shown >75% of runners with severe AKI because of distance running presented in a delayed fashion, sometimes up to a week after the race.[2] Further study is required to identify risk factors that may inform clinicians of poor renal outcomes. It is crucial for medical directors of endurance events to keep in contact with athletes for up to a week after the event is over to monitor AKI cases. With only 15 runners requiring dialysis previously reported in the literature, there may be underreporting of severe AKI cases in runners because of this delayed presentation and medical teams being unaware of hospitalization.

Although all 4 runners had elevated creatine phosphokinase (CPK) levels, they were within the range of laboratory values seen previously in the WS100.[1,6] While markedly elevated CPK levels almost invariably result in hospital admission, most runners with elevated CPK levels have normalization of their laboratory values without medical interventions. Improved identification of risk factors for severe, symptomatic AKI due to ER may prevent unnecessary hospitalizations by initiating treatments, such as IV fluid resuscitation, before athletes leave the race venue.

Although it is concerning that these runners required protracted dialysis, their kidney dysfunction resolved completely, and all have resumed running. Normalization of kidney function has been previously demonstrated in runners with less severe kidney injury.[12] It remains unclear whether repeated bouts of exercise-related AKI can eventually lead to CKD, as seen in Mesoamerican nephropathy and other forms of recurrent AKI.[8] Longitudinal follow-up of renal function is recommended in runners with severe AKI.

Moving forward, we are considering methods to help our medical team better guide runners to complete the WS100 while avoiding hospitalization and dialysis. Current considerations may be point-of-care urine testing or using iStat devices for blood testing.[13,14] Before implementation, we must determine laboratory value thresholds at which runners would be held or disqualified. Finally, we have made a practice of limiting IV fluids and encouraging oral postrace hydration. We are now reconsidering this practice, especially for runners with persistent nausea and vomiting. More aggressive hydration with hypertonic saline in the face of hyponatremia or normal saline if runners have normal serum sodium levels could potentially reduce the incidence and severity of AKI. In the future, measurement of baseline electrolytes and renal function markers will allow us to better

understand the trajectory of chronic heat stress on renal function during ultramarathon running.

Acknowledgments: We thank the Western States 100 for their support of this manuscript.

Author Contributions: review of patient records (AVP); manuscript preparation (AVP); manuscript editing (AVP, CNT, JHH, JCO, THB); nephrology input (JHH); expertise on hydration/hyponatremia (THB); and approval of final manuscript (AVP, CNT, JHH, JCO, THB).

Financial/Material Support: None.

Disclosures: AVP is the Nevada Medical Director for VaxCare.

References

1. Bruso JR, Hoffman MD, Rogers IR, Lee L, Towle G, Hew-Butler T. Rhabdomyolysis and hyponatremia: a cluster of five cases at the 161-km 2009 Western States Endurance Run. *Wilderness Environ Med*. 2010;21(4):303–8.
2. Hodgson L, Walter E, Venn R, Gallooway R, Pitsiladis Y, Sardat F, et al. Acute kidney injury associated with endurance events—is it a cause for concern? A systematic review. *BMJ Open Sport Exerc Med*. 2017;3(1):e000093.
3. Lecina M, Castellar-Otín C, López-Laval I, Páez LC, Pradas F. Acute kidney injury and hyponatremia in ultra-trail racing: a systematic review. *Medicina (Kaunas)*. 2022;58(5):569.
4. Eichner ER. Is heat stress nephropathy a concern for endurance athletes? *Curr Sports Med Rep*. 2017;16(5):299–300.
5. Bennett BL, Hew-Butler T, Hoffman MD, Rogers IR, Rosner MH. Wilderness Medical Society practice guidelines for treatment of exercise-associated hyponatremia. *Wilderness Environ Med*. 2013;24(3):228–40.
6. Hoffman MD, Ingwerson JL, Rogers IR, Hew-Butler T, Stuempfle KJ. Increasing creatine kinase concentrations at the 161-km Western States Endurance Run. *Wilderness Environ Med*. 2012;23(1):56–60.
7. Junglee NA, di Felice U, Dolci A, Fortes M, Jibani M, Lemmey A, et al. Exercising in a hot environment with muscle damage: effects on acute kidney injury biomarkers and kidney function. *Am J Physiol Renal Physiol*. 2013;305(6):813–20.
8. Sorensen C, Garcia-Trabanino R. A new era of climate medicine—addressing heat-triggered renal disease. *N Engl J Med*. 2019;381(8):693–6.
9. Ellis C, Cuthill J, Hew-Butler T, George SM, Rosner MH. Exercise-associated hyponatremia with rhabdomyolysis during endurance exercise. *Phys Sportsmed*. 2009;37(1):126–32.
10. Zingg MA, Knechtle B, Rüst CA, Rosemann T, Lepers R. Analysis of participation and performance in athletes by age group in ultramarathons of more than 200 km in length. *Int J Gen Med*. 2013;6:209–20.
11. Stuempfle KJ, Hoffman MD. Gastrointestinal distress is common during a 161-km ultramarathon. *J Sports Sci*. 2015;33(17), 1824–21.
12. Hoffman MD, Weiss RH. Does acute kidney injury from an ultramarathon increase the risk for greater subsequent injury? *Clin J Sport Med*. 2016;26(5):417–22.
13. Hoffman MD, Stuempfle KJ, Fogard K, Hew-Butler T, Winger J, Weiss RH. Urine dipstick analysis for identification of runners susceptible to acute kidney injury following an ultramarathon. *J Sports Sci*. 2012;31(1):20–31.
14. Khodaee M, Saeedi A, Irion B, Spittler J, Hoffman MD. Proteinuria in a high-altitude 161-km (100-mile) ultramarathon. *Phys Sportsmed*. 2021;49(1):92–9.

WILDERNESS & ENVIRONMENTAL MEDICINE 2023; 34(2): 225–30

CASE REPORT

Managing an Unidentified Jellyfish Sting with Mixed Envenomation Syndrome at a Noncoastal Hospital: Is This a New Form of Jellyfish Envenomation?

Naresh Kumar Sivanasworn, MD; Geetha Anantham, MD; Shamsuriani Md Jamal, DrEmMed; Munawar Mohamed Hatta, DrEmMed; Ahmad Khaldun Ismail, DrEmMed

Department of Emergency Medicine, Faculty of Medicine, Universiti Kebangsaan Malaysia, Kuala Lumpur, Malaysia

Jellyfish stings are the most common cause of marine envenomation in humans. Various species of box jellyfish have been identified around Penang Island, Malaysia, and these include multitentacled and four-tentacled box jellyfish (class Cubozoa). The typical syndrome following envenomation from these jellyfish has been poorly documented, posing a greater challenge when managing an unidentified jellyfish sting from Penang Island. We report a case of a 32-y-old man from Penang Island who was stung by an unidentified jellyfish while walking into the sea. The patient reported that he felt an immediate and severe electric current–like pain over both thighs, left flank, and left forearm, followed by chest discomfort and breathlessness. Vinegar was applied over the affected areas, and he was rushed to a hospital, where he was treated with analgesia, steroids, and antihistamine. He refused hospitalization and was discharged against medical advice. He then presented to a noncoastal hospital 377 km away in Kuala Lumpur on the following day with severe pain over the affected sites as well as chest discomfort, shortness of breath, and abdominal cramps. The electrocardiograph demonstrated features of Wolff-Parkinson-White. Serial blood test results showed elevated creatine kinase but normal troponin I levels. The patient was managed symptomatically over a period of 4 d and was discharged with cardiology follow-up. Appropriate health-seeking behavior needs to be emphasized. This case report provides an opportunity to document the signs and symptoms of envenomation from possibly an undescribed jellyfish species near the coastal waters of Penang Island.

Keywords: clinical toxinology, cubozoa, Malaysia, Penang

Introduction

Jellyfish are the most common cause of marine stings; however, there is scarce documentation of harmful jellyfish species in Malaysia.[1] There are marked differences in the envenomation syndrome of the various groups of harmful jellyfish. Among the many harmful jellyfish species, those of the class Cubozoa (eg, box jellyfish) are the most harmful to humans, particularly children and the elderly. *Chironex* species, a large multitentacled box jellyfish, has the most toxic venom and may cause death within 70 min. Smaller-sized box jellyfish from the family *Carukiidae* are also known to have caused envenomation known as the Irukandji syndrome.[2,3]

A study by Low[4] described 9 scyphozoan jellyfish species found in Peninsular Malaysia: *Chrysaora chinensis*, *Cyanea* sp, *Versuriga anadyomene*, *Rhopilema hispidum*, *Rhopilema esculentum*, *Phyllorhiza punctata*, *Acromitus flagellatus*, *Lobonemoides robustus*, and *Lychnorhiza malayensis.* A preliminary survey report of jellyfish diversity and distribution along coastal waters of Peninsular Malaysia identified 8 different species of jellyfish inhabitants: *Chironex* sp, *Chrysaora hysoscella*, *Chrysaora quinquecirrha*, *P punctata*, *Cyanea capillata*, *Cyenea lamarckii*, *Rhyzostoma pulmo*, and *Lobonema smithii*.[5] A study of monthly abundance and distribution

Corresponding author: Professor Madya Dr Ahmad Khaldun Ismail, Department of Emergency Medicine, Faculty of Medicine, Universiti Kebangsaan Malaysia, Kuala Lumpur, Malaysia; e-mail: khaldun_ismail@yahoo.com.

Submitted for publication September 2022.

Accepted for publication January 2023.

https://doi.org/10.1016/j.wem.2023.01.010

of jellyfish population in the coastal waters of Penang National Park identified *P punctata*, *Chrysaora* sp, *Rhopilema* sp, *Chiropsoides buitendijki*, and *Carybdea morbakka*.[6] In Sabah, 6 species belonging to 2 classes and 6 families have been reported: *Chironex yamaguchii*, *Acromitus maculosus*, *Crambione mastigophora*, *Linuche aquila*, *Netrostoma* sp, and *P punctata*.[7] The frequency and severity of jellyfish stings appear to be increasing in Southeast Asia; however, it may be significantly underestimated in Malaysia.[8] There have been reports of severe and fatal cases of chirodropid-type stings occurring in coastal waters of Langkawi and Sabah.[1] A 3-y study of jellyfish stings in Langkawi reported that a significant number of patients presented with mild Irukandji and Irukandji-like syndromes.[9] A recent study of 45 cases at the western coast of Peninsular Malaysia has also identified similar presentations.[10] However, the diagnosis of these cases was not verified. There could also be incidences of multitentacled box jellyfish stings that were mistakenly documented as Irukandji and Irukandji-like syndrome. Therefore, a careful documentation of all clinical presentations of jellyfish sting is important and needs verification. We present a case of an unidentified jellyfish sting presenting with mixed features of box jellyfish envenomation syndromes, which may suggest the possibility of a new type of multitentacled box jellyfish envenomation syndrome or possibly distinct from it as well.

Case Report

A 32-y-old West African man presented to the emergency department of a private hospital in Penang Island after he was stung by an unidentified jellyfish. He had traveled to Penang Island for a vacation and stayed at a hotel by the beach. According to the patient, at 0635, while performing a religious ritual, he walked into the sea to the waist level, when he suddenly felt an electric current−like pain over both thighs, left flank, and left forearm. He did not see the offending agent. He complained of severe pain over the affected areas, with chest discomfort and breathlessness. Hotel workers attended to him and sprayed the affected areas (most likely with vinegar). At a nearby private hospital 1 h 35 min after the sting, his initial vital signs were blood pressure 136/104 mm Hg, heart rate 102 beats/min, SpO_2 100% on nasal cannula 3L/min oxygen, and pain score 9/10 on verbal numerical rating scale (VNRS). Vinegar soap was applied to the affected area. He denied any comorbidities, medication, or allergies. He was given IV pethidine 50 mg, parecoxib 40 mg, pantoprazole 40 mg, hydrocortisone 200 mg, tramadol 50 mg, intramuscular chlorphenamine 10 mg, and oral paracetamol 1 g. He did not want to be admitted because of logistical reasons and was discharged against medical advice with oral etoricoxib, tramadol, and diclofenac gel. No skin sampling (scraping/biopsy) for nematocyst was obtained for analysis.

The following day, he traveled by public transportation to a teaching hospital in Kuala Lumpur 377 km south of the initial treating facility, 30 h after the initial incident. He complained of persistent pain over his thighs and left flank, generalized body ache, fever, mild drowsiness, numbness over the affected limbs, sore throat, and abdominal cramps. Vital signs at presentation were temperature 36.5°C, blood pressure 139/85 mm Hg, heart rate 83 beats/min, SpO_2 97%, respiratory rate 18 breaths/min, and pain score 7/10. Examination of the cardiovascular, respiratory, and abdominal systems was normal. Examination of the sting area showed red to purplish skin lesions (Figure 1a).

A 12-lead electrocardiogram (ECG) demonstrated features of Wolff-Parkinson-White (WPW), with a short PR interval and delta waves, secondary ST segment changes, and left ventricular hypertrophy according to limb leads criteria. Cardiac ultrasound revealed good cardiac contractility with no regional wall hypokinesia and a thickened left ventricular wall. The patient was given IV tramadol 50 mg and saline hydration. Blood investigation showed elevated creatine kinase (CK) level of 647 U/L, with troponin I level at <10 pg/nL (Table 1). The chest radiograph was normal. Repeat ECG showed no evolving changes.

The Remote Envenomation Consultancy Service (RECS) was consulted, and he was referred to the cardiology team. Once again, he did not want to be admitted and discharged himself against advice with an outpatient cardiology clinic appointment. The patient returned to the emergency department 22 h later with persistent pain over the affected sites (Figure 1b). He denied chest pain or breathlessness. Vital signs and physical examination were unremarkable. An ECG showed persistent WPW changes, and the troponin level was <10 pg/nL. However, the CK level increased to 1216 U/L. He was admitted for observation and pain management, and his condition gradually improved. The CK level on the following day was 763 U/L, and his ECG remained unchanged. He was discharged after 2 d of admission with a final CK level of 392 U/L with an outpatient echocardiography and cardiology clinic appointment (Figure 1c). A review of patient progress 30 d after injury did not reveal any persistent signs of envenomation or chest pain. The wound from the sting has healed with minimal scarring (Figure 1d). A repeat ECG showed no changes (Figure 1e).

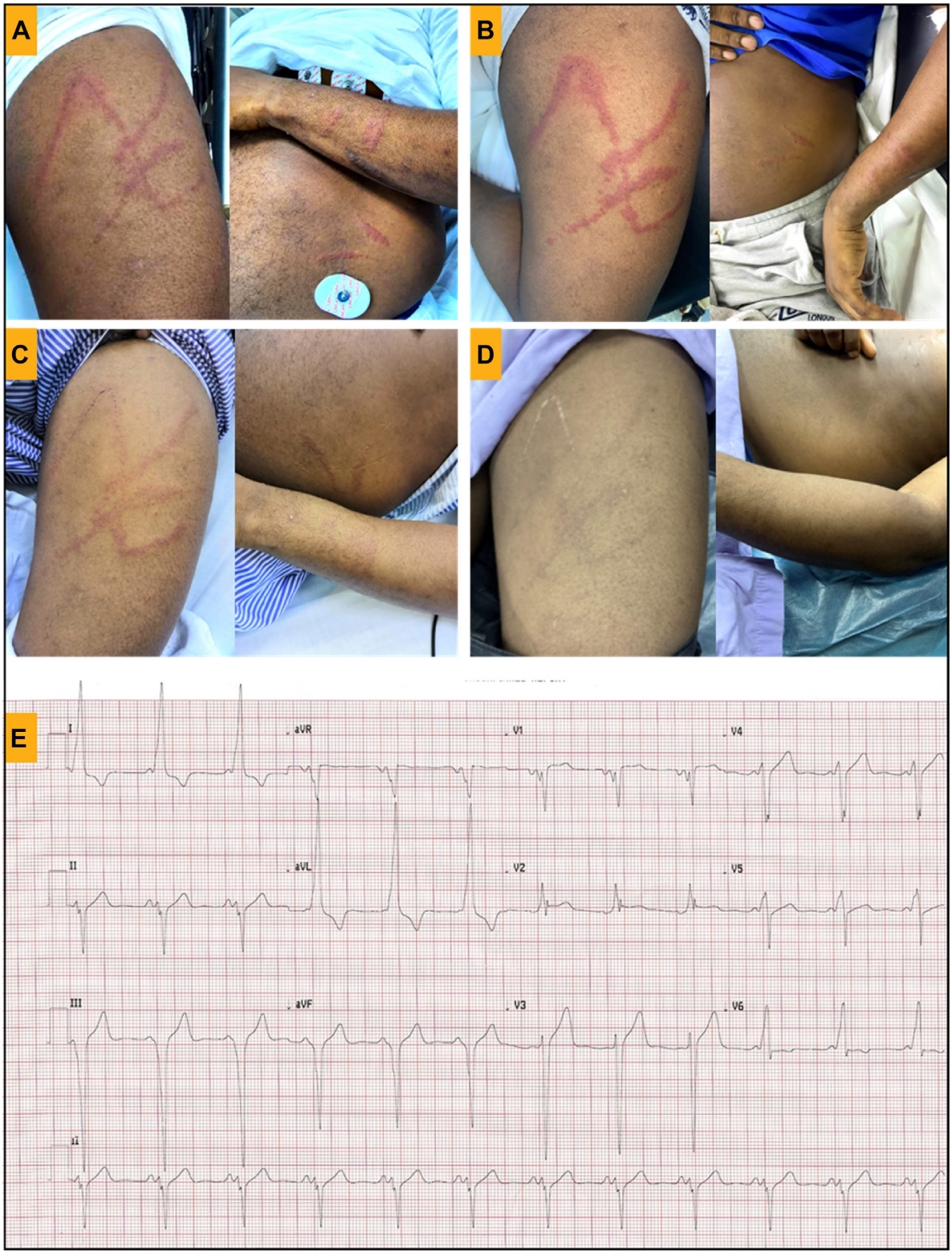

Figure 1. Jellyfish sting lesion over left anterior thigh, forearm, and flank at A, 30 h; B, 62 h; C, 140 h; D, at 30 d after the incident; E, electrocardiograph showing Wolff-Parkinson-White with short PR interval and delta waves, with secondary ST segment changes and left ventricular hypertrophy according to limb leads criteria.

