Axioms Altered With Research

Joseph C. Wenke, PhD

Joseph R. Hsu, MD

on Behalf of the Extremity War Injuries VII Research Panel[a]

Abstract

The medical community is actively engaged in research to provide the highest level of evidence to support clinical practice. The care of wounded warriors creates unique challenges, and conducting research that provides evidence for clinical practice is important to outcomes in this patient population. When the current wars began, much debate centered on the best way to care for wounded warriors. To address these concerns, we use a *MythBusters* format, based on the popular television show, to describe how recent research has dispelled some earlier misconceptions and clarify how clinical practice has been changed. In addition, we assess the progress that has been made on addressing the original prioritized research objectives of the first Extremity War Injuries symposium.

Lessons learned from previous wars and from civilian trauma help guide the care of wounded warriors, but each conflict introduces a different enemy, theater, and chain of evacuation. Because of new treatment challenges as well as the inherent complexity of following patients injured in combat to establish complication rates and outcomes, it is difficult to determine which therapies are best for a wounded warrior's outcome. Care of the battlefield-injured is often not evidence-based.

The goal of this session was to demonstrate that the funding opportunities for a concerted research effort focused on issues associated with military casualties have provided evidence sufficient to change practice behavior. We used a *MythBusters* approach, based on that used in the popular television series, to challenge many of the beliefs and practices that existed during the beginning of the war and that were the focus of many conversations and debates during the first Extremity War Injuries (EWI) symposium in January 2006. In addition, we provide an update on the progress of the prioritized research efforts that were the result of that first EWI symposium.[1]

"Negative-pressure wound therapy during medical evacuation is bad"

Negative-pressure wound therapy (NPWT) is a common practice for early management of open wounds and has been shown to reduce complications.[2] Early reports of the use of NPWT for combat-related wounds in Iraq suggested that the addition of this modality could dramatically improve infection rates compared with historical controls.[3] However, anecdotal evidence alleged that in-flight failure of the devices during medical evacuation, with resultant wound compromise, resulted in adverse outcomes. The most common evacuation route for severely injured casualties is from the theater to Landstuhl, Germany, and then to a medical treatment facility in the con-

[a] COL James R. Ficke, MD, Joseph R. Hsu, MD, LTC(P) Clinton K. Murray, MD, LTC Brett D. Owens, MD, Andrew N. Pollak, MD, Andrew H. Schmidt, MD, and Joseph C. Wenke, PhD

From the US Army Institute of Surgical Research (Dr. Wenke) and the Department of Orthopaedics and Rehabilitation (Dr. Hsu), San Antonio Military Medical Center, San Antonio, TX.

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tinental United States. The anecdotal evidence led to cessation of the use of the device in-flight from Germany to the United States.

Two studies were subsequently performed to specifically address the question of the feasibility and safety of NPWT during intercontinental aeromedical transport. Pollak et al[4] reviewed 218 patients who received NPWT for 298 wounds during aeromedical evacuation from theater to Germany. Although wound complications developed in 19% of patients, most were minor, and in no case was failure of the NPWT device in-flight implicated in the genesis of a complication. Fang et al[5] prospectively investigated the feasibility and safety of NPWT during intercontinental aeromedical evacuation (from Germany to the continental United States) of 30 patients with 41 separate wounds. The authors reported no significant in-flight complications, negligible impact on flight crew workload, and positive subjective feedback from both flight crews and patients. These data suggest that NPWT does not harm the wounds. Most severe wounds are now being treated with NPWT from the time of initial débridement in theater through the evacuation chain until time of closure or other definitive coverage. The information from these studies has led to change in practice.

"Outbreak of *Acinetobacter*"

At the onset of the wars in Iraq and Afghanistan, US military treatment facilities reported that casualties were developing infections with multidrug-resistant (MDR) *Acinetobacter baumannii*, a pathogen not typically reported from these facilities previously.[6] Initial thoughts were that this pathogen had been seen in previous wars (axiom 1), that the pathogen was located in the dirt and introduced into the wounds at the time of injury (axiom 2), and that the pathogen led to excess mortality and morbidity (axiom 3). Based on these factors, deployed clinicians used increasingly broad-spectrum antimicrobials (eg, imipenem) at the time of initial care to assist in the control of wound infection. To better understand the role of *Acinetobacter* in wound infections, however, these three axioms were evaluated.

Review of the literature noted that *Acinetobacter* had been seen in the Iran-Iraq War and the Lebanon War of 1982-1983 but not in the Vietnam War; in addition, *Acinetobacter* was noted for its overall low level of virulence.[7] Regarding the source of *Acinetobacter* in wounds, studies revealed that soldiers were not colonized with MDR *Acinetobacter*; neither was the pathogen located in the dirt.[8] However, data supported the role of nosocomial transmission with initial introduction of the pathogen into US military treatment facilities by local host-nation patients.[9,10] Furthermore, studies demonstrated that *Acinetobacter* is fairly common in wound cultures or surveillance cultures after evacuation to the United States and that the pathogen apparently became more resistant as increasingly broad-spectrum antibiotics (eg, imipenem) were used during initial surgical care in Iraq and Afghanistan. Finally, continued research into the morbidity and mortality of *Acinetobacter* demonstrated that, although the pathogen was recovered in wounds, this has been decreasing during the past 2 to 3 years; that there are effective, but limited, drug options for MDR strains; and that *A baumannii* is not the major cause of excess morbidity or mortality in the combat-injured.

Ongoing research regarding *Acinetobacter* changed the emphasis to focus on all MDR gram-negative bacilli, such as extended-spectrum β-lactamase–producing *Enterobacteriaceae* (eg, *Escherichia coli*, *Klebsiella pneumoniae*), *Pseudomonas aeruginosa*, and the gram-positive bacteria methicillin-resistant *Staphylococcus aureus*, which have greater virulence. In addition, early therapy has been directed toward standard non-MDR pathogen coverage, while infections that result later in a casualty's course are treated based on culture results. Finally, increased focus has been placed on infection control and on preventing indiscriminate use of broad-spectrum antibiotics.[11]

"Altitude causes compartment syndrome"

A long-standing axiom is that aircraft flight causes extremity edema, which would increase the risk of compartment syndrome in patients with limb injuries. However, urgent aeromedical evacuation of casualties is the practice followed in Operation

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Iraqi Freedom and Operation Enduring Freedom. These injured soldiers sustained a burden of musculoskeletal injury that was associated with significant morbidity and/or mortality because of inadequate or delayed fasciotomy.[12] Thus, the possible contribution of urgent aeromedical evacuation to further limb swelling and tissue injury in these combat-injured soldiers became an important question for research.

Three studies funded by the US Department of Defense have evaluated the effects of altitude on limb muscle compartments. Ritenour et al[13] created an ischemia-reperfusion injury in rats and compared normobaric and hypobaric conditions. Greater edema was seen in the normobaric group. McGill et al[14] measured intramuscular pressures in the uninjured limbs of anesthetized pigs that underwent a simulated 5-hour flight at 10,000 feet altitude. An increase in intracompartment pressure of 2.7 mm Hg was observed, an effect that is likely clinically insignificant. Kalns et al[15] used an angioplasty balloon to create a muscle injury in the anterior compartment of swine. Four groups of pigs were studied; 5 or 6 hours of compressive injury were followed by 8 hours of observation at sea level or simulated altitude (2,135 m). Muscle damage was assessed histologically, and levels of proinflammatory cytokines were measured. The 6-hour control limbs had a 100% incidence of compartment syndrome compared with 30% of the 5-hour animals. A very similar pressure response was seen in the pigs maintained at simulated altitude. Consistent differences were seen in the cytokine profiles of the standard and hypobaric groups, with the latter showing elevated levels of some markers. Interestingly, histopathologic evaluation showed less muscle degeneration and microvascular thrombosis in the hypobaric group than in the normobaric group. A series of small- and large-animal investigations revealed that, although subtle differences in muscle physiology may occur at altitude, these differences are not sufficient to consider that altitude causes compartment syndrome.

"Traumatic brain injury is the signature injury of the war"

Traumatic brain injury (TBI) has received funding for research as well as a great deal of attention in both the popular press and the peer-reviewed literature.[16] Although the incidence of TBI has increased, it is unclear how much of this is the result of improved surveillance and screening measures. Most of these injuries are classified as mild (ie, akin to a concussion). A large retrospective characterization of 1,566 battlefield-injured service personnel demonstrated that only 8% of the injuries were to the head, whereas 54% were to the extremities.[17] Moreover, these extremity injuries accounted for approximately two thirds of inpatient hospitalization, rehospitalization, medical retirement benefits, and medical unfitting conditions.[18-20] Cross et al[20] examined soldiers injured between October 2001 and January 2005 and reported the medical unfitting condtions and ranked them by impact. This revealed that in terms of medical retirement impact (defined as frequency × average percentage of disability) TBI has the 12th highest impact on medical retirement, and most of the higher ranking conditions were orthopaedic. A recent study prospectively followed 4,122 soldiers deployed to Iraq during the surge of early 2007; orthopaedic injuries were again the most common combat injury.[21]

Although TBI can be extremely challenging to wounded service personnel and does occur frequently, the marked increase in funding for research is not proportional to the burden of injury. TBI received approximately $477 million in funding for research in Fiscal Year 07-11.[22] Funding for research for orthopaedic injuries during this time has been approximately one third of this amount.[23] We feel that, in order to be just to the tens of thousands of those wounded in these recent conflicts, it would be best to not designate a single signature injury. Rather, we should recognize that the injured are polytrauma patients with many different injuries. The one constant, however, is that extremity injuries are the most common and account for the majority of the costs, morbidity, and disability.

"Status of the 2006 research priorities: Where are we now?"