Table 1. Laboratory investigation of the patient from admission to the emergency department until discharge

Investigation	*Unit*	*Reference range*	*Day from jellyfish sting*			
			2	*3*	*4*	*5*
White blood cell	×10	4-10	5.8	10.2	7.4	4.9
Hemoglobin	g/dL	13-17	16.1	16.0	14.8	15.3
Hematocrit	%	40-50	48.0	46.4	42.0	42.9
Platelet	x10	150-410	234	248	215	218
CRP	mg/dL	<0.5	0.36	4.86		
Urea	mmol/L	3.2-7.4	4.9	4.1	4.4	4.0
Creatinine	umol/L	63.6-110.5	101.4	108.9	89.1	86.1
Sodium	mmol/L	136-145	137	138	137	136
Potassium	mmol/L	3.5-5.1	3.9	4.1	3.7	4.0
Calcium	mmol/L	2.14-2.58	2.44		2.27	2.38
Magnesium	mmol/L	0.66-1.07	0.89		0.85	0.83
Phosphate	mmol/L	0.74-1.52	1.20		1.04	1.41
CK	U/L	30-200	647	1216	763	392
Troponin I	pg/mL	<34.2	<10	<10	<10	
PT	s	11.6-14.9	13.5	13.9		
APTT	s	30.3-46.5	30.7	31.2		
INR	Ratio	-	0.98	1.01		
Albumin	g/L	35-50	46	45	38	38
Total protein	g/L	64-83	81	79	66	70
Bilirubin	μmol/L	3.4-20.5	33.3	36.1	19.8	11.7
ALP	U/L	40-160	52	56	46	49
ALT	U/L	0-55	47	47	31	31

CRP, C-reactive protein; CK, creatinine kinase; PT, prothrombin time; aPTT, activated partial thromboplastin time; INR, international normalized ratio; ALP, alkaline phosphatase: ALT, alanine transaminase.

Discussion

Few jellyfish sting cases have been reported in Malaysia, although it is the most common marine envenomation consulted to RECS (unpublished data). Being in proximity to Thailand and the Philippines, where 20 to 50 sting-related deaths were reported to occur annually, a similar problem is likely to occur in Malaysia.[11-12] To date, in regular on-site surveys by the Centre for Marine and Coastal Studies (CEMACS) of the waters around Penang Island, *Chironex fleckeri* and *C yamaguchii* have yet to be identified.[1] The Cubomedusae that have been identified were *C buitendijki* and *Morbakka* spp. *C yamaguchii* is indigenous to Sabah waters. There is however an abundance of *C chinensis* in the waters of Penang Island. This finding is also supported by regular specimens collected by local fishermen of Penang.

Both Irukandji and Irukandji-like syndrome have been diagnosed among jellyfish sting patients in Langkawi and the west coast of peninsular Malaysia.[10] Irukandji syndrome is a complex of symptoms and signs indicating a particular type of envenoming and can be caused by a variety of jellyfish belonging to multiple genera. Although Irukandji syndrome was originally described after stings by *Carukia barnesi*, other jellyfish such as *Morbakka* spp, including *Morbakka fenneri*, can cause similar presentations.[13,14] Irukandji syndrome is described as a minor local sign and symptom with the hallmark of severe musculoskeletal pain occurring after the sting from *C barnesi* jellyfish.[2,14] Some patients with identified nematocysts consistent with *C barnesi* have reported rapidly developing dyspnea and musculoskeletal pain.[15] Symptoms of Irukandji syndrome typically occur within 30 min but can range anywhere from 5 to 120 min.[14,16] The rapid onset of symptoms is attributed to the length of the penetrant tubules, which allow the toxins from the venom to enter directly into pierced capillaries.[17] Irukandji syndrome typically presents with causes delayed symptoms compared with those caused by multitentacled box jellyfish stings, that is, the victim is often out of the water by the time they recognize they have been stung by a four-tentacled box jellyfish compared with those stung by multitentacled box jellyfish who develop symptoms immediately. Local symptoms are typically mild stinging pain at the affected site within seconds with later papular erythematous skin lesions, approximately 2 cm in diameter.[16] The recent publications on "Irukandji-like" cases from Thailand reported clinical presentations that are quite different from

those of Irukandji-like syndrome reported in Australia.[18] Most of the clinical manifestations in this report were not consistent with those of Irukandji-like syndrome and may represent a new syndrome of jellyfish envenoming, quite possibly distinct from Irukandji.

The skin lesion in our patient appears to be similar to one of the cases previously described as "Irukandji-like" syndrome in Thailand.[18] Recent cases consulted to RECS have also observed similar skin lesions with confirmation of nematocyst sampling pointing to *Chrysaora* spp sting. The skin lesion from a large-sized *Morbakka* spp sting may also appear similar to that in the case presented. This is most likely due to the broad ribbon-like tentacles of these species rather than the thin, vermicelli-like tentacles of smaller-sized four-tentacled box jellyfish species. There was immediate onset of extensive pain over a large area of the presumed tentacle contact, with delayed manifestation of abdominal cramps and generalized body aches. These presentations are not strictly consistent with "Irukandji-like" syndrome. Instead, they may represent a new type of jellyfish envenomation, perhaps closer to a multitentacled box jellyfish (*Chironex* spp) envenomation, but possibly distinct from that as well. The later systemic features including the cardiac features would fit just as well as a slightly atypical box jellyfish envenomation. It is important to acknowledge the difference between classical Irukandji syndrome and clinical presentation mimics possibly from other jellyfish species that should not have been labeled as "Irukandji-like."[9,10,18] The patient's clinical course was not consistent with the classic interpretation of Irukandji syndrome. Besides experiencing immediate pain and having significant skin markings, the described clinical evolution does contain some elements consistent with mild-to-moderate manifestation of Irukandji syndrome, such as dyspnea, hypertension, abdominal cramps, severe myalgia, and other uncommon effects that may be associated with catecholamine storm.[19,20] Anxiety following the sting incident may also contribute to the confusion.

ECG changes and elevated cardiac marker levels have been reported in box jellyfish envenomation.[21-24] To date, no WPW changes on ECG have been documented in cases of jellyfish sting envenomation. The WPW feature in our patient appears to have persisted and therefore might have been pre-existing. This feature is not consistent with the West African repolarization variant and is most likely not related to the jellyfish sting envenomation. However, the chest discomfort may have been triggered from catecholamine surge, causing coronary vasospasm. Therefore, such an abnormality incidentally discovered following a jellyfish sting should be documented and closely monitored.

Treatment for jellyfish sting is mainly supportive, and to date, no specific antivenom is available except that for *C fleckeri*. Therefore, preventive measures are the best option, and these include avoidance or minimization of contact, especially during the jellyfish season.[12] Full-body Lycra stinger suits or the equivalent have been shown to provide adequate protection from stings.[25,26] Topical sting inhibitors and thick layers of petroleum-based ointments may help in minimizing sting frequency and severity.

Initial first aid should consist of removing the victim from the water in order to prevent further contact with jellyfish tentacles and risk of drowning. The intention of first aid for jellyfish sting is to decrease venom exposure as soon as possible and provide a reasonable measure of pain relief prior to arrival at a medical facility. Household vinegar (containing acetic acid 5%) is traditionally recommended to deactivate nematocysts prior to removal of remaining tentacles on the skin. However, this long recommended first aid has recently become controversial because of an in vitro finding of the effect on nematocyst discharge upon contact with vinegar.[27] Different species of harmful jellyfish are present in Penang waters, and therefore, vinegar alone may not be appropriate for first aid.[28-31] Seawater is recommended as a rinsing agent, and lidocaine spray has been shown to relieve pain as well as prevent nematocyst discharge.[28] First responders and prehospital care providers should be aware of recommended first aid measures for stings by the locally relevant jellyfish species.[31] The use of heat has been shown to relieve pain; however, the availability on site could limit its use. Cold compression for noncubozoan sting has been shown to have a similar analgesic effect as heat application, and it is likely more readily available and accessible at the beach.[32]

Public awareness of the appropriate preventive methods against jellyfish sting and health-seeking behavior needs to be encouraged in Malaysia. Healthcare providers in Malaysia need to be aware of harmful jellyfish sting envenomation management. Careful identification and documentation of clinical effects in comparison with reported syndromes can provide helpful guidance for ultimately determining optimal clinical management even for unidentified species that cause semi-identifiable envenomation. An interagency collaboration on jellyfish surveillance and related injuries could enhance policies and guidelines on local management and train emergency response teams in high-risk areas.

Acknowledgments: The authors thank Professor Colin Robertson (Edinburgh) and Mr Idwal Jones (Hamburg) for reviewing this article.

Author Contributions: conceptualization (AKI); validation (NKS, GA, SMJ, MMH, AKI); resources (NKS, AKI); writing − original draft (NKS, AKI); writing − review and editing (NKS, GA, SMJ, MMH, AKI); visualization (NKS, AKI); supervision (SMJ, AKI). All authors approved the final manuscript.

Financial/Material Support: None.

Disclosures: None.

References

1. Tan ATS, Peng CTC, Nilamani N, Yasin Z. Harmful Jellyfish Country Report in Western Pacific. *Penang*. Malaysia: Universiti Sains Malaysia, Centre for Marine and Coastal Studies; 2019.
2. Barnes JH. Cause and effect in Irukandji stingings. *Med J Aust*. 1964;1:897−904.
3. Little M, Pereira P, Carrette T, Seymour J. Jellyfish responsible for Irukandji syndrome. *QJM*. 2006;99(6):425−7.
4. Low LB. *Characterisation of Selected Scyphozoan Jellyfish Species and Geometric Morphometric Analysis of Chrysaora chinensis in Peninsular Malaysia. Kuala Lumpur*, Malaysia: University of Malaya; 2017.
5. Rizman-Idid M, Farrah-Azwa AB, Chong VC. Preliminary taxonomic survey and molecular documentation of jellyfish species (Cnidaria: Scyphozoa and Cubozoa) in Malaysia. *Zool Stud*. 2016;55:e35.
6. Sim Y. *The monthly distribution and abundance of Jellyfish (Medusae) species in the coastal waters of Penang National Park, Penang, Malaysia*. Technical Report. Langkawi, Malaysia: Universiti Sains Malaysia; 2012.
7. Chuan CH, Venmathi Maran BA, Yap TK, Cheong KC, Syed Hussein MA, Saleh E. New records of cubozoan and scyphozoan jellyfish from Sabah Waters, Malaysia. *Diversity*. 2021;13(9):420.
8. Lippmann JM, Fenner PJ, Winkel K, Gershwin LA. Fatal and severe box jellyfish stings, including Irukandji stings, in Malaysia, 2000−2010. *J Travel Med*. 2011;18(4):275−81.
9. Mohd Suan MA, Tan WL, Soelar SA, Cheng HP, Osman M. Jellyfish stings on Langkawi Island, Malaysia. *Med J Malaysia*. 2016;71(4):161−5.
10. Mubarak AI, Wan Mohd, Shukri WNA, Ismail AK. Estimation of local incidence of jellyfish envenomation in developed marine coastal areas and large populated island on the western coast of Peninsular Malaysia using case surveillance of government health facilities in Manjung, Perak and Langkawi Island. *Int Marit Health*. 2021;72(2):93−8.
11. Burnett JW, Burnett J, Rifkin JF. *Venomous and Poisonous Marine Animals: a Medical and Biological Handbook*. Sydney, Australia: University of New South Wales Press; 1996.
12. Verdadero FXD, Licuanan WY, Ang JL, de los Santos Jr B, Metillo EB. Harmful jellyfishes are manageable. *Philipp J Fisheries*. 2022;29(2):2021−32.
13. Gershwin LA. *Morbakka fenneri*, a new genus and species of Irukandji jellyfish (Cnidaria: Cubozoa). *Mem Qld Museum*. 2008;54(1):23−33.
14. Tibballs J, Li R, Tibballs HA, Gershwin LA, Winkel KD. Australian carybdeid jellyfish causing "Irukandji syndrome". *Toxicon*. 2012;59(6):617−25.
15. Pereira P, Barry J, Corkeron M, Keir P, Little M, Seymour J. Intracerebral hemorrhage and death after envenoming by the jellyfish *Carukia barnesi*. *Clin Toxicol (Phila)*. 2010;48(4):390−2.
16. Carrette TJ, Underwood AH, Seymour JE. Irukandji syndrome: a widely misunderstood and poorly researched tropical marine envenoming. *Diving Hyperb Med*. 2012;42(4):214−23.
17. Rifkin J, Endean R. The structure and function of the nematocysts of *Chironex fleckeri* Southcott, 1956. *Cell Tissue Res*. 1983;233(3):563−77.
18. Thaikruea L. Irukandji-like syndrome caused by single-tentacle box jellyfish found in Thailand, 2007−2019. *Int Marit Health*. 2020;71(2):91−6.
19. Fenner P, Carney I. The Irukandji syndrome. A devastating syndrome caused by a north Australian jellyfish. *Aust Fam Physician*. 1999;28(11):1131−7.
20. Fenner PJ, Hadok JC. Fatal envenomation by jellyfish causing Irukandji syndrome. *Med J Aust*. 2002;177(7):362−3.
21. Huynh TT, Seymour J, Pereira P, Cullen P, Seymour J, Carrette T, et al. Severity of Irukandji syndrome and nematocyst identification from skin scrapings. *Med J Aust*. 2003;178(1):38−41.
22. Little M, Pereira P, Mulcahy R, Cullen P, Carrette T, Seymour J. Severe cardiac failure associated with presumed jellyfish sting. Irukandji syndrome? *Anaesth Intensive Care*. 2003;31(6):642−7.
23. Nickson CP, Waugh EB, Jacups SP, Currie BJ. Irukandji syndrome case series from Australia's Tropical Northern Territory. *Ann Emerg Med*. 2009;54(3):395−403.
24. Little M, Pereira P, Seymour J. Differences in cardiac effects of venoms from tentacles and the bell of live *Carukia barnesi*: using non-invasive pulse wave Doppler. *Toxins*. 2020;13(1):19.
25. Gershwin L. Jellyfish responsible for Irukandji syndrome. *QJM*. 2006;99(11):801−2; author reply 803.
26. Tibballs J. Australian venomous jellyfish, envenomation syndromes, toxins and therapy. *Toxicon*. 2006;48(7):830−59.
27. Welfare P, Little M, Pereira P, Seymour J. An in-vitro examination of the effect of vinegar on discharged nematocysts of *Chironex fleckeri*. *Diving Hyperb Med*. 2014;44(1):30−4.
28. Birsa LM, Verity PG, Lee RF. Evaluation of the effects of various chemicals on discharge of and pain caused by jellyfish nematocysts. *Comp Biochem Physiol C Toxicol Pharmacol*. 2010;151(4):426−30.
29. Pyo MJ, Lee H, Bae SK, et al. Modulation of jellyfish nematocyst discharges and management of human skin stings in *Nemopilema nomurai* and *Carybdea mora*. *Toxicon*. 2016;109:26−32.
30. Wilcox CL, et al. Assessing the efficacy of first-aid measures in *Physalia* sp. envenomation using solution- and blood agarose-based models. *Toxins*. 2017;9(5):149.
31. Tan ATS, Ismail AK, Miyake H. GeneralManagementGuide for Harmful Jellyfish Stings in the Western Pacific and Adjacent Areas. *Penang*. Kuala Lumpur, Malaysia: Malaysia Society on Toxinology; 2019.
32. Haddad Jr V, da Silveira FL, Cardoso JL, Morandini AC. A report of 49 cases of cnidarian envenoming from southeastern Brazilian coastal waters. *Toxicon*. 2002;40(10):1445−50.

WILDERNESS & ENVIRONMENTAL MEDICINE 2023; 34(2): 243–52

LESSONS FROM HISTORY

One Cool Guy: Scientific Contributions of John Hayward, Cold Water Pioneer

Curtis Leclerc, MSc[1]; Gordon G. Giesbrecht, PhD[1,2]

[1]*Faculty of Kinesiology and Recreation Management, University of Manitoba, Winnipeg, Manitoba, Canada;* [2]*Faculty of Medicine, Departments of Anesthesia and Emergency Medicine, University of Manitoba, Winnipeg, Manitoba, Canada*

John Hayward, PhD (1937–2012), was an early and significant contributor to the understanding of cold water immersion physiology and survival. This article summarizes his work on the 50th anniversary of his first publication in this area. He described areas of high heat loss and emphasized the importance of protecting these areas during cold exposure using the Heat Escape Lessening Posture (HELP) and the potential for heat donation to these areas during rewarming. He described several factors that affect the rate of core cooling, including body composition, behavior (swimming increases cooling whereas the HELP position decreases cooling), wet and wind, and thermal protective garments (dry suits offered much more protection than wet suits). Hayward determined breath-hold duration in children as young as 4 y and had his own heart catheterized for 3 d to complete 3 hypothermia rewarming trials. His work provided early understanding of the cold shock response and ways to mitigate its threat to survival. Hayward provided valuable contributions to prediction models for heat production, heat loss, and core cooling rates in cold water. He also developed a human model for severe hypothermia and patented the UVic Thermofloat Jacket. Finally, as evidence of his stature in the cold physiology community, Hayward was a coauthor of the initial State of Alaska guidelines for the treatment of hypothermia. John Hayward was truly a cold water pioneer.

Keywords: hypothermia, rewarming, cold shock response, survival prediction, thermal protection garments

Introduction

In 1975, the University of Victoria (Canada) published a brochure, *Man in Cold-Water* (Figure 1), highlighting the recent work of one of its new professors of biology, John Hayward, PhD. The brochure addressed several cold water–related topics, such as: 1) human studies on physiology and physics of heat loss; the effects of behavior, thermal protection, and alcohol on heat loss; and early references to the cold shock response; and 2) mathematical prediction of shivering heat production and core cooling in cold water. Importantly, the brochure introduced the UVic Thermofloat Jacket, a patented design that was at the forefront of thermoprotective garments for cold water survival. This brochure was significant for 3 reasons: 1) Hayward had only started studying human cold exposure since arriving at the University of Victoria in 1969; 2) most of the topics came from 3 articles published in 1973[1] and 1975,[2,3] and the remainder came from soon-to-be-published data or future work; and 3) all but a few conclusions have stood the test of time and still make up the foundation for what is currently taught about cold water immersion half a century later. We are unaware of any attempt to summarize the scientific contributions of this trailblazer in cold water safety and survival.

John Stanley Hayward, PhD (1937–2012), initially published 20 articles on temperature regulation in animals in the 1960s. He then started his innovative work on human responses to extreme environmental conditions in the 1970s. Hayward's research program followed a

Corresponding author: Gordon G Giesbrecht, PhD; Faculty of Kinesiology and Recreation Management, University of Manitoba, Winnipeg, Manitoba, Canada; e-mail: gordon.giesbrecht@umanitoba.ca.

Submitted for publication October 2022.
Accepted for publication April 2023.

https://doi.org/10.1016/j.wem.2023.04.001

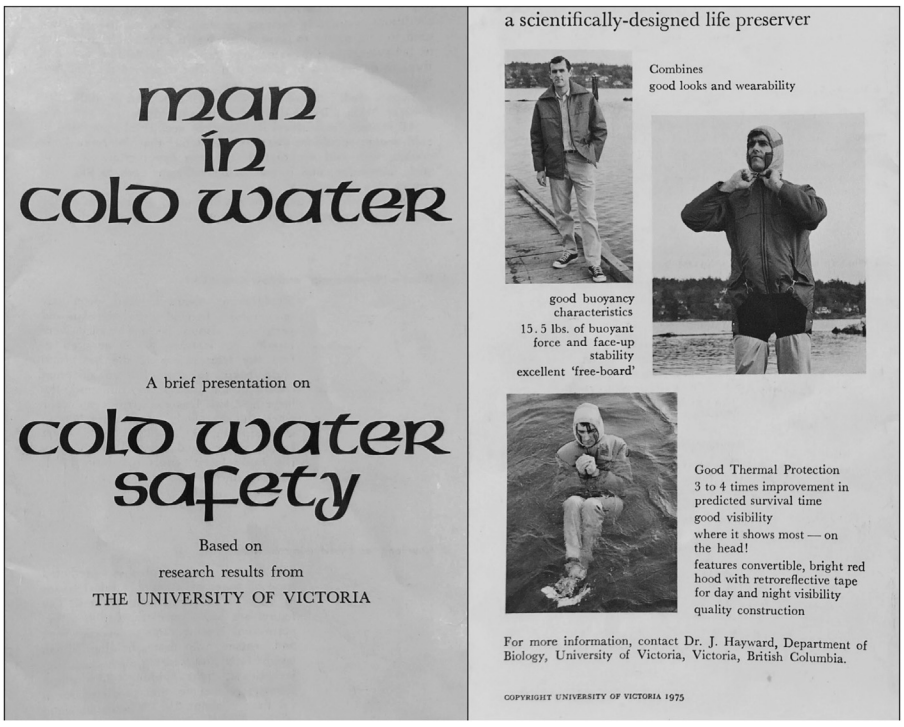

Figure 1. Cover pages of brochure "Man in Cold Water," published by the University of Victoria in 1975.

logical progression from describing long-term and acute responses to cold water immersion, to determining factors affecting core cooling rates in cold water, to treating cold individuals, and finally to contributing to guidelines for handling cold patients in prehospital scenarios. Following his retirement in 1992, he continued to inspire research and to publish articles (see Table 1 for brief summaries of all related articles).[1-23]

Long-term Responses to Cold Water Immersion

The year 2023 is the 50th anniversary of Hayward's first publication involving human subjects[1] (on 4 males and 1 female, including the authors), which provided valuable infrared thermography to illustrate the regional differences in skin temperature, and therefore heat loss, after being still or swimming in cold water (Figure 2). These thermographs revealed areas of highest heat loss in the axillae, groin, and neck where large blood and lymph vessels pass close to the skin. This article provided early indications that heat loss increases considerably during muscular exercise, such as swimming, compared with being still (Figure 2, panel c vs panel b).[1] The results were also valuable in recognizing that areas of high heat loss could also be targeted for heat donation to the core during rewarming. This information also influenced future work on the design of the UVic Thermofloat Jacket (see Figure 1).

Hayward's group demonstrated that core temperature (T_{co}) increased for the first 10 to 20 min of cold water immersion before starting to decrease.[4] They also demonstrated an initial spike in metabolism upon immersion followed by a gradual increase until a plateau was reached. This study also developed a prediction equation for shivering heat production, which had an inverse linear relationship with T_{co}. This relationship described a linear "gain" to the response. This and other studies provided early parameters for thermoregulatory responses, which include threshold for response onset, response gain, and the maximum response (these terms also apply to sweating and vasomotion).

Hayward also studied the effect of hypothermia on brain electrical activity.[5] The study determined that brain electrical activity begins to significantly decline only at or below a T_{co} of 33.5°C. This is useful in understanding the cognitive impairments of patients experiencing mild hypothermia (T_{co}, 32–35°C).

One of Hayward's more creative works was his research on wet-wind-cold exposure.[6] He built a 25-m "Wet Walk" track on his own property. The track was sheltered by a weather-protective cover that simulated

Table 1. Summaries of cold–related human studies by Hayward and colleagues grouped in topic areas.

Ref	*Y*	*Brief summary*
Physiologic responses to cold		
[1]	1973	Infrared thermography was used to determine regional heat loss while being still or swimming in cold water.
[4]	1977	Demonstrated core temperature and metabolic responses to CWI and developed prediction equation for shivering intensity.
[20]	1977	Determined relationship between skin temperature and sympathetic activity.
[21]	1980	Alcohol increases urine flow rate by almost 7-fold during CWI.
[10]	1979	Alcohol decreases metabolic heat production while holding still in cold water but not during exercise.
[22]	1987	Hypothermia decreases the values of the breath-alcohol decay curve below the blood-alcohol decay curve by ~7%/°C below normal T_{co}.
[23]	1989	Hyperthermia increases the values of the breath-alcohol decay curve above the blood-alcohol decay curve by ~9%/°C above normal T_{co}.
[5]	1984	Brain electrical activity does not decline until T_{co} decreases below 33.5°C.
[6]	1996	During walking in windy cold air, rain increases heat loss and shivering and decreases exercise endurance.
[7]	1997	Pharmacological inhibition of shivering increases T_{co} afterdrop amount and duration.
Dive and cold shock responses		
[8]	1984	BHD decreases with water temperature (attributed to the cold shock response), but cardiovascular responses are unaffected. Habituation to CWI increases BHD.
[9]	1987	BHD decreases with age in children but not adults. The magnitude of diving bradycardia was similar in children and adults.
[19]	1989	Two-staged entry attenuates the hyperventilation response to CWI. See Figure 4b.
Factors affecting core cooling		
[2]	1975	Swimming in cold water increases heat production and core cooling rate.
[3]	1975	During CWI, the HELP and Huddle increase survival time compared with drownproofing and treading water.
[10]	1979	Alcohol does not affect core cooling rate or afterdrop during CWI.
[11]	1984	Core cooling rate is inversely correlated to skinfold thickness but not affected by sex.
[12]	1984	Survival suits can increase survival time during CWI from hours to days.
[13]	1987	Dry suits are superior to wet suits during CWI in both calm and rough water.
Thermophysiological predictions		
[2,3]	1975	Core cooling rate, heat loss, and survival time were predicted based on T_{water}.
[4]	1977	T_{co} and T_{sk} were used to predict metabolic heat production.
[14]	1980	Core rewarming rate was predicted based on height, weight end-cooling T_{co} and T_{sk}.
[11]	1984	Survival time prediction was based on assumptions of linear cooling rates below experimental T_{co}, and "incipient death" occurring at T_{co} of 30°C.
Rewarming effectiveness		
[15]	1975	Inhalation warming may be a safe and effective warming treatment.
[16]	1979	Hyperventilation resulting from partially rebreathing expired air increases effectiveness of inhalation warming.
[17]	1984	Swan-Ganz catheterization of right pulmonary artery was used to demonstrate that esophageal temperature accurately measures heart temperature and that warm bath immersion decreases mean arterial pressure and increases heart rate and cardiac output compared with control and inhalation warming.
Miscellaneous		
[18]	2006	Description of outcomes of a rowing crew after capsizing in cold water.

CWI, cold water immersion; BHD, breath-hold duration; HELP, Heat Escape Lessening Posture; T_{co}, core temperature; T_{water}, water temperature; T_{sk}, skin temperature.

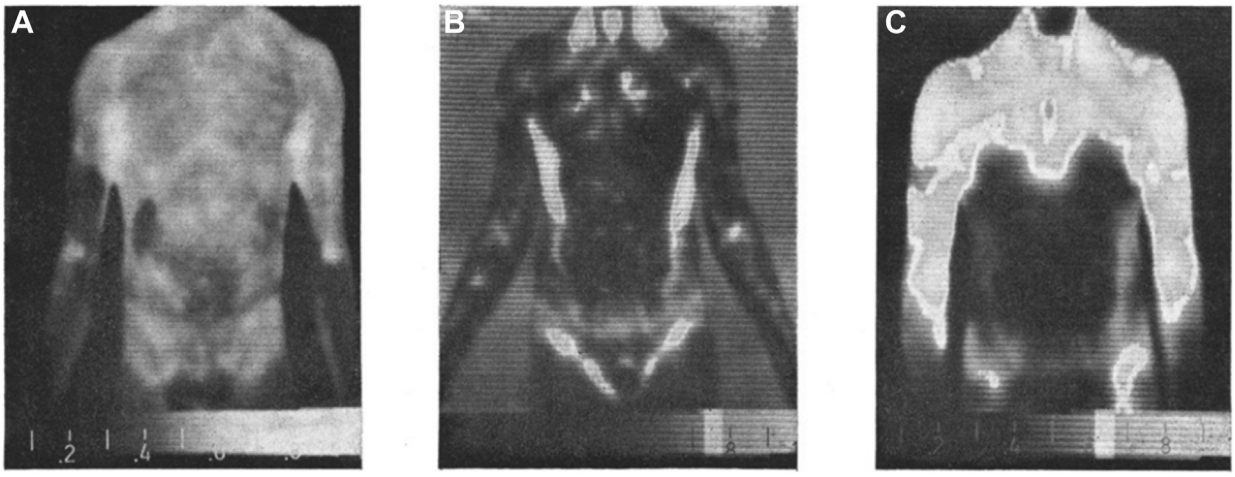

Figure 2. Infrared thermographs illustrating temperature distribution of the front of a male subject before immersion in 7.5°C water (a), after holding still in the water for 15 min (b), and after swimming for 15 min (c).[1]

adverse conditions with a rain-generating sprinkler system and large fans. The participants attempted to walk in this track at 5°C for 5 h. After 1 h, either wind (control) or wind and rain were turned on. All 16 subjects completed the "no rain" trials, but only 5 could complete the "rain" trials. Results showed that wetness caused an increased metabolic rate (due to shivering) and a drop in core temperature (Figure 3a).[6] The breadth of human variability was also demonstrated, as some subjects reached the cutoff core temperature of 35°C in as little as 2.5 h (Figure 3b).[6]

Hayward realized that human cooling studies had a confounding factor of intense shivering. This background heat production prevented the quantification of isolated effects of any source of heat donation on rewarming. As a result, a human model for severe hypothermia was created by pharmacologically inhibiting shivering with meperidine in hypothermic patients.[7] Shivering inhibition

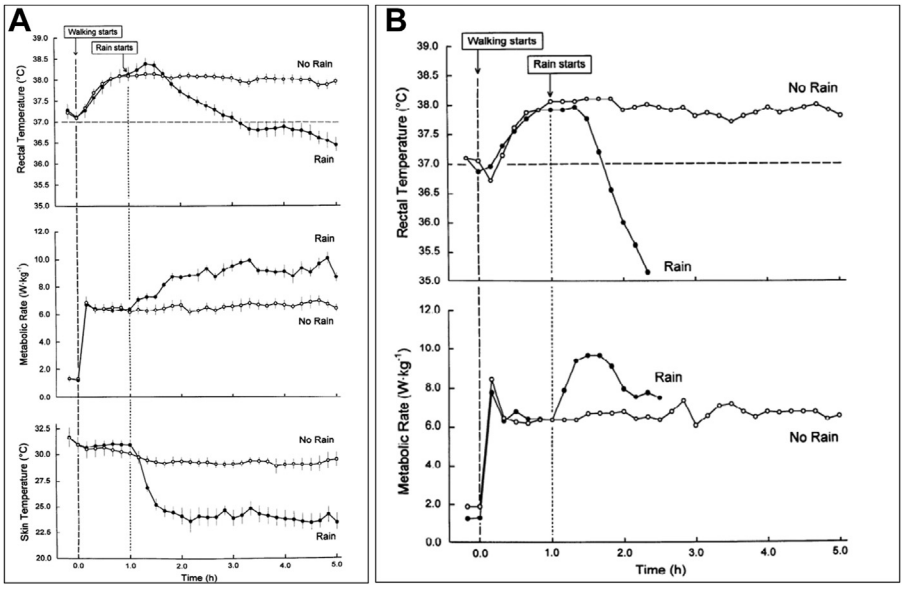

Figure 3. Wet walk. (a) Thermal and metabolic responses of 5 male subjects to wetting by rain while walking at 5.1 km/h in 5°C air (bars, SE). (b) Individual responses for ectomorphic subject experiencing rapid cooling in rain condition.[6]

resulted in a 3.2-fold increase in core temperature afterdrop and a 4.2-fold increase in duration. These results illustrate the importance of shivering heat production in attenuating postcooling afterdrop, and they laid a groundwork for future research to test methods of rewarming in the absence of shivering.

Acute Responses to Cold Water Immersion—Dive and Cold Shock Responses

In the 1980s, Hayward extended his research to the effect of cold water on the dive and cold shock responses. In 1984, Hayward studied the effect of cold water on the human dive response, which includes breath holding, bradycardia, and redistributing blood flow to the brain.[8] It was previously believed that the dive response improved the survivability of cold water drowning victims because it redistributed a limited oxygen supply to the brain, an effect that increased as water temperature decreased. Children seemed to have increased survivability in cold water drownings, and it was believed this was because of their superior dive response.

On the contrary, Hayward's research showed that breath-hold duration decreased as water temperature decreased from 35 to 0°C (Figure 4a)[8,19]; this is now attributed to the cold shock response, which includes gasping followed by hyperventilation. He reasoned that reduced breath-hold duration experienced in cold water likely contributed to drowning through the forced inhalation of water. His research also contradicted previous interpretations that the cardiovascular alterations of the dive response are temperature dependent. He found no difference in heart rate during diving bradycardia in water from 35 to 0°C and concluded that decreased breath-hold duration was a major contribution to cold water drowning. Hayward subsequently concluded that the survivability of cold water drowning victims was dependent on the degree of hypothermia rather than the effectiveness of the dive response. Thus, the advantage of children in cold water drowning was their small body mass, larger surface area-to-mass ratio, and resultant increased core cooling rate.

In 1987, Hayward went on to compare responses to breath holding in 29°C water between children (4–13 y) and adults (20–70 y).[9] Breath-hold duration decreased with age in the children but not the adults (Figure 5),[9] and the magnitude of diving bradycardia was similar (~37%) in children and adults. To our knowledge, this study was the first to show objectively that the dive response was not the major factor in improved resuscitation outcomes for children after cold water drowning. Once again, Hayward suggested that increased cooling rates of children (due to their smaller size) explained their improved outcomes because greater brain cooling provided protection under anoxic conditions of drowning.

Factors Affecting Core Cooling

Hayward's earliest cooling trials were conducted on males and females in the ocean waters off the coast of Vancouver Island. The first study compared holding still and swimming in 4.6 to 18.2°C water.[2] Although swimming increased metabolic heat production to 250% of resting levels, the core cooling rate increased by 35% compared with holding still. As part of the planned efforts to create prediction equations, Hayward's group determined that when holding still, metabolic heat production was inversely related to water temperature, and the response was similar to the response to the same air temperature in a low wind condition (2.24 m/s).

The second ocean study compared thermal responses with various behaviors in 9 to 10°C water[3]; the drawings of these behaviors have been commonly reproduced in related literature throughout the years (Figure 6). Drownproofing and treading water without a personal flotation device (PFD) increased the core cooling rate by 82% and 34%, respectively. Conversely, the Heat Escape Lessening Posture (HELP), which reduces heat loss through high heat loss areas in the axillae and groin),[1] and huddling with 2 other subjects decreased the core cooling rate by 31% and 34%, respectively. These results supported the advice that any swimming in cold water should only be attempted if a PFD is worn.

Hayward's group demonstrated that a blood-alcohol concentration of 82 mb/100 mL decreased heat production in 10°C water by 13%, but this did not affect the core cooling rate, afterdrop, or the core temperature increase during rewarming.[10] They attributed the deleterious effects of alcohol to dangerous behavior rather than to thermoregulatory effects.

Finally, when men and women were immersed in 0°C water, the core cooling rate was negatively correlated to skinfold thickness and endomorphy.[11] However, there was no effect of sex on core cooling rate or metabolic heat production. Part of the explanation for similar cooling rates for the smaller, lighter females was their greater percentage of body fat (20.3% vs 11.5%).

In 1984, Hayward returned to the ocean to study the thermal protection of 5 dry and insulating survival suits during 6 h of immersion in 1°C water.[12] He demonstrated the significant impact that dry and insulating survival suits can have in cold water. Although it is predicted that those without survival suits may only survive approximately 1 to 1.5 h in 1°C water, this study used the overall

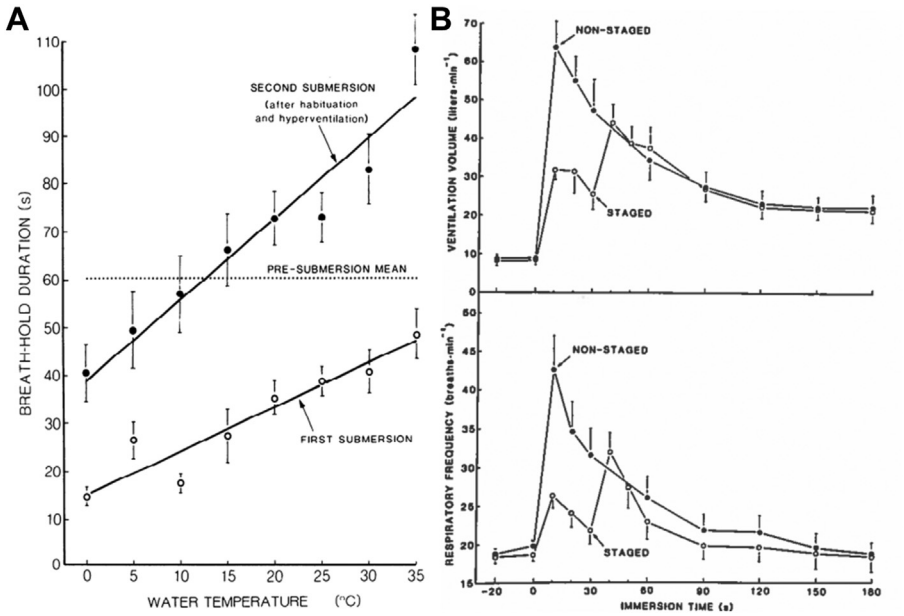

Figure 4. (a) Effect of water temperature on maximum breath-hold duration of humans after a first submersion and then after a second submersion after habituation with 2 min of immersion and 10 s of hyperventilation.[8] (b) Comparison of initial respiratory response to cold water immersion (15°C) to when entry is staged (lower body first immersed for 30 s).[19]

cooling rate of 0.13°C/h and assumed a lethal T_{co} of 27°C to predict that those wearing dry and insulative survival suits might survive up to 78 h.