The first EWI symposium produced a seminal list of research priorities[1] that have influenced subsequent funding opportunities. Progress in research is often slow because of funding cycles, animal and human study regulatory requirements, and publishing requirements and timelines. Nevertheless, substantial progress has been made, and we have developed a report card with grades determined by the following criteria: A, Evidence influencing practice/clinical trials; B, Large-animal study validated or published; C, Small-animal/translational study published; D, Proof of concept/funded only; and F, No progress made.

Development of data-collection systems

Grade: A. The Military Orthopaedic Trauma Registry has been created and is funded by the Program Objective Memorandum (Fiscal Year 13-17). The registry is located within

the Department of Orthopaedics and Rehabilitation at Brooke Army Medical Center. This database is much more specific to orthopaedic injuries, procedures, and outcomes than the current trauma registry.[24]

Optimal timing of treatment to include débridement

Grade: B. A substantial amount of work has been done in an effort to use biomarkers to help guide wound closure timelines.[25] Multiple animal models suggest that early débridement and antibiotic administration is more effective in removing and killing the bacteria.[26-28]

Temporary stabilization and definitive stabilization

Grade: B. Several studies have described the complications associated with damage-control orthopaedics (ie, early temporary external fixation followed by definitive fixation,[29,30] definitive fixation with ring fixators,[31] and urgent fixation).[32] The Major Extremity Trauma Research Consortium (METRC) has an ongoing prospective study that will compare intramedullary nails to ring fixators in severe open tibia fractures. [23]

Débridement techniques

Grade: B. An extremely well-powered prospective, randomized controlled trial has been funded, the Fluid Lavage of Open Wounds, to address questions regarding pressure and irrigants during débridement. Pilot data from that study suggest that high-pressure devices may cause deleterious effects.[33] A large-animal study corroborates this finding.[34]

Challenges unique to evacuation

Grade: C. A limited number of studies demonstrate the safety of evacuation transport during administration of NPWT as well as transportation with evacuees in external fixation; this is the case even with marginally stable patients under the care of a critical care air evacuation treatment team. However, controversy remains regarding the development and morbidity of evolving compartment syndromes, the timing and indications for stabilization, and the transport of patients with vertebral column injury.

Soft-tissue coverage and antibiotic management

Grade: B. A recently published, updated guideline describes current practices and makes strong statements regarding the treatment and prevention of combat-related infections.[11] However, level I and II trials demonstrating a clear benefit to early soft-tissue coverage, local application of antibiotic-impregnated materials, reduction or elimination of biofilms, or enhanced gram-negative coverage or prophylaxis are lacking. In clinical applications, infection and adequate reliable soft-tissue coverage remain areas in need of study and definitive answers.

Management of segmental bone defects

Grade: C. Research funding for study of extremity war injuries has reached unprecedented levels in the past 5 years. In large part, the EWI symposia have placed emphasis on these areas, and in response, METRC has received support. One of the METRC studies funded is directed toward identifying the optimum type of graft material for large segmental defects. This area, among all of the original prioritized research areas, remains the single largest need. Reliable, safe, and accelerated union of otherwise salvageable limbs by use of segmental bone defects demands additional study. Ideally, the bone graft should be effective in contaminated defects.[35]

Blast-injury survival model to validate translational inquiry

Grade: A. A reliable rat model replicating the effects of blast injury in the limb has been validated, and translational studies are underway.[36] Large-animal models for infection, fracture, acute spine injury, and various aspects of the injury pattern have also been funded by the Peer Reviewed Orthopaedic Research Program but are not completed at this time.

Best practices for amputee care

Grade: A. The three armed forces centers for advanced rehabilitation are the Military Advanced Training Center at Walter Reed Army Medical Center in Washington, DC, the Center for the Intrepid at the San Antonio Military Medical Center, and the Comprehensive Combat and Complex Casualty Care Center in the Naval Medical Center San Diego. These facilities have demonstrated substantial improvement in the care of the combatant amputee and have recently collaborated to publish a textbook on the topic.[37]

Prevention of heterotopic ossification

Grade: B. Although observational series and basic science studies have been published that demonstrate the prevalence and clinical management of heterotopic ossification,[38] the etiology and prevention of the disorder have not been clearly identified. Funded efforts are now under way through the Peer Reviewed Orthopaedic Research Program as well as the Orthopaedic Extremity Trauma Research Program.

Summary

Once-held beliefs have now been proved wrong because funding was

available for research on these topics; such updated information likely will improve patient outcomes. Much progress has been made in a very short amount of time. The topics discussed here focused only on the challenges regarding medical evacuation, wounding patterns, and bioburden. The most pressing topics, those related to reconstruction of extremity injuries, require more resources and time to address. Most Department of Defense funding for orthopaedic research has recently gone toward multicenter clinical trials, which will allow our civilian collaborations to answer some of these important questions. These research consortia position the military and civilian communities to respond as new challenges and improved technologies become available.

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