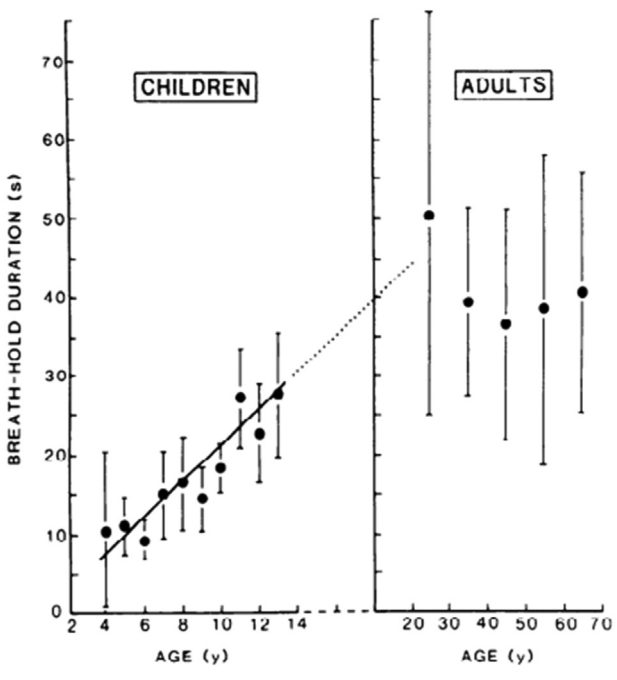

Figure 5. Effect of age on maximum breath-hold duration of children and adults during submersion in 29°C water.[9]

In 1987, in one of his works that had the greatest impact, Hayward collaborated with the US Coast Guard in the first study to determine the impact of rough seas (1–2 m waves with occasional 1.5-m breaks) on the effectiveness of antiexposure suits during immersion in 11°C water for 90 min.[13] Each subject wore each of the garment ensembles, which included 1 uninsulated flight suit (control), 3 loose-fitting wet suit garments, 2 tight-fitting wet suits, and 2 insulated dry suits (Figure 7).[13] Rough seas only increased cooling rates with the 3 loose-fitting wet suits because of increased flushing of water through them. The study confirmed that dry suits were superior in both calm and rough sea conditions and would be preferred for those at risk of accidental cold water immersion.

Hayward regularly used data from his studies to create predictive equations for cooling and rewarming. Early on, he and his colleagues developed equations to predict core cooling rate, heat loss, and survival time using the single variable of water temperature.[2,3] They later used core and skin temperatures to predict metabolic heat production.[4] This group even predicted rewarming rates based on end-cooling core and skin temperature as well as body anthropometry, such as $(\text{height/weight})^{0.5}$.[14] A final contribution to modeling came from Hayward's most severe test involving up to 40 min immersion in stirred 0°C water.[11] Final calculations predicted that in 0°C water, it would take 1 to 1.5 h for the average person to reach a T_{co} of 30°C.

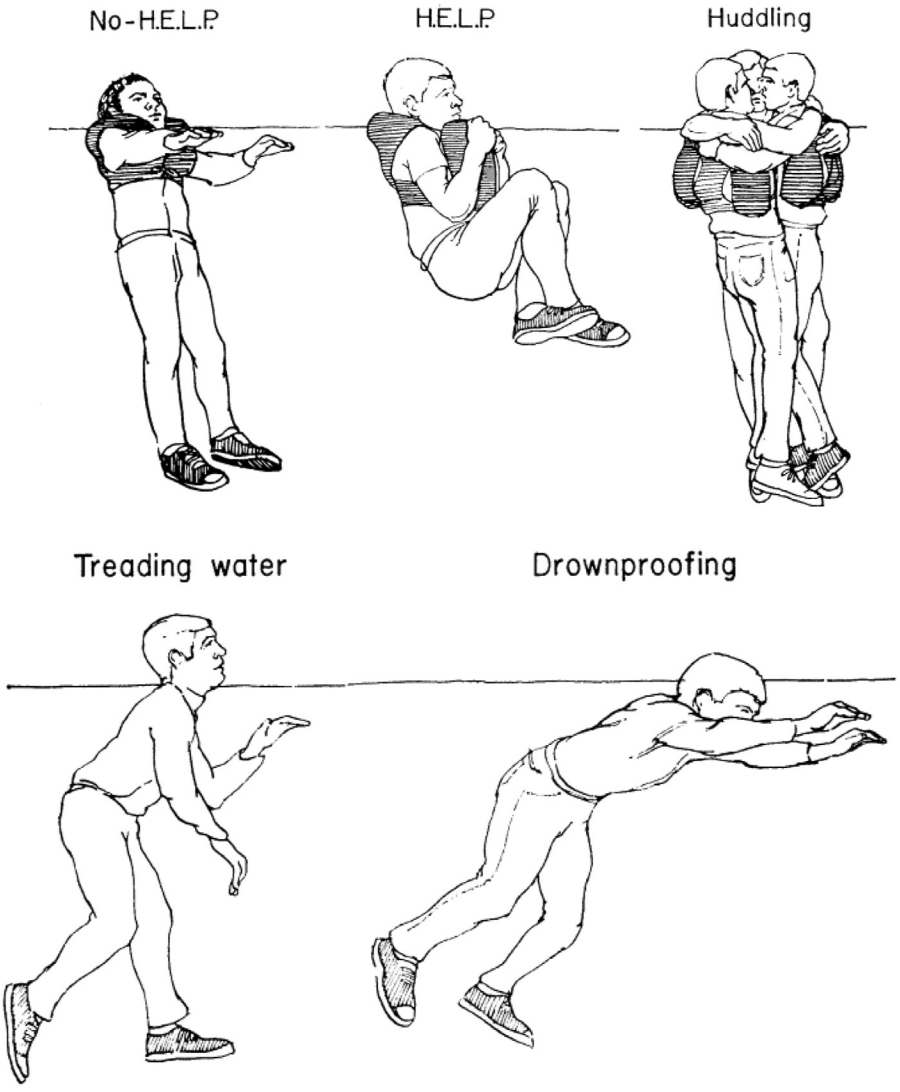

Figure 6. Behavior variables while holding still (a) and while moving (b).[3] HELP, Heat Escape Lessening Posture.

Rewarming Effectiveness

Hayward conducted several studies on the effectiveness of inhalation warming (saturated 45°C air) and warm bath immersion (rapidly warmed from about 30 to 41°C). He felt that inhalation warming could reduce the risk of physiological dangers associated with peripheral vasodilation from external rewarming. In 1975, his first study found no differences in core rewarming rates between inhalation and warm water warming.[15] However, he reasoned that inhalation rewarming was superior for its ability to oxygenate the blood and directly warm the lower brain stem to reverse the cold-induced depression of respiratory and thermoregulatory control centers. Hayward then tried to enhance inhalation warming by having subjects partially rebreathe expired air, increasing minute ventilation to 50 L/min. This technique increased core rewarming by 77% from 1.21 to 2.15°C/h.[16]

In his final landmark work on rewarming hypothermic victims, Hayward studied the cardiovascular changes experienced during 3 methods of rewarming.[17] In 1984, Hayward was the lone subject and had a Swan-Ganz catheter inserted into his right pulmonary artery for 3 d. After 3 successive immersions for 100 min in 10°C water, cardiovascular changes were determined during spontaneous warming (no external heat source), inhalation warming, and warm bath immersion. Results confirmed esophageal temperature as an accurate measure of core (heart) temperature (Figure 8a).[17] The study also identified important cardiovascular changes during each

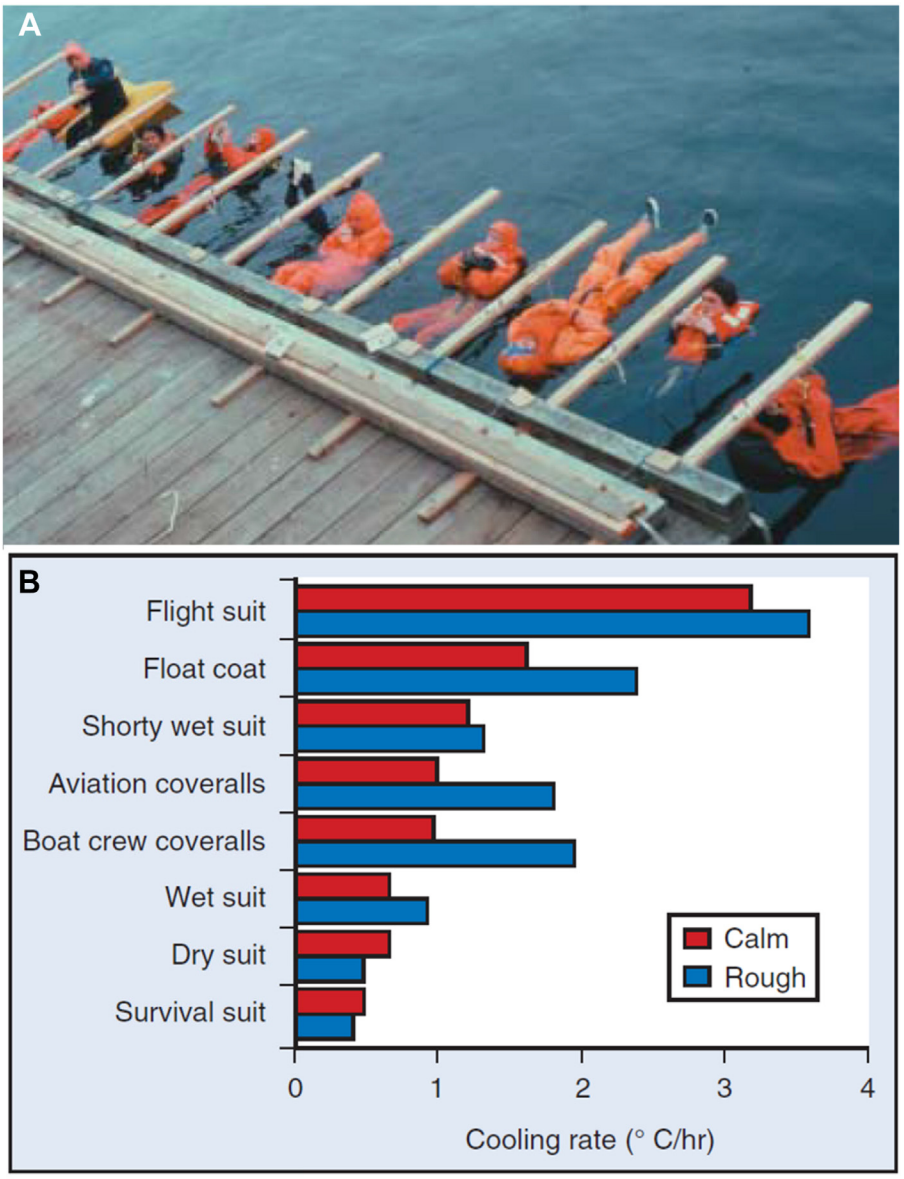

Figure 7. (a) Survival suit testing in the ocean (Photo courtesy of University of Victoria). (b) Comparative core cooling rates for 8 cold protective ensembles in calm and rough water (11°C).[13]

of the rewarming techniques, such as a large drop in mean arterial pressure and an increase in heart rate and cardiac output due to peripheral vasodilation in the warm bath (Figure 8b).[17] This resulted in an afterdrop with the warm bath but not with spontaneous and inhalation rewarming. These results confirmed recommendations for rescuers to avoid warm bath immersion.

Hayward patented several inventions, but only 1 has stood the test of time. After his early work in the 1970s on heat loss during cold water immersion, Hayward designed the UVic Thermofloat (Figure 1) with Mustang Survival in Vancouver. The novel design included a flap (also termed a "beaver tail"), which could be pulled under the groin and snapped into place on the front. The flap covered the high heat loss areas in the groin, decreased flushing of water within the suit by 50%, and doubled the insulation value of the jacket. In this configuration, the Thermofloat Jacket increased predicted survival time of the average person in 10°C water from 2.7 to 9.5 h.

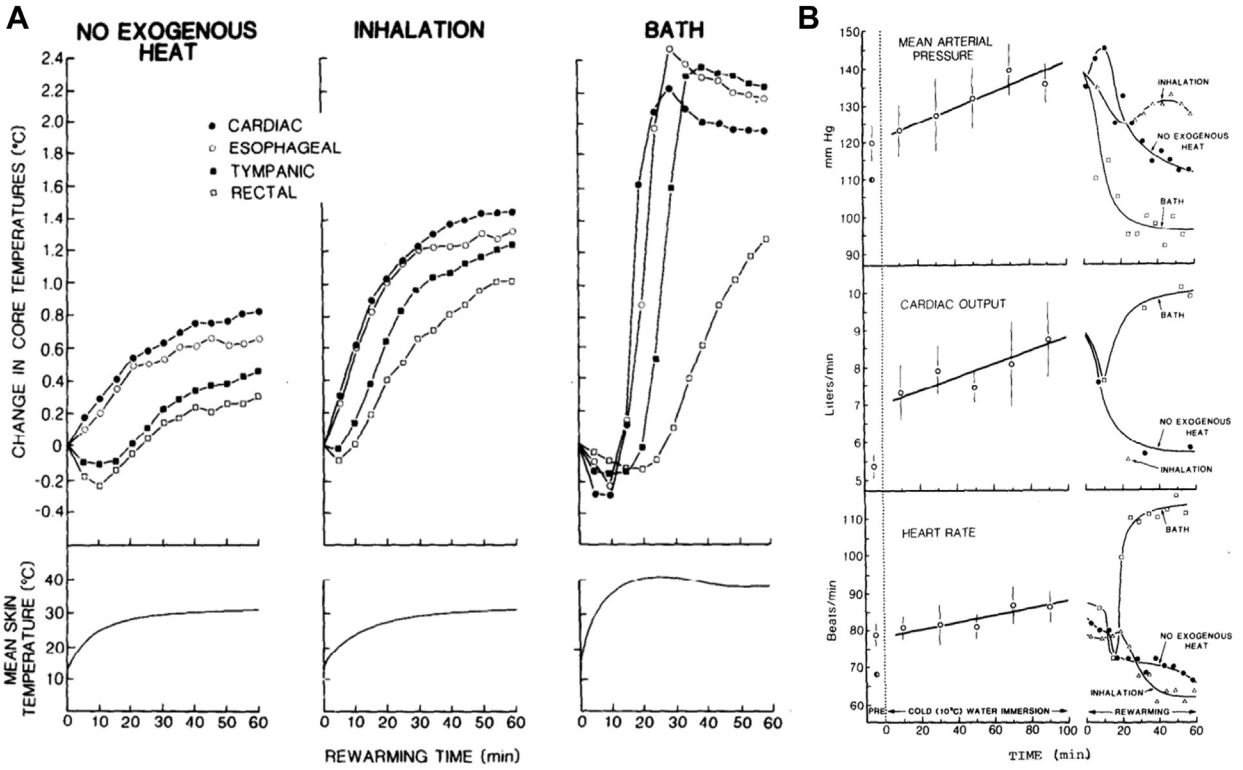

Figure 8. Thermal (a) and cardiovascular (b) responses during cold water immersion and rewarming by 3 procedures.[17]

Conclusion

John Hayward was an early and key contributor to the understanding of cold water immersion physiology and survival. He described the groin and axillae as areas of high heat loss and emphasized the importance of protecting these areas during cold exposure (eg, the HELP position) and the potential for heat donation during rewarming. He determined that the rate of core cooling is inversely proportional to skinfold thickness, is increased by swimming, decreased by assuming the HELP position and wearing thermal protection (dry suits offered much more protection than wet suits), and is not affected by alcohol or sex.

Hayward conducted some studies that might not be repeatable today. For example, he determined breath-hold duration in children as young as 4 y and had his own heart catheterized for 3 d to complete 3 hypothermia rewarming trials. It is important to note that these studies received ethical approval and, at the time, were not considered controversial and were within normal parameters.

He determined that breath-hold duration decreases with age in children but is not age-dependent in adults and that breath-hold duration can be increased by staged immersion or habituation. This work provided an early understanding of the cold shock response and ways to mitigate its threat to survival. He used Swan-Ganz catheterization of the right pulmonary artery and demonstrated the dangers of warm bath immersion because it decreased mean arterial pressure and increased cardiac output and afterdrop of T_{co}.

Hayward provided valuable contributions to prediction models for heat production, heat loss, and core cooling rates in cold water. He also developed a human model for severe hypothermia and patented the UVic Thermofloat Jacket. Finally, as evidence of his stature in the cold physiology community, Hayward was a coauthor of the initial State of Alaska guidelines for the treatment of hypothermia.[24] John Hayward was truly a cold water pioneer.

References

1. Hayward JS, Collis M, Eckerson JD. Thermographic evaluation of relative heat loss areas of man during cold water immersion. *Aerosp Med*. 1973;44(7):708–11.
2. Hayward JS, Eckerson JD, Collis ML. Thermal balance and survival time prediction of man in cold water. *Can J Physiol Pharmacol*. 1975;53(1):21–32.
3. Hayward JS, Eckerson JD, Collis ML. Effect of behavioral variables on cooling rate of man in cold water. *J Appl Physiol*. 1975;38(6):1073–7.
4. Hayward JS, Eckerson JD, Collis ML. Thermoregulatory heat production in man: prediction equation based on skin and core

temperatures. *J Appl Physiol Respir Environ Exerc Physiol*. 1977;42(3):377–84.
5. FitzGibbon T, Hayward JS, Walker D. EEG and visual evoked potentials of conscious man during moderate hypothermia. *Electronencephalogr Clin Neurophysiol*. 1984;58(1):48–54.
6. Thompson RL, Hayward JS. Wet-cold exposure and hypothermia: thermal and metabolic responses to prolonged exercise in rain. *J Appl Physiol (1985)*. 1996;81(3):1128–37.
7. Giesbrecht GG, Goheen MSL, Johnston CE, Kenny GP, Bristow GK, Hayward JS. Inhibition of shivering increases core temperature afterdrop and attenuates rewarming in hypothermic humans. *J Appl Physiol (1985)*. 1997;83(5):1630–4.
8. Hayward JS, Hay C, Matthews BR, Overweel CH, Radford DD. Temperature effect on the human dive response in relation to cold water near-drowning. *J Appl Physiol Respir Environ Exerc Physiol*. 1984;56(1):202–6.
9. Ramey CA, Ramey DN, Hayward JS. Dive response of children in relation to cold-water near-drowning. *J Appl Physiol (1985)*. 1987;63(2):665–8.
10. Fox GR, Hayward JS, Hobson GN. Effect of alcohol on thermal balance of man in cold water. *Can J Physiol Pharmacol*. 1979;57(8):860–5.
11. Hayward JS, Eckerson JD. Physiological responses and survival time prediction for humans in ice-water. *Aviat Space Environ Med*. 1984;55(3):206–11.
12. Hayward JS. Thermal protection performance of survival suits in ice-water. *Aviat Space Environ Med*. 1984;55(3):212–5.
13. Steinman AM, Hayward JS, Nemiroff MJ, Kubilis PS. Immersion hypothermia: comparative protection of anti-exposure garments in calm versus rough seas. *Aviat Space Environ Med*. 1987;58(6):550–8.
14. Morrison JB, Conn ML, Hayward JS. Accidental hypothermia: the effect of initial body temperatures and physique on the rate of rewarming. *Aviat Space Environ Med*. 1980;51(10):1095–9.
15. Hayward JS, Steinman AM. Accidental hypothermia: an experimental study of inhalation rewarming. *Aviat Space Environ Med*. 1975;46(10):1236–40.
16. Morrison JB, Conn ML, Hayward JS. Thermal increment provided by inhalation rewarming from hypothermia. *J Appl Physiol Respir Environ Exerc Physiol*. 1979;46(6):1061–5.
17. Hayward JS, Eckerson JD, Kemna D. Thermal and cardiovascular changes during three methods of resuscitation from mild hypothermia. *Resuscitation*. 1984;11(1–2):21–33.
18. Giesbrecht GG, Hayward JS. Problems and complications with cold-water rescue. *Wilderness Environ Med*. 2006;17(1):26–30.
19. Hayward JS, French CD. Hyperventilation response to cold water immersion: reduction by staged entry. *Aviat Space Environ Med*. 1989;60(12):1163–5.
20. Johnson DG, Hayward JS, Jacobs TP, Collis ML, Eckerson JD, Williams RH. Plasma norepinephrine responses of man in cold water. *J Appl Physiol Respir Environ Exerc Physiol*. 1977;43(2):216–20.
21. Cupples WA, Fox GR, Hayward JS. Effect of cold water immersion and its combination with alcohol intoxication on urine flow rate of man. *Can J Physiol Pharmacol*. 1980;58(3):319–21.
22. Fox GR, Hayward JS. Effect of hypothermia on breath-alcohol analysis. *J Forensic Sci*. 1987;32(2):320–5.
23. Fox GR, Hayward JS. Effect of hyperthermia on breath-alcohol analysis. *J Forensic Sci*. 1989;34(4):836–41.
24. Samuelson T, Doolittle W, Hayward J, Mills W, Nemiroff M. Hypothermia and cold water near drowning: treatment guidelines. *Alaska Med*. 1982;24(6):106–11.

WILDERNESS & ENVIRONMENTAL MEDICINE 2023; 34(2): 172–81

WILDERNESS MEDICAL SOCIETY CLINICAL PRACTICE GUIDELINES

Prevention and Treatment of Nonfreezing Cold Injuries and Warm Water Immersion Tissue Injuries: Supplement to Wilderness Medical Society Clinical Practice Guidelines for the Prevention and Treatment of Frostbite CME

Ken Zafren, MD[1,2,3]; Sarah Hollis, MBChB, MA, MSc[4]; Eric A. Weiss, MD[2]; Daniel Danzl, MD[5]; Jessie Wilburn, PA-C[6]; Nadia Kimmel, MS, RN, W-EMT[7]; Chris Imray, MD, PhD[8]; Gordon Giesbrecht, PhD[9]; Mike Tipton, PhD[10]

[1]Department of Emergency Medicine, Alaska Native Medical Center, Anchorage, AK; [2]Department of Emergency Medicine, Stanford University Medical Center, Stanford, CA; [3]International Commission for Mountain Emergency Medicine (ICAR MEDCOM), Zürich, Switzerland; [4]Regional Occupational Health Team, Defence Medical Services MOD, Catterick Garrison, UK; [5]Department of Emergency Medicine, University of Louisville School of Medicine, Louisville, KY; [6]Department of Emergency Medicine, Mayo Clinic, Rochester, MN; [7]Desert Mountain Medicine, Wilson, WY; [8]Coventry National Institute for Health Research, Clinical Research Facility, University Hospital Coventry & Warwickshire, NHS Trust, Coventry, UK; [9]Faculty of Kinesiology and Recreation Management and Departments of Emergency Medicine and Anesthesia, University of Manitoba, Winnipeg, Manitoba, Canada; [10]Extreme Environments Laboratory, School of Sport, Health & Exercise Science, University of Portsmouth, Portsmouth, UK

We convened an expert panel to develop evidence-based guidelines for the evaluation, treatment, and prevention of nonfreezing cold injuries (NFCIs; trench foot and immersion foot) and warm water immersion injuries (warm water immersion foot and tropical immersion foot) in prehospital and hospital settings. The panel graded the recommendations based on the quality of supporting evidence and the balance between benefits and risks/burdens according to the criteria published by the American College of Chest Physicians. Treatment is more difficult with NFCIs than with warm water immersion injuries. In contrast to warm water immersion injuries that usually resolve without sequelae, NFCIs may cause prolonged debilitating symptoms, including neuropathic pain and cold sensitivity.

Keywords: trench foot, immersion foot, warm water immersion foot, tropical immersion foot, paddy foot

Introduction

Cold and warm water immersion injuries have afflicted military personnel and civilians for centuries. Nonfreezing cold injury (NFCI) can result from prolonged exposure to cold, often wet, conditions that do not cause freezing of tissue. It is likely that trench foot, immersion foot, and cold immersion injury are types of NFCI. Warm water immersion injuries, including warm water immersion foot (WWIF) and the more severe tropical immersion foot (TIF), differ from NFCIs. Both NFCIs and warm water immersion injuries can be painful, debilitating conditions. Nonfreezing cold injuries can be difficult to manage and may cause prolonged debilitating symptoms, including neuropathic pain and cold sensitivity that may be refractory to treatment. Warm water immersion injuries, once recognized, can be easily treated, resolve completely, and seldom have chronic sequelae.

Corresponding author: Ken Zafren, MD, Department of Emergency Medicine, Stanford University Medical Center, Stanford, CA; e-mail: zafren@stanford.edu.

Accepted for publication February 2023.

https://doi.org/10.1016/j.wem.2023.02.006

Methods

We convened a multidisciplinary expert panel to develop evidence-based clinical guidelines for evaluation,

treatment, and prevention of NFCIs and warm water immersion injuries. We selected panelists based on clinical and research experience. The panelists generated a list of questions to define the most significant areas of interest (see online Supplemental Table 1). We performed a literature search to identify relevant articles using a keyword search of the MEDLINE database. Keywords were nonfreezing cold injury, trench foot, immersion foot, immersion injury, warm water immersion foot, tropical immersion foot, jungle foot, and paddy foot. We also searched manually for additional articles using the reference lists of the articles we identified in the original search. We relied on peer-reviewed randomized controlled trials, observational studies, case series, and case reports to formulate recommendations.

We assessed the level of evidence supporting each diagnostic, therapeutic, and preventive modality. We cited review articles only to provide background information. We did not use conclusions from review articles as bases for recommendations.

We used a consensus approach to develop recommendations. The panel graded each recommendation based on the quality of supporting evidence and the balance between the benefits and risks/burdens according to the criteria of the American College of Chest Physicians (see online Supplemental Table 2).[1]

Definitions

NFCI (TRENCH FOOT OR IMMERSION FOOT)

Nonfreezing cold injuries occur after prolonged exposure of extremities to cold, often wet, conditions, with water temperatures <15°C (59°F). Nonfreezing cold injuries without exposure to wet conditions may be a different condition and likely require exposure to air temperatures significantly <15°C (59°F).[2,3] Feet are the most commonly affected body parts, but any peripheral body parts, especially legs and hands, can also be affected. Nonfreezing cold injury affecting the hand of a diver exposed to water at 6°C has been reported.[4] Dependent body parts, such as the buttocks when sitting and knees when kneeling, may also be injured, most likely from pressure in combination with cold and often wet conditions. Other terms for NFCI, related to the mechanism of exposure, include "sea boot foot" and "bridge foot."[3]

Conditions such as "shelter foot" or "shelter limb"[3] affected people who sat for long periods in cold air-raid shelters in World War II.[5] These conditions were the result of nerve compression and dependent limbs and did not involve moisture. They are different than the injuries we refer to as NFCIs and are beyond the scope of the current guidelines. Also beyond the scope of the current guidelines are other conditions that have sometimes been called NFCIs, including chilblains (pernio) and cold-induced peripheral neuropathies that do not involve exposure to wet conditions.

We consider trench foot and immersion foot to be similar or identical injuries. Immersion foot in sailors is equivalent to trench foot in soldiers. Both injuries exhibit the same progression of stages. In the absence of standard diagnostic criteria, some clinicians believe that NFCIs, with mild or no sequelae, can occur after a few hours of exposure without moisture. There is a paucity of data on these possible injuries. We do not discuss them in the guidelines.

WARM WATER IMMERSION INJURIES

Warm water immersion foot and TIF are transient syndromes caused by prolonged exposure to warm water. Warm water immersion foot presents with white, wrinkled soles of the feet. Tropical immersion foot is more severe than WWIF. Tropical immersion foot presents with symmetrical erythema, swelling, and tenderness of the skin of the ankles and dorsa of the feet. Warm water immersion foot is caused by exposure to water at temperatures of 15 to 32°C (59–90°F) for <3 d.[6] Another term for WWIF is "paddy-field foot."[7] Warm water immersion foot has also been incorrectly called "tropical immersion foot."[8] It resolves in 1 to 3 d if the feet are dried and elevated.[9] Warm water immersion foot can also affect the hands.[10] Tropical immersion foot is caused by exposure to warm water at temperatures of 22 to 32°C (72–90°F) for >3 d.[8] It is also treated by drying and elevation of the feet. Recovery takes from 4 to 12 d. Neither WWIF nor TIF causes sequelae. The term "jungle foot" and the related terms "tropical jungle foot," "jungle rot," and "paddy foot" are not well defined. Jungle foot usually refers to TIF.[8]

NFCIs

EPIDEMIOLOGY OF NFCIs

Nonfreezing cold injuries can occur when extremities are subjected to cold, often wet, conditions that overwhelm their capacity to maintain warmth, leading to peripheral cooling, with or without central cooling. Nonfreezing cold injuries usually occur only after continuous exposure to cold for at least 1 to 3 d,[11,12] although they have been reported after immersion in cold sea water at 0 to 8°C (32–46°F) for 14 to 22 h.[2] Some authors have suggested, based on anecdotes, that an NFCI can occur in as short a time as 1 h.[13] There is 1 report of shipwrecked sailors who sustained injuries that might have been NFCIs at

water temperatures about 16 to 21°C (61–70°F) after 8 d with continuously wet feet.[14]

Environmental factors that increase the rate of cooling, such as wind or moisture, likely increase the risk of NFCI. Nonfreezing cold injuries are especially common with wet footwear in cold conditions and are often associated with fatigue, malnutrition, dehydration, immobility, and dependent limbs. Military personnel are believed to have the greatest risk during combat and training. Other occupational groups, such as harbor and cannery workers, may also be affected. Wilderness travelers, mountaineers, homeless people, alcoholics, and the elderly are at risk when they are unable to remove wet footwear during prolonged exposure to cold, wet conditions.

INDIVIDUAL RISK FACTORS FOR NFCI

Individuals vary widely in susceptibility to cold injury. Associated injuries, such as fractures of the extremities or multiple trauma, increase the risk of NFCI. Conditions that affect the circulation, such as peripheral vascular disease and Raynaud's phenomenon, may increase the risk and severity of NFCI. Mental illness and alcohol use may impair behavioral responses, increasing the risk of NFCI. Smoking, older age, and African ethnicity have also been suggested as possible risk factors.[15] A retrospective study of UK soldiers suggested that NFCI had the highest incidence during winter training in younger, less-experienced soldiers. This study did not find that smoking was a risk factor. Personnel with Afro-Caribbean ethnicity seemed to have greater risk than Caucasians.[16]

PHYSIOLOGY OF SKIN COLD EXPOSURE

The skin contributes to thermoregulation by acting as a surface for heat exchange. Vasodilation leads to increased skin blood flow, facilitating heat loss, while vasoconstriction decreases skin blood flow, limiting heat loss. Skin blood flow is controlled by sympathetic innervation and local vascular mechanisms. Central hypothalamic control mechanisms respond to central and peripheral temperature afferent information to cause reflex neurogenic vasoconstriction or vasodilation. If core and average skin temperatures allow, local temperature changes in the skin can also cause locally mediated vasodilation or vasoconstriction independent of the central nervous system or reflex neurogenic mechanisms. Skin blood flow can decrease by approximately 90% in a cold environment compared with resting blood flow in a thermoneutral environment while still meeting the lower metabolic needs of cold skin. Skin blood flow can also decrease in dependent extremities during immobility and from pressure produced by constrictive clothing or footwear in combination with edema.

Cooling of the skin to about 15°C (59°F) increases vasoconstriction of hands or feet, making them vulnerable to cold injury. Further local cooling causes cold-induced vasodilation (CIVD), with cyclic increases in blood flow that likely protect against cold injury. Cold-induced vasodilation, also known as the "Lewis hunting response," occurs in cycles as short as 5 to 10 min that lengthen with duration and increased cooling.[17] Decreasing the core temperature decreases the magnitude and frequency of the cycles.[18] Cold-induced vasodilation can be abolished in hypothermia. People who have repeated, long-duration exposures to cold have more rapid cycles, with warmer peak temperatures than those without such exposures.

PATHOPHYSIOLOGY OF NFCI

Nonfreezing cold injury is a neurovascular injury, with impaired circulatory control and damage to the microcirculation.[13] Animal studies have demonstrated thrombosis and endothelial injury in the microcirculation. Nerves can be injured directly by cold or can be affected by injury to their microvascular circulation.[19,20] Direct neural damage from cold has been reported in victims with severe hypothermia and may also occur in victims with isolated NFCI.[21,22]

Prolonged, profound vasoconstriction plays a role in the pathogenesis of NFCI[13,23] but is likely not the only cause.[24] Nonfreezing cold injuries occur when an extremity is subjected to cold, usually with external moisture, for prolonged periods of time.[3] The extent of tissue injury seems to be greater with lower temperatures and longer exposures. Repeated cold exposures with incomplete recovery between exposures cause greater injury than a single, long exposure, possibly because of reperfusion injury.[20] A rat study showed that nerve injury and production of reactive oxygen species were greater when nerves were subject to intermittent cooling with periods of warming compared to continuous cooling conditions.[25] This suggests an important role of free radicals. The exact parameters of temperature and duration that can cause NFCI are unknown.

We believe that NFCI alone is unlikely to cause loss of tissue. Tissue loss is most likely caused by pressure necrosis from edema caused by NFCI, associated with constricting footwear or clothing. Extreme cases of pressure can potentially lead to a compartment syndrome. Victims who must walk with swollen feet may also sustain tissue loss caused by mechanical factors.

DIAGNOSIS AND CLINICAL COURSE OF NFCI

Nonfreezing cold injury is a clinical diagnosis. In severe NFCI, affected extremities pass through 4 stages.[2,13] There can be great variability in the lengths of the stages.

First stage: during cold exposure

The first stage, during cold exposure, is characterized by a loss of sensation. Victims often complain that the affected areas feel numb and like a block of wood. A retrospective study found that the most common initial symptom of NFCI was loss of sensation lasting >30 min.[16] Loss of proprioception can cause clumsiness and gait disturbances. Affected extremities are usually painless. They can be bright red initially, later becoming pale or white because of severe vasoconstriction. In the later part of the first stage, peripheral pulses are diminished.

Second stage: following cold exposure

The second stage occurs when the victim is moved to a warm environment and continues during and after rewarming. Usually, this stage lasts for a few hours but may continue for several days. Hands and feet become a mottled pale blue because of slightly increased blood flow. The color change may not be readily visible in victims with highly pigmented skin. Peripheral pulses are diminished initially but later become bounding, although capillary refill is still delayed. Affected extremities may swell. They remain cold and insensate during the second stage.

Third stage: hyperemia

The third stage usually begins abruptly and lasts for days or weeks, as long as 6 to 10 wk in severe cases. This stage is characterized by bright red, edematous extremities with bounding pulses and delayed capillary refill, likely caused by microvascular injury. Affected extremities are extremely painful and hyperalgesic, although some distal areas may remain insensate. There is usually no tissue damage, but areas that were affected by pressure and are nonviable may develop blisters or discoloration.

Fourth stage: following hyperemia

The fourth stage may last from a few weeks to years and may be permanent in severe cases. Unless there is tissue loss, affected extremities appear normal. One of the most common persisting manifestations of NFCI is increased sensitivity to subsequent cold exposure. Cold sensitivity may begin at any time, as long as 6 wk after the injury, even in mild cases when neuropathic symptoms resolved in the first week. Injured extremities cool more easily when exposed to cold, are more uncomfortable, and are slow to rewarm. Subsequent cold exposure may cause intense vasoconstriction, often persisting for hours, even after a short cold exposure. In a retrospective case series, victims had subjectively colder extremities, abnormal pinprick sensation, and decreased sensation to light touch but no proprioceptive loss or gait disturbance.[16] Many victims with severe injuries have chronic pain, often exacerbated by cold exposure. There may still be small insensate areas. Hyperhidrosis is a common sequela in severe cases. Victims may also develop chronic neuropathic conditions such as complex regional pain syndrome (CRPS) or similar syndromes. Rarely, tissue affected by pressure necrosis at the time of injury may become frankly necrotic in the fourth stage, requiring amputation. Sensory neuropathy can also lead to complications such as trauma and infections, including osteomyelitis or sepsis.

Nonfreezing cold injury is not a progressive condition. The worst symptoms occur in the first few days. Afterward, symptoms caused by NFCI usually improve or remain stable. Worsening symptoms should not be attributed to NFCI.

Recommendations. In conditions sufficient to cause significant peripheral cooling, especially in a wet, cold environment with a water temperature <15°C (59°F), a victim with an extremity that has been cold and numb for hours to days may have NFCI (1C).

A victim who is asymptomatic, with a normal physical examination and no persistent neurologic symptoms after rewarming, does not have NFCI (1C).

When neurologic symptoms or signs persist beyond 1 wk after cold exposure affecting 1 or more extremities and other causes of peripheral neuropathy have been excluded, the diagnosis is likely NFCI (1C).

Worsening of symptoms attributed to NFCI after the first 2 to 3 d following the injury should prompt a search for other causes (1C).

DIFFERENTIAL DIAGNOSIS OF NFCI

Frostbite, unlike NFCI, occurs only at air temperatures well below freezing and cannot occur in cold water, even sea water. Frostbite and NFCI can theoretically occur together if tissue with NFCI subsequently freezes. Frostbite that is still frozen appears pale blue, yellow, or white. Unlike tissue with NFCI, frostbitten tissue that has not been thawed is firm or hard and looks waxy.

Pressure injury can occur in association with NFCI because of swelling inside constrictive clothing and footwear. Pressure injury is painful unless the tissue is

insensate, as in cold injury. Pressure injury can cause ischemia, with local tissue loss (gangrene). In severe cases, compartment syndrome, with distal loss of tissue, may also occur. Tissue necrosis after exposure to temperatures well below freezing is most likely to be caused by frostbite.

Infections can cause redness and swelling of the skin, with subsequent necrosis, usually unilaterally. Infections seldom involve only the distal portion of an extremity. Systemic symptoms and signs are often present with infection and are rare with uncomplicated NFCI.

Raynaud's phenomenon, severe vasoconstriction in response to cold, usually affects hands or feet bilaterally. Blanching is rapid and well demarcated with adjacent areas of unaffected skin. There is full recovery, without sequelae, after rewarming.

Frostbite, pressure necrosis, infection, and Raynaud's phenomenon can all occur in association with NFCI.

Recommendations. Use the history of environmental exposure, clinical manifestations, and physical examination to distinguish NFCI from frostbite, pressure necrosis, infection, and Raynaud phenomenon (1C).

TREATMENT OF NFCI

There are no well-conducted case-control or cohort studies to support recommendations for treatment of NFCI. Our recommendations are based primarily on research, experience, and retrospective studies.

Prehospital care

Further cooling should be prevented.[26] Hypothermia should be treated before treating other injuries, including frostbite and NFCI.[27] Rapid rewarming of NFCI has not been shown to improve outcomes. Immersion in warm water increases pain and edema[28] and also increases the metabolic demands of injured skin.[2] Extremities with NFCI are damaged and susceptible to further trauma. Nonfreezing cold injuries are likely to be insensate until they are at least partially rewarmed.

Recommendations. Victims with swollen feet should not walk unless walking is necessary for evacuation. Victims who must walk should wear thick socks for padding in nonconstricting footwear, if possible (1C). Treat associated conditions, including hypothermia and frostbite, before treating NFCI (1B). Extremities with NFCI should be rewarmed passively at room temperature (1A) and should be elevated (1B). Rewarming with warm water, forced air, or a heating pad should not be attempted (1A). Administer analgesia as needed for pain (1A).

Emergency department and in-hospital care

Tetanus prophylaxis, according to standard guidelines, is indicated for associated injuries such as frostbite and other wounds.[27] A case report described the use of iloprost within 24 h to limit tissue loss in severe NFCI.[29] The authors of the report suggested that the use of iloprost was safe and allowed delayed amputation, with less tissue loss than expected based on apparent tissue damage on initial assessment. Antibiotics are not indicated in NFCI unless there is evidence of infection. Although there are no specific data, prophylaxis of venous thromboembolism may be indicated in immobile victims.

Recommendations. Treat hypothermia before treating NFCI (1A).

Allow extremities with NFCI to rewarm passively at room temperature (1A), with bed rest, elevation, and air drying at room temperature (1B).

Administer analgesia as needed for pain (1A). Give tetanus prophylaxis if indicated (1C).

No recommendation can be made concerning the early use of iloprost because there are insufficient data.

Administer antibiotics only if there are signs of infection (1A).

Pain relief

Elevation of hands and feet can decrease pain during the hyperemic stage.[13] Hands and feet can be open to air or covered with light, loose dressings. Cooling the feet with ice bags wrapped in towels has been studied but is contraindicated because it may cause frostbite.[30]

Nonsteroidal anti-inflammatory drugs and opioids are usually ineffective as the sole treatment for relief of pain.[13] Nifedipine, a vasodilator, has not been shown to be effective for pain relief.[13] Amitriptyline (50–100 mg daily at bedtime) may be effective, especially if started as soon as pain develops.[13] If amitriptyline is not adequate, medications that treat neuropathic pain, such as gabapentin, can be administered. Lumbar sympathectomy is an obsolete procedure that was reported to relieve cold sensitivity, in some cases, for as long as a few months, after which symptoms returned, as severe as, or worse than, those before the procedure.[13]

Recommendations. Elevate affected extremities. Protect extremities from constriction. Keep affected extremities open to air or lightly dressed using loose dressings (1A). If nonsteroidal anti-inflammatory drugs and opioids are not effective, administer amitriptyline for pain (1C). If

pain is not controlled adequately by amitriptyline, consider a trial of gabapentin (1C).

Infection

A low-grade fever (38–38.5°C [100.4–101.3°F]) often develops in the first 12 to 36 h.[31] Infection is rare. Infection does not usually develop after NFCI unless traumatic blisters become secondarily infected.

Recommendations. Do not treat a victim with an isolated low-grade fever with antibiotics unless there are other clinical manifestations of infection (1C). Prophylactic antibiotics are not indicated (1C). Obtain emergent surgical consultation for suspected tissue necrosis (1C). Antibiotic treatment for cellulitis should cover staphylococci, streptococci, and pseudomonas species (1C).

Laboratory and imaging studies

There are no specific laboratory or imaging studies that can help establish the diagnosis of NFCI. Diagnostic studies may be necessary for coexisting conditions. There is no known role for computed tomography angiography, magnetic resonance angiography, or radioisotope scanning to assess circulation in an extremity with NFCI. Infrared thermography is no longer used in the UK to guide postdischarge management. Use of infrared thermography alone was not shown to be effective in controlled trials.

Recommendations. Obtain x-rays of affected extremities if trauma is known or suspected (1A). Obtain computed tomography or magnetic resonance imaging to assess coexisting conditions, when indicated (1A).

LONG-TERM MANAGEMENT, PROGNOSIS, AND SEQUELAE

Sequelae can include chronic neuropathic pain and CRPS. In an open-label study, nicotinyl tartrate (oral nicotine) alleviated symptoms in 16 of 36 victims, with improvement in pain, paresthesias, and exercise tolerance.[32] Other vasodilators, including theophylline and papaverine, were not effective.[32]

In a case report, iloprost, a prostaglandin analog with anti-inflammatory and vasodilator properties, was used to treat a 41-y-old military veteran with foot pain and limited mobility 20 y after an NFCI.[33] The first infusion of iloprost was followed by 4 wk of pain relief and increased mobility, with symptoms returning to the preiloprost baseline over the next several weeks. The second infusion, given 3 mo later, was followed by increased pain, again returning to preiloprost baseline a few months later.

An open-label study of capsaicin patch treatment of 16 military participants with long-term sequelae of NFCI showed a reduction in neuropathic pain that was statistically significant but not clinically significant.[34] The study also found a statistically significant increase of intraepidermal nerve fibers. The study was limited by the lack of a control group.

Recommendations. No recommendations can be made for the use of iloprost or capsaicin patches for chronic neuropathic pain associated with NFCI because of insufficient data.

The UK military has a standard regimen for management of soldiers with NFCI after hospital discharge. Some soldiers recover with time. Individuals who are asymptomatic, with a normal examination, are gradually re-exposed to increasingly cold environments. If they have normal responses to cold, they are returned to full duty. Outdoor work is allowed if symptoms are minimal and if the individual can stay warm enough to prevent numbness. Individuals meeting these criteria have no increased risk of further episodes of NFCI, although they may experience cold sensitivity symptoms. Individuals with peripheral neuropathy are referred to a clinic for further assessment, including intraepidermal nerve fiber density. A low density in an individual with a clinical history and physical examination suggesting NFCI increases the likelihood that the individual has small-fiber neuropathy secondary to NFCI. Measurement of intraepidermal fiber density can also help predict occupational recovery time. There is still no definitive test for NFCI. The use of diagnostic testing will likely continue to evolve. Individuals with persistent pain are referred to a specialist pain clinic.

Recommendations. Follow a standard regimen for postdischarge management (1B). Asymptomatic individuals with a normal examination and normal responses to cold can resume normal activities (1B). Individuals with neuropathy should undergo assessment, including intraepidermal nerve fiber density, to aid in diagnosis and prediction of recovery time (1C). Victims with chronic neuropathic pain and CRPS should be referred to a pain specialist (1B).

PREVENTION OF NFCI

Regular rotation of personnel out of cold, wet environments is the mainstay of prevention of NFCI.[35] There is little evidence about specific regimens to prevent NFCI.

A prospective study suggested that prevention of NFCI could be facilitated by pairing soldiers with instructions to regularly inspect the feet and footwear of their paired companions. A soldier was more likely to remove boots and dry socks and feet if reminded by their companion soldier.[36]

Other helpful measures include adequate nutrition and insulating, nonconstricting clothing that keeps personnel, especially their hands and feet, warm and dry. Specific recommendations for foot care are based on prevention of warm water immersion injuries. The recommendation to air dry feet for at least 8 h daily is based on prevention of WWIF.[6,28] Recommendations to keep feet dry for 24 h after 48 h of immersion apply to TIF.[9]

Stress can precipitate vasoconstriction. Preparation and training for operating in cold, wet conditions may decrease stress and mitigate vasoconstriction, reducing the likelihood of NFCI.[37]

In World War I, trench foot was almost completely eliminated in allied troops when waterproof bags with clean, dry socks were sent to the trenches every night with increased rations.[12] Other measures that were effective were the prohibition against using puttees (constricting wraps around the lower leg above the boots), encouraging soldiers to move around as much as possible, and the use of gum boots and foot powder (asbestos-free talcum powder) instead of oils.[12]

Vapor barrier boots provide insulation but can become wet on the inside from insensible loss of water vapor or from sweating. Neoprene socks are warm but constricting. They may pose a risk for WWIF.

Recommendations. Limit exposure to cold, wet conditions (1A). Ensure adequate nutrition and insulating, nonconstricting clothing that keeps personnel, especially their hands and feet, warm and dry (1B). Do not re-expose victims with previous NFCI to cold environments (1A). Rotate personnel regularly out of cold, wet environments (1A). Encourage personnel to move around frequently and to avoid having the legs and feet dependent (1C). Train for operations in cold, wet conditions (1C).

Keep feet as dry as possible (1A). In wet conditions, change into dry socks 2 or 3 times daily (1C). If using vapor barrier boots, use asbestos-free talcum powder in addition to regular changes of socks (1C). Do not use neoprene socks (1C). Keep hands dry and warm (1C). Do not use grease or oils on feet or hands (1A).

Warm Water Immersion Injuries

EPIDEMIOLOGY OF WARM WATER IMMERSION INJURIES

Warm water immersion injuries primarily occur in military settings in warm climates, such as the Vietnam War in the mid-1960s, when soldiers with wet feet are unable to remove their footwear and dry their feet for periods longer than a day.

INDIVIDUAL RISK FACTORS FOR WARM WATER IMMERSION INJURIES

The primary risk factor for warm water immersion injuries is continuous immersion of the feet in water >15°C (59°F) for longer than a day with no opportunity to dry the feet or to replace wet socks and boots with dry ones.[8] Heavy callouses are a risk factor for WWIF.[8] Victims with prior episodes of TIF are more likely to have subsequent episodes.[8]

PATHOPHYSIOLOGY OF WARM WATER IMMERSION INJURIES

There has been little research regarding the pathogenesis of warm water immersion injuries. Warm water immersion foot is likely due to hyperhydration (waterlogging) of the plantar stratum corneum in warm water exposures of <72 h.[8] In TIF, water diffuses through the waterlogged epidermis into the dermis with warm water exposures of >72 h.[8]

DIAGNOSIS AND CLINICAL COURSE OF WARM WATER IMMERSION INJURIES

Warm water immersion injuries can usually be diagnosed clinically by history and physical examination.

Warm water immersion foot results from immersion in warm water at 15 to 32°C (59–90°F) for as long as 3 d.[8] The feet are painful, with white, wrinkled plantar surfaces and sometimes with mild swelling. Weight bearing causes pain and paresthesias of the feet, with tingling or a feeling of "walking on rope."[8]

Tropical immersion foot results from immersion in warm water at 22 to 32°C (72–90°F) for >3 d.[8] Initially, there is burning pain, greater on the dorsal aspects of the feet than on the soles, that increases with walking. The feet are usually too swollen to replace the boots after the victim removes them.[8] By the time the victim is admitted to the hospital, the feet are usually bright red, with demarcation above the level of the top of the boots and pitting edema of the dorsa and the ankles. The skin is initially cool but,

within 12 h, becomes warm, with full pulses and brisk capillary refill. In severe cases, fever and inguinal lymphadenopathy can occur, without lymphangitis.[8]

Tropical immersion foot is often associated with abrasions from wet socks and ulcers in areas of the feet or ankles where footwear causes pressure on swollen tissue. Ulcers are uncommon over bony prominences, where there is little tissue to become swollen. Plantar surfaces are hyperhydrated and wrinkled. During the Vietnam War, victims with severe TIF developed fever and inguinal lymphadenopathy, in contrast to victims described in the South Pacific during World War II, who did not develop these signs.[8]

In victims recovering from TIF, fever, adenopathy, pain, and tenderness resolve and plantar surfaces return to normal within 2 to 3 d following removal from the wet environment. Red dorsal surfaces and ankles transition to diffuse blotchy ecchymoses, with tiny vesicles and a fine maculopapular rash. Edema resolves in 4 to 7 d. The skin desquamates and subsequently returns to normal. There are no sequelae.[8]

Recommendations. A victim whose feet were immersed in warm water for no longer than 3 d and who has painful, white, wrinkled soles and paresthesias most likely has WWIF (1C). A victim whose feet were immersed in warm water for >3 d and who has redness of the dorsal surfaces and ankles, with a burning sensation more severe on the dorsal surfaces than on the plantar surfaces, most likely has TIF (1C).

DIFFERENTIAL DIAGNOSIS OF WARM WATER IMMERSION INJURIES

Differential diagnosis of warm water immersion injuries includes NFCI and frostbite. These can be distinguished from WWIF or TIF by a history of exposure to cold temperatures or cold water rather than warm water. Pressure necrosis can mimic or coexist with warm water injury. Tropical immersion foot can cause ulcerations in areas of swollen tissue.[8] Like TIF, soft-tissue infections can cause erythema and edema, sometimes with fever and lymphadenopathy. Bacterial infections, including streptococcal cellulitis, and fungal infections can occur as sequelae and should also be considered in the differential diagnosis. Infections are usually unilateral and well demarcated, unlike TIF, which is usually symmetrical and diffuse. Wet-sock erosions are superficial skin erosions that occur only in areas that experience friction or pressure, especially areas under bootlaces, unlike the lesions in TIF that cover the dorsum and ankle.[8]

Recommendations. Use clinical characteristics to distinguish WWIF and TIF from each other and from NFCI or frostbite, pressure-induced injury, soft-tissue infection, and wet-sock erosions (1C).

TREATMENT OF WARM WATER IMMERSION INJURIES

If the feet are kept dry, WWIF resolves in 2 to 3 d, without sequelae.[8] To treat TIF, the feet should be dried. The victim should be placed at bed rest with the feet elevated. Recovery, with resolution of edema, takes 4 to 5 d, except in severe cases, which may require 10 to 12 d of treatment. If skin integrity is compromised, there may be a risk of tetanus. As with NFCI, amitryptiline[13] or medications with neuropathic pain, such as gabapentin,[38,39] may be effective for pain during the recovery period.

Recommendations. Treat WWIF by drying the feet and keeping them dry for 2 to 3 d (1B). Treat TIF by drying the feet, keeping them dry, and placing the victim at bed rest with the feet elevated for 4 to 5 d (1B). Give tetanus prophylaxis according to standard guidelines if skin integrity is compromised (1C). Administer medications, including amitryptiline (2B) or gabapentin (2B), for pain relief. Once symptoms resolve, the victim can return to previous activities (1A).

COMPLICATIONS OF WARM WATER IMMERSION INJURIES

Fungal infections are the most common complication of warm water immersion injuries.[6] Bacterial infections can also occur. Prophylactic antibiotics are not indicated. Fungal infections should be treated with topical antifungal agents. Cellulitis or other bacterial soft-tissue infections should be treated with systemic antibiotics. There are no known long-term sequelae of WWIF or TIF.

Recommendations. Do not give prophylactic antibiotics (1B). Treat infections that occur as complications of warm water immersion injuries with topical antifungals or antibiotics, as appropriate (1A).

PREVENTION OF WARM WATER IMMERSION INJURIES

Warm water immersion foot can be prevented by allowing the feet to dry every night after prolonged exposure to warm water.[6] If drying the feet every night is not possible, prevention of WWIF can be achieved by twice-daily application of silicone grease to the soles, between the toes, and to the dorsa and ankles up to the malleoli.[9]

Tropical immersion foot can be prevented by keeping the feet dry for 1 d after each 2 to 3 d period of continuous exposure to water.[8]

Recommendations. When feet are continuously wet, prevent warm water immersion injuries by drying them every night or by applying silicone grease (1C). If feet must be continuously wet for 2 to 3 d, keep them dry for 1 d between exposures (1C).

Conclusions

To improve care for victims, we have developed evidence-based guidelines for diagnosis, treatment, and prevention of NFCI and warm water immersion injuries. Prevention is key. Treatment strategies are limited and not well studied. Many of our recommendations are based on weak evidence. There is ample scope for further research.

Author Contributions: first draft (KZ, GG, DD); revision of the manuscript (all authors); approval of the final manuscript (all authors).

Financial/Material Support: None.

Disclosures: SH is employed by the UK Ministry of Defence. The opinions expressed in this article do not necessarily reflect the views of the UK Ministry of Defence.

Supplemental Material(s)

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.wem.2023.02.006.

References

1. Guyatt G, Gutterman D, Baumann MH, Addrizzo-Harris D, Hylek EM, Phillips B, et al. Grading strength of recommendations and quality of evidence in clinical guidelines: report from an American College of Chest Physicians task force. *Chest*. 2006;129(1):174–81.
2. Ungley CC, Channell GD, Richards RL. The immersion foot syndrome. *Br J Surg*. 1945;33(129):17–31.
3. Adnot J, Lewis CW. Immersion foot syndromes. In: James WD, ed. *Military Dermatology*. Washington, DC: Borden Institute; 1994:55–68.
4. Laden GD, Purdy G, O'Rielly G. Cold injury to a diver's hand after a 90-min dive in 6 degrees C water. *Aviat Space Environ Med*. 2007;78(5):523–5.
5. Knight BW. "Trench foot" in civilians. *Br Med J*. 1940;2(4165):610–1.
6. Buckels LJ, Gill Jr KA, Anderson GT. Warm water immersion foot. *Res Rep U S Nav Med Field Res Lab*. 1967;17(5):1–8.
7. Paddy-field foot. *Lancet*. 1967;1(7498):1043.
8. Allen AM, Taplin D. Tropical immersion foot. *Lancet*. 1973;2(7839):1185–9.
9. Taplin D, Zaias N, Blank H. The role of temperature in tropical immersion foot syndrome. *JAMA*. 1967;202(6):546–9.
10. Forbes KE, Foster P. An unusual case of an immersion hand presentation in a military signaller operating in the jungle in Belize. *J R Army Med Corps*. 2017;163(6):422–4.
11. Smith JL, Ritchie J, Dawson J. On the pathology of trench-frostbite. *Lancet*. 1915;186(4802):595–8.
12. Haller Jr JS. Trench foot—a study in military-medical responsiveness in the Great War, 1914-1918. *West J Med*. 1990;152(6):729–33.
13. Thomas JR, Oakley HN. Nonfreezing cold injury. In: Pandolf KB, Burr RE, eds. *Medical Aspects of Harsh Environments*. Washington, DC: Borden Institute; 2001:467–90.
14. Webster DR, Bigelow WG. Injuries due to cold, frostbite, immersion foot and hypothermia. *Can Med Assoc J*. 1952;67(Spec Issue):534–8.
15. DeGroot DW, Castellani JW, Williams JO, Amoroso PJ. Epidemiology of U.S. Army cold weather injuries, 1980-1999. *Aviat Space Environ Med*. 2003;74(5):564–70.
16. Kuht JA, Woods D, Hollis S. Case series of non-freezing cold injury: epidemiology and risk factors. *J R Army Med Corps*. 2019;165(6):400–4.
17. Greenfield AD, Shepherd JT, Whelan RF. Cold vasoconstriction and vasodilatation. *Ir J Med Sci*. 1951;(309):415–9.
18. Daanen HA, Van de Linde FJ, Romet TT, Ducharme MB. The effect of body temperature on the hunting response of the middle finger skin temperature. *Eur J Appl Physiol Occup Physiol*. 1997;76(6):538–43.
19. Montgomery H. Experimental immersion foot. III. Oxygen utilization by muscle and nerve of the rabbit leg two hours after its prolonged exposure to water at 3°C. *Trans Am Clin Climatol Assoc*. 1954;66:192–8.
20. Jia J, Pollock M. The pathogenesis of non-freezing cold nerve injury. Observations in the rat. *Brain*. 1997;120(4):631–46.
21. Collier T, Patel A, Rinaldi R. Hypothermia-induced peripheral polyneuropathy after an episode of drowning. *P M R*. 2012;4(3):230–3.
22. Løseth S, Bågenholm A, Torbergsen T, Stalberg E. Peripheral neuropathy caused by severe hypothermia. *Clin Neurophysiol*. 2013;124(5):1019–24.
23. Whayne TF, DeBakey ME. *Cold Injury, Ground Type*. Washington, DC: Office of the Surgeon General, Department of the Army; 1958.
24. Montgomery H. Experimental immersion foot; review of the physiopathology. *Physiol Rev*. 1954;34(1):127–37.
25. Geng Z, Tong X, Jia H. Reactive oxygen species (ROS) mediates non-freezing cold injury of rat sciatic nerve. *Int J Clin Exp Med*. 2015;8(9):15700–7.
26. Dow J, Giesbrecht GG, Danzl DF, Brugger H, Sagalyn EB, Walpoth B, et al. Wilderness Medical Society clinical practice guidelines for the out-of-hospital evaluation and treatment of accidental hypothermia: 2019 update. *Wilderness Environ Med*. 2019;30(4):S47–69.
27. McIntosh SE, Freer L, Grissom CK, Auerbach PS, Rodway GW, Cochran A, et al. Wilderness Medical Society clinical practice guidelines for the prevention and treatment of frostbite: 2019 update. *Wilderness Environ Med*. 2019;30(4):S19–32.

28. Wrenn K. Immersion foot: a problem of the homeless in the 1990s. *Arch Intern Med*. 1991;151(4):785–8.
29. Tam A, Lyons T, Vennam S, Barnes R, Imray C. Early use of iloprost in nonfreezing cold injury. *Wilderness Environ Med*. 2022;33(3):344–7.
30. Graham CA, Stevenson J. Frozen chips: an unusual cause of severe frostbite injury. *Br J Sports Med*. 2000;34(5):382–3.
31. Webster DR, Woolhouse FM, Johnston JL. Immersion foot. *J Bone Joint Surg Am*. 1942;24(4):785–94.
32. Redisch W, Brandman O. The use of vasodilator drugs in chronic trench foot. *Angiology*. 1950;1(4):312–6.
33. Ionescu AM, Hutchinson S, Ahmad M, Imray C. Potential new treatment for non-freezing cold injury: is iloprost the way forward? *J R Army Med Corps*. 2017;163(5):361–3.
34. Anand P, Privitera R, Donatien P, Misra VP, Woods DR. Capsaicin 8% patch treatment in non-freezing cold injury: evidence for pain relief and nerve regeneration. *Front Neurol*. 2021;12:722875.
35. Francis TJ. Non freezing cold injury: a historical review. *J R Nav Med Serv*. 1984;70(3):134–9.
36. Anand P, Privitera R, Yiangou Y, Donatien P, Birch R, Misra P. Trench foot or non-freezing cold injury as a painful vaso-neuropathy: clinical and skin biopsy assessments. *Front Neurol*. 2017;8:514.
37. Francis TJ, Golden FS. Non-freezing cold injury: the pathogenesis. *J R Nav Med Serv*. 1985;71(1):3–8.
38. Aldington DJ, McQuay HJ, Moore RA. End-to-end military pain management. *Philos Trans R Soc Lond B Biol Sci*. 2011;366(1562):268–75.
39. McGreevy K, Bottros MM, Raja SN. Preventing chronic pain following acute pain: risk factors, preventive strategies, and their efficacy. *Eur J Pain Suppl*. 2011;5(2):365–72.

WILDERNESS & ENVIRONMENTAL MEDICINE 2023; 34(2): 164–71

ORIGINAL RESEARCH

Search and Rescue in California: The Need for a Centralized Reporting System

Alex B. Levine, BA[1]; Richard S. Feinn, PhD[1]; John L. Foggle, MD, MBA[1,2]

[1]*Frank H. Netter MD School of Medicine, Quinnipiac University, North Haven, CT;* [2]*Department of Emergency Medicine, Alpert School of Medicine, Brown University, Providence, RI*

Introduction—There is no published information on the epidemiology of wilderness rescues in California outside of national parks. The objective of this study was to investigate the epidemiology of wilderness search and rescue (SAR) missions in California and identify risk factors for individuals requiring rescue due to accidental injury, illness, or navigation errors in the California wilderness.

Methods—A retrospective review of SAR missions in California from 2018 to 2020 was conducted. This was done from a database of information collected by the California Office of Emergency Services and the Mountain Rescue Association from SAR teams, who submitted voluntarily. The subject demographics, activity, location, and outcomes of each mission were analyzed.

Results—Eighty percent of the initial data were excluded because of incomplete or inaccurate data. Seven hundred forty-eight SAR missions involving 952 subjects were included in the study. The demographics, activities, and injuries of our population were consistent with those reported from other epidemiological SAR studies, and there were significant differences in outcomes based on the subject's activity. For example, water activities were highly correlated with a fatal outcome.

Conclusions—The final data show interesting trends, but it is difficult to draw firm conclusions because so much of the initial data had to be excluded. A uniform system for reporting SAR missions in California may be helpful for further research, which may aid both SAR teams and the recreational public in understanding risk factors. A proposed SAR form for easy entry is included in the discussion section.

Keywords: wilderness medicine, epidemiology, emergency medical services

Introduction

California is the most populous state, the third largest by area, and one of the most commonly visited, with hundreds of millions of visitors per year.[1,2] It is also one of the most geographically diverse states, featuring numerous types of wilderness environments, the highest point in the contiguous United States (Mt. Whitney), and the lowest point (Death Valley) in the entire United States. These diverse geographical features are often easily accessible from the urban areas of California, bringing recreational wilderness travelers from inside and outside the state.

The organization and co-ordination of search and rescue (SAR) activities in California are the responsibility of each county's sheriff. There are 58 counties, so there are a minimum of 58 individual SAR teams throughout the state, although many counties have more than 1 team. For example, Los Angeles County has 7 SAR teams divided by geographic region, each operating semi-independently but all officially under the sheriff's department. Other counties have teams divided by skill set, such as off-road teams, mountain rescue teams, dive teams, and the like. County SAR teams in California are generally made up of unpaid volunteers, whereas national parks typically have professional SAR teams consisting of both National Park Service (NPS) rangers and volunteers. It is difficult to obtain an accurate count of SAR

Corresponding author: Alex B. Levine, BA, Frank H. Netter MD School of Medicine, Quinnipiac University, North Haven, CT; e-mail: alexbl1994@gmail.com.

Submitted for publication August 2022.

Accepted for publication January 2023.

https://doi.org/10.1016/j.wem.2023.01.011

teams in California because not all SAR teams are members of the Mountain Rescue Association (MRA) or another national organization. It is also difficult to obtain accurate information about SAR incidents in California. Although certain states, such as Oregon and Washington, require that each SAR team submit an after-action report to a state coordinator after each mission,[3] California has no such requirement at the state level, and reporting is voluntary. National Park Service SAR teams within California do record their incidents, but these are reported independently of and separately from the county SAR teams.

Previous studies have sought to define the epidemiology of SAR incidents in various national and state parks in multiple states, with varying results depending on the locale.[4-7] Several studies have also examined SAR operations in specific national parks within California.[8-10] No published studies to our knowledge have examined the epidemiology of SAR operations throughout the state of California as a whole, including areas outside of national parks. More information on this could potentially provide both SAR organizations and recreational wilderness visitors in California with preventive tools to avoid high-cost and high-risk rescue situations. Due to the significant geographical diversity of the state, the results may be able to be applied to a number of localities with varying environments and, therefore, extrapolated to other states or even nations. The objective of this study was to investigate the epidemiology of wilderness SAR missions in California and identify risk factors for individuals requiring rescue in the California wilderness, specifically recreational users involved in accidental incidents.

Methods

Data were obtained from a database of information about SAR missions in California from 2018 to 2020 collected jointly by the California Office of Emergency Services (Cal OES) and MRA. Search and rescue teams could voluntarily submit information to the Cal OES and MRA database via a secure online portal after each of their callouts. The submitted information included the date, number of volunteers, use of aircraft, subject demographics, activity, experience level, outcome, injuries, level of medical care provided, and co-ordinates. It is unclear why only certain teams decided to submit data and what percentage of their total incidents each team actually submitted. The identity of the SAR team submitting the information for each mission was also not included in the database. Official NPS SAR incident reports were not included in this database.

INCLUSION AND EXCLUSION CRITERIA

Our study intended to focus on intentional wilderness users who required SAR because of accidental injury, illness, or navigation error. Missions were first limited to incident types that matched these criteria. These incident types were as follows: avalanche, "car over" (presumed to refer to a car over a cliff or embankment, but the exact meaning is unclear), cave search/rescue, dive rescue/recovery, medical aid, mine SAR, recovery, rescue, search, and swiftwater rescue.

Missions were excluded if the type of incident or subject activity did not match this (eg, "evidence search" as the incident type and "suicidal ideations" as the activity were excluded). Missions were excluded if they were missing pertinent information to the study, such as any subject demographics, activity, or experience level.

DATA ANALYSIS

Of the remaining missions, each was individually reviewed for completeness and accuracy. If data were incomplete, such as missing types of injuries, an attempt was made to locate information about the particular mission on the SAR team's website or in news sources. Using Google Earth and Google Maps (Google, Mountain View, CA), the co-ordinates of each mission were analyzed to identify the county, elevation, and approximate location of each mission. If missing information could not be located or the location was not in a wilderness area (eg, in the center of a city at a location where recreational wilderness activities would not normally be performed), the mission was excluded.

Microsoft Excel (Microsoft, Redmond, WA) and SPSS v27 were used to analyze the data. Descriptive statistics were used to characterize the subject demographics, activities, injuries, and counties. For group comparisons, activities with similar risks were combined into the following 4 larger categories to increase the sample size of each group:

1. High-impact activities (biking, driving, 4-wheel driving, horseback riding, motorcycling, off-highway vehicle/all-terrain vehicle, snow skiing, snowboarding, and snowmobiling)
2. Land-based activities (climbing, hiking, jogging/running, and mountaineering)
3. Water-based activities (boating, canoeing/kayaking/rafting, fishing, and swimming)
4. Miscellaneous activities (camping, gathering, hunting, mine exploration, other, photography, snow shoeing, and working)

Comparisons between these groups were performed using the generalized linear model with binomial

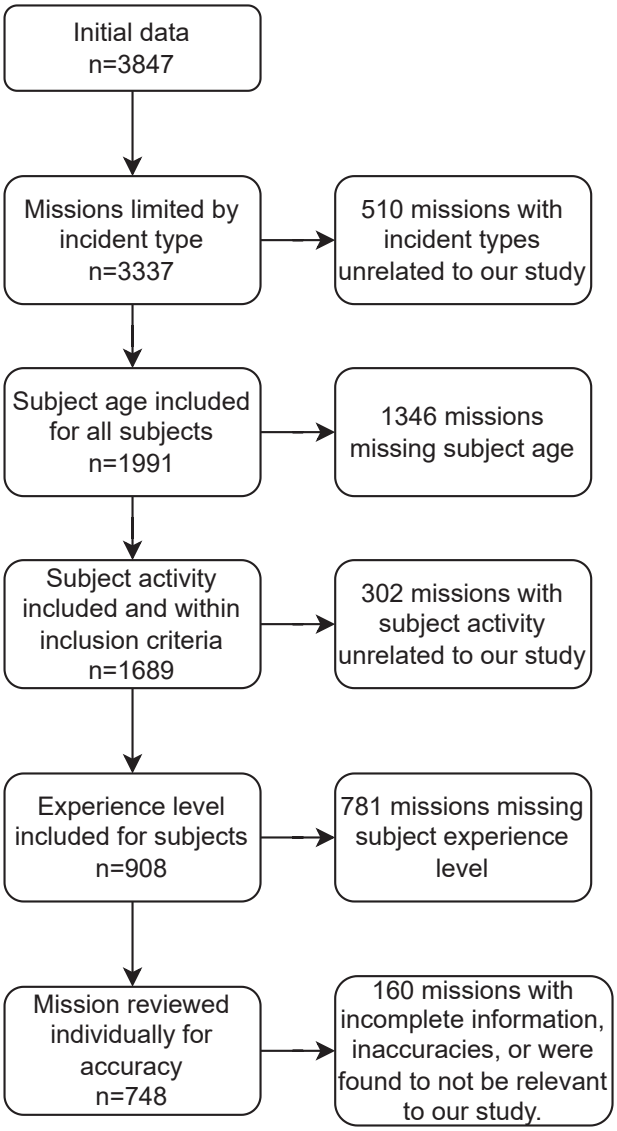

Figure 1. Process of exclusion.

distribution and pairwise comparisons or Pearson χ^2 for cross-tabulation tables. Statistical significance was set at an alpha level of <0.05, with no adjustment for multiple comparisons. The Quinnipiac University institutional review board deemed this study exempt owing to the retrospective and deidentified nature of the data.

Results

There were initially 3847 missions in the dataset. Based on the exclusion criteria, 3099 missions were excluded, and the remaining 748 missions involving 952 subjects were analyzed (Figure 1).

Table 1. Demographic characteristics of subjects

Demographic	*No. of subjects*	*Percentage of subjects*
Sex		
Male	655	69
Female	297	31
Age (y)		
Under 18	70	7
18–39	512	54
40–65	295	31
Over 65	75	8

DEMOGRAPHICS AND LOCATIONS

The mean age of the subjects was 37.5 y (SD, 17.3 y), and the median age was 33 y. Sixty-nine percent (n=655) of the subjects were male and 31% (n=297) were female (Table 1). Thirty-one percent (n=293) of the subjects were reported to have a "poor" level of experience, and 4% (n=37) were reported to have an "excellent" level of experience (Figure 2).

Data were reported from 36 counties, with Los Angeles (n=211), Madera (n=105), and Riverside (n=78) counties comprising the highest number of reported missions (Figure 3). The mean elevation was 1602 m, with a range of −50 m (near Salton Sea) to 4250 m (Mount Whitney). The data included information from a variety of locales, including national forests, national parks, state parks, county parks, and other undesignated areas. The most common locations were the Angeles National Forest/San Gabriel Mountains National Monument (n=202), Inyo National Forest (n=89), and Sierra National Forest (n=75).

ACTIVITIES AND OUTCOMES

The most common subject activity in which SAR activation was required was hiking (53%), followed by driving (9%) (the definition of "driving" was unclear but believed to be subjects operating a vehicle on standard roads in wilderness areas), motorcycling (8%), and climbing (4%) (Table 2). In total, 61% of subjects were found alive and well, 31% were found injured, 5% were found deceased (DOA), and 2% were not found (it is unclear whether the "not found" subjects were later found). However, the proportion of outcomes varied greatly by activity.

INJURIES AND LEVEL OF CARE

Thirty-seven percent (n=280) of the incidents involved injury or illness. Of these, 81% (n=228) were trauma-related and 19% (n=52) were medical incidents. Of the subjects found ill or injured, extremity trauma was the most commonly reported injury (38%), followed by head trauma

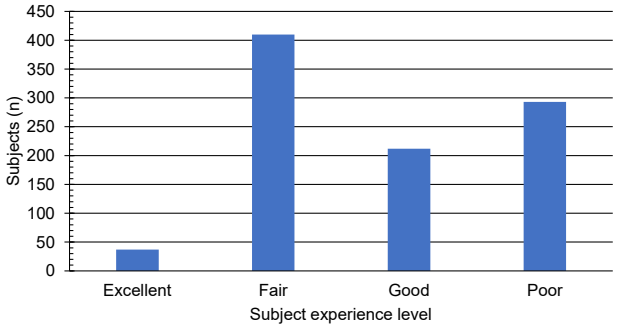

Figure 2. Reported level of experience of subjects.

(17%) (Figure 4). Spine and chest trauma was reported at equal proportions (9%). Excluding trauma, environmental illness (eg, hypothermia, heat exhaustion) was the most common medical complaint (8%). These results included subjects with both single and multiple traumatic injuries.

Of the missions in which the subject was found ill or injured, advanced life support (ALS) was provided 62% of the time and basic life support was provided 20% of the time (Figure 5). However, it was not always clear whether the reported level of care came directly from the SAR team or from the responding emergency medical services (EMS).

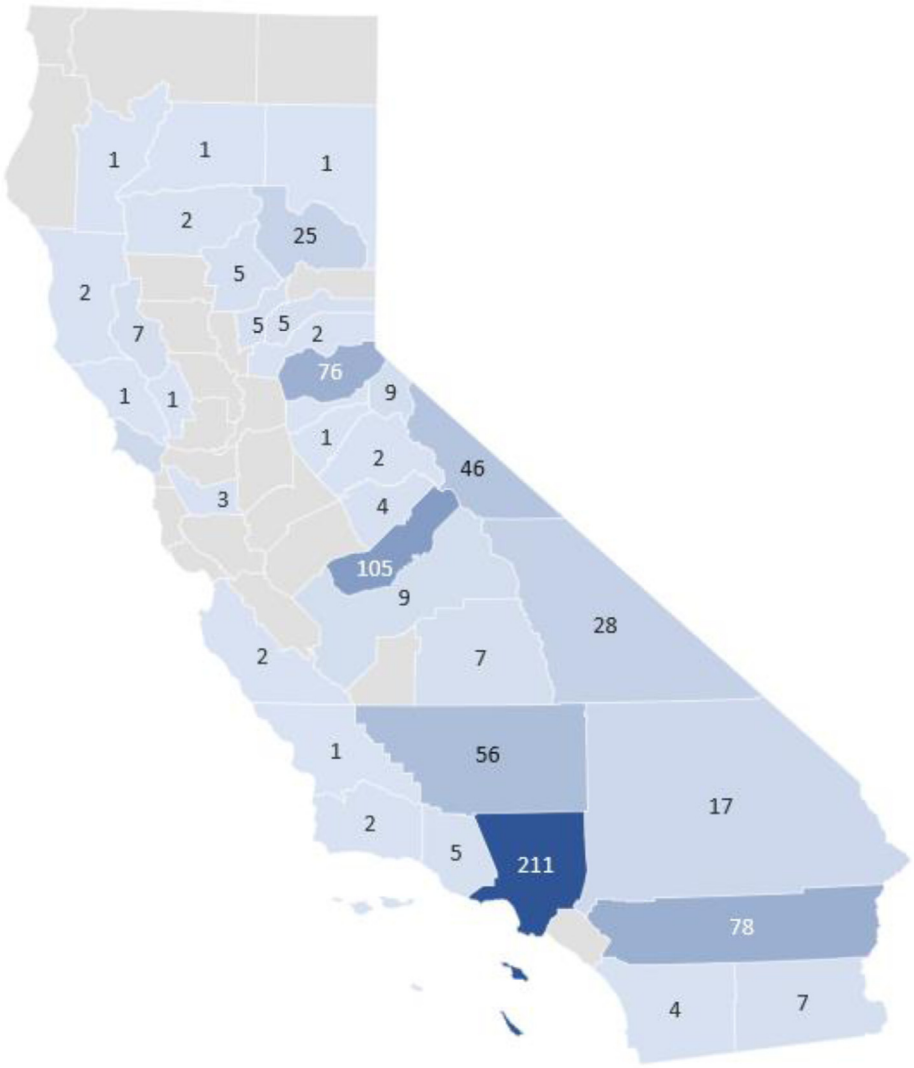

Figure 3. Heat map of missions by county. Darker hues denote more missions, and numbers denote the number of missions.

Table 2. Top 10 activities with outcomes

Activity	*Total number of subjects*	*Well*	*Injured*	*DOA*	*Not found*
Biking	23	7	15	1	0
Canoeing/ Kayaking/ Rafting	22	20	1	1	0
Climbing	50	30	17	3	0
Driving	90	60	21	6	3
Four-wheel driving	27	26	1	0	0
Hiking	504	328	146	18	12
Motorcycling	65	6	57	2	0
OHV/ATV	40	33	7	0	0
Skiing	22	12	8	1	1
Swimming	29	17	1	11	0

DOA, deceased; OHV, off-highway vehicle; ATV, all-terrain vehicle.

GROUP COMPARISONS

Alive and well

There was a significant difference in the proportion of subjects found alive and well by activity overall (P=0.004; Table 3). Pairwise comparisons revealed that the percentage of subjects found alive and well was significantly less in the high-impact activities group (53%) than in the land-based activities (64%; P=0.003) and miscellaneous activities (74%, P=0.005) groups. The difference in percentage found alive and well between the other groups was not statistically significant. Sixty-five percent of subjects participating in water-based activities were found alive and well.

Injured

There was a significant difference in the proportion of subjects found injured by activity overall (P<0.001; Table 3). Pairwise comparisons revealed that the percentages of subjects found injured in each group were all statistically different between activities (P<0.05), except water-based activities (5%) and miscellaneous activities (17%; P=0.054). Forty-two percent of high-impact activities and 30% of land-based activities resulted in injury.

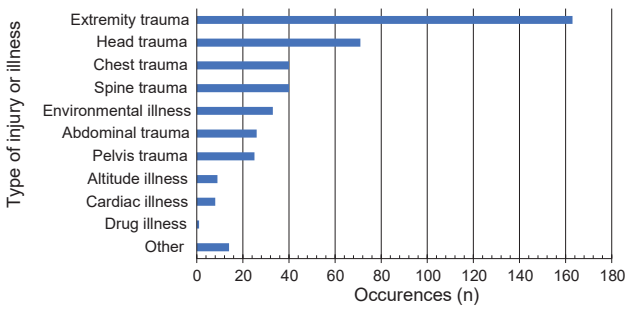

Figure 4. Frequency of trauma and illness.

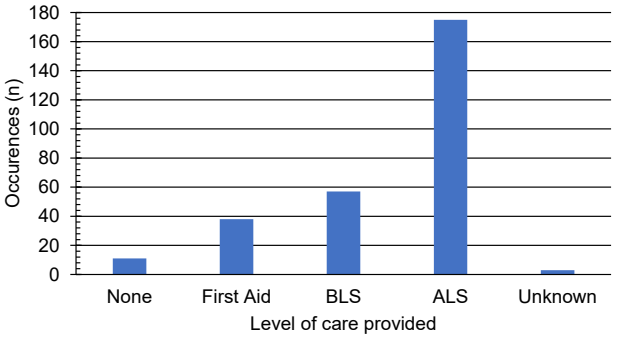

Figure 5. Frequency of levels of care provided. ALS, advanced life support; BLS, basic life support.

DOA

There was a significant difference in the proportion of subjects found DOA by activity overall (P<0.001, Table 3). Pairwise comparisons revealed that the percentages of subjects found DOA in each group were all statistically different (P<0.05), except for high-impact (4%) and land-based activities groups (4%, P=0.93). The percentage of subjects found DOA in the water-based activities group (30%) was statistically significantly higher than that in all other groups. The miscellaneous activities group had no subjects found DOA.

Not Found

There was a significant difference in the proportion of subjects not found by activity overall (P=0.010; Table 3). There was 1 significant pairwise difference between the land-based (2%) and water-based (0%, P=0.005) activities group. Although the miscellaneous activities group had the highest percentage (10%), it also had the lowest number of subjects, making the estimate imprecise. One percent of the subjects in the high-impact activities group was not found.

Discussion

The demographics of our population are similar to those in other studies of SAR in wilderness areas, most notably the age and sex breakdown. A 2015 study in Baxter State Park, Maine, found a mean age of 39 y and a proportion of 60% male subjects,[4] whereas a 2004 study in New

Table 3. Frequency (percentage) of outcomes by activity

	High-Impact, n (%)	*Land-Based, n (%)*	*Miscellaneous, n (%)*	*Water-Based, n (%)*	P *value*[a]
Well	147 (53)	361 (64)	31 (74)	43 (65)	0.004[b]
Injured	117 (42)	172 (30)	7 (17)	3 (05)	<0.001[b]
DOA	10 (04)	21 (04)	0	20 (30)	<0.001[b]
Not found	4 (01)	12 (02)	4 (10)	0	0.010[b]

DOA, deceased.
[a]*P* values are based on overall χ^2.
[b]indicates significant difference

Hampshire found a mean age of 36 y and 65% male subjects.[7] Men between 18 and 39 y of age appear to be more likely to require SAR in the wilderness overall; however, the outcomes are variable beyond that. The submitted data include counties with major population centers and those with small populations but popular wilderness areas.

Subjects engaged in high-impact activities were most likely to be injured and least likely to be found alive and well, whereas water-based activities were more likely to lead to fatal incidents than others. The predominance of traumatic injuries, as opposed to medical issues, is also consistent with other studies. For example, a 2013 study of Yosemite National Park found that extremity trauma alone made up 53% of their EMS incidents.[10] Similarly, a 2018 study of Sequoia and Kings Canyon National Parks found that 46% of their EMS incidents involved traumatic injury.[9] The level-of-care results are, as mentioned previously, not entirely clear as to whether the provided care came from the SAR team itself or the responding EMS. A recently published study surveying SAR teams in California found that, of the teams that responded, 12% had at least 1 nurse practitioner on their team, 21% had at least 1 physician assistant, 45% had at least 1 member with emergency medical technician-paramedic certification, and 61% had at least 1 registered nurse or physician[11]; therefore, ALS being provided directly by the SAR team is not improbable.

Approximately 80% of the original incidents had to be excluded based on the exclusion criteria, and we do not know what additional conclusions we could have drawn from these missing data. In addition, it is unknown how many more missions took place in California during this time frame that were not officially recorded and submitted. A standardized, simple form that would be quick and easy for rescuers to complete would likely provide access to more accurate and larger amounts of data. A proposed user-friendly form for SAR team members to complete can be found in Table 4. Examples of mandatory SAR forms from Washington and Oregon can be found in the reference list.[12,13]

LIMITATIONS

The major limitation of this study is also an important point of this article: the lack of a centralized, streamlined system for reporting SAR incidents in California. Thousands of the missions initially in the dataset were missing pertinent information and had to be excluded. In addition, because the data are voluntarily reported, it is unknown exactly how many more missions took place in the time span that could have added to the results.

An additional limitation of this study is the subjective nature of the collected data. For example, although we included recorded levels of experience in the results, there was no objective measure for this in the survey. Additionally, although our study was aimed at identifying risk factors for those requiring rescue because of accidental circumstances, it is unknown how many of the incidents listed as "DOA" or "not found" were, unbeknownst to the SAR teams, actually suicide or homicide incidents. Although some of this information would be impossible to ascertain, a more detailed reporting form may lead to a better understanding of the situation.

Finally, we did not include official NPS SAR incident reports in our study. Although some incidents in national parks were included in the final data, this is likely the result of mutual aid calls or overlapping jurisdictions with county SAR teams and not from the NPS teams themselves.

Conclusions

The results of our study show interesting demographic trends and significant differences in outcomes. However, we were limited by incomplete data and thousands of excluded data points. Although the complete dataset may very well lead to the same findings, it is impossible to draw that conclusion with the limited dataset available. The limitations of this study lead to a question of whether California should develop a centralized, uniform reporting system for all SAR operations, as is done in other states, such as Oregon and Washington. This system would require each team to complete a standardized form

Table 4. Proposed form for search and rescue teams

Question	*Response (multiple choice or free response)*
Date/Time of initial incident report	
Date/Time of incident conclusion	
County of incident	
Co-ordinates of the last known position (from initial report)	
Co-ordinates of found position (if applicable)	
SAR team(s) involved	
Incident type	Recovery (removal of a known deceased person) Rescue (when the subject's location is known) Search (when the subject's location is unknown) Other: _____
Subject activity (circle all that apply)	Land-based: bicycling, camping, climbing, hiking, running, other land activity: _____ Snow-based: skiing, snowboarding, Snowmobiling, other snow activity: _____ Vehicle-based: all-terrain vehicle, motor vehicle (street or off-road), motorcycling, other vehicle activity: _____ Water-based: boating, fishing, swimming, other water activity: _____
Subject demographics	Subject 1: (sex/age)
Outcomes (circle all that apply)	Subject 1: well/injured/ill/deceased/missing
Injuries/illness (if applicable, circle all that apply)	Subject 1: Medical condition (ie, diabetes) Environmental illness (ie, hypothermia) Trauma (body location[s]: _____) Other: _____
Training level of SAR team providers (if applicable, circle all that apply)	First Aid, EMT-B, EMT-I, EMT-P, RN, APRN, PA, MD/DO, other: _____
Circumstances of incident	Accidental, intentional (ie, suicidal ideation), unknown
Method of extrication	Aircraft, vehicle, foot, N/A, other: _____
Brief summary of incident	

SAR, search and rescue; EMT-B, emergency medical technician-basic; EMT-I, emergency medical technician-intermediate; EMT-P, emergency medical technician-paramedic; RN, registered nurse; APRN, advanced practice registered nurse; PA, physician assistant; MD, doctor of medicine; DO, doctor of osteopathic medicine N/A, not available.

after each mission with questions designed to elicit objective responses about subject demographics and the specific outcomes for each subject. A uniform system for collecting SAR incident data in California will provide researchers and authorities with better data for analyzing the risk factors and epidemiology leading to wilderness rescues in California, which could be extrapolated to other places given California's diverse wilderness areas.

Acknowledgments: The authors thank Monty Bell of the California Office of Emergency Services and the Mountain Rescue Association for his assistance in providing the data used in this study and all the search and rescue members who serve the state of California.

Author Contributions: study concept and design (ABL, JLF); data collection (ABL); data analysis (ABL, RSF, JLF); manuscript drafting and revision (ABL, RSF, JLF); approval of the final manuscript (ABL, RSF, JLF).

Financial/Material Support: None.

Disclosures: None.

References

1. US Census Bureau. *United States Summary: 2010, Population and Housing Unit Counts*. Washington, DC: US Government Printing Office; 2012:30, 41.
2. Visit California. California travel-related spend & visitation forecast. https://industry.visitcalifornia.com/research/travel-forecast. Accessed May 25, 2022.
3. Adams AL, Schmidt TA, Newgard CD, Federiuk CS, Christie M, Scorvo S, et al. Search is a time-critical event: when search and rescue missions may become futile. *Wilderness Environ Med*. 2007;18(2):95–101.

4. Welter CR, Sholl JM, Strout TD, Woodard B. Epidemiology of search and rescue in Baxter State Park: dangers of descent and fatigue. *Wilderness Environ Med*. 2015;26(4):549–54.
5. Heggie TW, Amundson ME. Dead men walking: search and rescue in US National Parks. *Wilderness Environ Med*. 2009;20(3):244–9.
6. Sadeghi R, Konwinski JC, Cydulka RK. Adirondack Park incidents: a retrospective review of search and rescue reports from 2008 and 2009. *Wilderness Environ Med*. 2015;26(2):159–63.
7. Ela GK. Epidemiology of wilderness search and rescue in New Hampshire, 1999-2001. *Wilderness Environ Med*. 2004;15(1):11–7.
8. Heggie TW, Heggie TM. Saving tourists: the status of emergency medical services in California's National Parks. *Travel Med Infect Dis*. 2009;7(1):19–24.
9. Young M, Kim T, Lessard E, Campagne D, Spano S, Farshidpour L, et al. Emergency medical services and remote medical oversight in Sequoia and Kings Canyon National Parks, 2011-2013. *Wilderness Environ Med*. 2018;29(4):453–62.
10. Boore SM, Bock D. Ten years of search and rescue in Yosemite National Park: examining the past for future prevention. *Wilderness Environ Med*. 2013;24(1):2–7.
11. Ettinger S, Long A, Ganti A, Mortimer RB, Chiang W, Spano S. Search and rescue in the Pacific West States. *Wilderness Environ Med*. 2022;33(1):43–9.
12. State of Washington, Emergency Management Division. Search and rescue mission data sheet. Available at: https://mil.wa.gov/asset/5ba420d69bf05. Accessed August 15, 2022.
13. State of Oregon, Office of Emergency Management. Search and rescue annual report for 2014. p. 129. Available at: https://www.oregon.gov/OEM/Documents/2014_Annual_SAR_Report.pdf. Accessed August 15, 2022.