

Technical Evaluation Report

by Dr Howard Champion
UNITED STATES

HRCHAMPION@aol.com

The HFM Panel Symposium was held jointly with the ATACCC 2004 (Advanced Technology Applications for Combat Casualty Care) meeting. This annual meeting is hosted by the Combat Casualty Care Research Program HQ, USAMRMC, Fort Detrick, Maryland and sponsored by the US Department of Defense. The remit of this technical evaluation report is confined to the NATO/OTAN component of the meeting.

The Theme and Objective of the NATO component of the meeting were identified as follows.

1. THEME

In ground based tactical situations casualties can not be avoided. It is well documented that immediate haemostatic surgery can be life saving, and the most significant factor for survival is the time from injury to surgery. Late complications like septicemia and multi organ failure are in most cases sequelae of the initial hypo perfusion. In situations where evacuation will be delayed, the prehospital handling and management are of critical importance. In recent tactical situations with long distances to hospital, forward surgical teams have been deployed to reduce the time to surgery. Fast and correct decisions in questions of triage, evaluation and initial treatment are life saving and may reduce complications for the individual soldier. New technologies allow rapid location of casualties and advanced diagnostic aid and decision support in the field. The application of sensors to monitor vital signs and computers with embedded knowledge provide such support. Recent technology advances allow for non-invasive and remote monitoring of physiologic parameters and vital signs, thereby increasing the possibility for accurate treatment and management by ground personnel.

The main aim of casualty treatment is to secure oxygenation of critical tissues. Ventilation support, hemorrhage control and organ protection are thus crucial. Hemostatic devices such as improved bandages and tourniquets, haemostatic drugs, and agents such as platelet substitutes and oxygen carrier molecules based on per fluorocarbons or modified hemoglobin address the hemorrhagic challenge. Optimal fluid management, vasoactive drugs and resuscitation fluid additives to promote micro vascular perfusion may protect organ function and prevent organ failure and increase survival. During the last decades micro vascular sensitivity to inflammation has been identified as a major contributor to tissue hypo perfusion and various inhibitors of the inflammatory response have been tried to provide organ protection.

2. OBJECTIVE

The main objective of this symposium is to present recent knowledge on war casualty management, based on experience from tactical situations and scientific research. These findings will focus on state of the art and future devices and biological agents for location, triage, monitoring and resuscitation of casualties.”

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3. TOPICS TO BE COVERED

During the opening comments and welcoming addresses at the meeting, representative General staff identified further strategic objectives that the meeting should accomplish. Many of these are non-trivial in nature.

After summarizing the scope and nature of the command responsibilities of USAMRMC, Major General Martinez-Lopez, Commanding General of USAMRMC, sought to imbue the some 700 participants of the joint conference with a sense of urgency in addressing the issues of combat casualty care and stressed that the focus should be on the patient --the combat casualty. He asked participants to examine whether they are partnering, collaborating, cooperating sufficiently to address the urgency of this agenda.

Dr. Robert Angus, Director General of Defense R&D Canada, Chairman of the NATO RTO Human Factors and Medicine Panel, provided the history and current portfolio of the NATO Human Factors in Medicine panel, the goal of which is to optimize the performance of the soldier, through research and technology in human factors (individual, group and systems), human protection and operational medicine.

Major General Roger van Hoof (BE), Chairman of the Committee of Chiefs of the Military Medical Services in NATO (COMEDS) and Brigadier General Roedig (GE), Surgeon General of the German Air Force and HFM Panel Member, stressed the changing environment making great emphasis on the need for interoperability between collaborating national forces providing medical support to military expeditionary units. "Interoperability is the golden standard and requires a global integrated healthcare systems and effective multi-national evacuation system."

Dr. Erik Fosse (NO), Chairman of the Program Committee and HFM Panel Member, summarized the medical issues in international operations and the process by which the objectives of the meeting had been developed and papers selected.

The first session of the joint NATO/OTAN/ATACCC meeting was concluded with a panel discussion of recent experiences from Operation Iraqi Freedom led by Col. John Holcomb (US), the Trauma Consultant to the US Army Surgeon General and Commander of the US Army Institute of Surgical Research. These panels have been a standard introductory feature to ATACCC, whereat young men and women with recent and relevant experiences provide a generally unstructured account of the injuries encountered, care provided, their problems and frustrations. Representatives from helicopter CASEVAC crews, forward surgical and combat support hospitals were heard from including one young sergeant from the 101st Airborne who had received a bronze star for caring for 18 injured colleagues after himself being wounded. There was much emphasis on the need for flexibility and adaptability in medical support in Operation Iraqi Freedom as the op-tempo changed from rapid, mechanized maneuver phase to early and later insurgency phases, with changing enemy tactics, and the ability to operate from fixed and more sophisticated Combat Support Hospitals rather than FRS and FRSS settings. Persistent "needs" included:

- pediatric equipment to treat wounded and sick children
- address the problems with medical re-supply logistics
- a persistent plea for better and relevant training.

Other issues of significance that were catalogued including coagulopathy and hypothermia, ability to deliver certain blood products, the research challenges associated with duplicating the clear value of fresh whole blood (of which over 500 units had been used in theatre), the need to collect and aggregate data over an

appropriate denominator to achieve a picture of the epidemiology, nature and severity of combat casualties and their contemporary outcome, the need for adaptable trauma systems in operational settings; training, tourniquets, tension pneumothorax (as potentially preventable deaths), mortality and morbidity associated with extremity injuries, eye injuries, limitations of body armor, primary blast injury, diagnostic and monitoring devices (particularly the need for a small, easily-handled, self-contained vital sign monitor), extraction equipment, patient warming equipment, pain medication, the need for CASEVAC helicopters to talk to the ground directly as opposed to through 3 or 4 intermediaries, and the pressing need for an improved medical records system that could travel with the patient.

This panel consistently grounds researchers and others in the realities of combat casualty care, and though unstructured and somewhat unscientific in nature, continues to be of value.

Distribution of topics and papers. The NATO/OTAN component and the joint sessions incorporated some 80 presentations and posters. Although there was significant duplication between some of the presentations and posters, the relative distribution by topic is given in the table below.

1.	Resuscitation including TBI	30%
2.	Hemostasis	20%
3.	Wounds & Extremities	20%
4.	Monitoring & Triage	20%
5.	Evacuation Systems & Logistics	10%

Resuscitation. As the global deaths from injury continue to rise towards 10 million by the time we are in the second decade of the 21st Century, some 2 to 3 million individuals die per year from post-traumatic hemorrhage and its sequelae improved if not patient specific resuscitation from hemorrhagic shock is a high priority in both civilian and military circles. Low cube weight resuscitation fluid has long been a military research priority. Some twenty years ago (1984) US ARMY MRMC embarked on a mission to provide such a solution. This resulted in Hypertonic Saline Dextran, a product though in use in Europe is still unavailable in the United States. It is fitting that the first scientific paper of this joint symposium should focus on Hypertonic Saline/ Hypertonic Saline Dextran solutions.

Shawn Rhind gave us a masterful summary of the immunological effects observed in series of animal, in vitro and clinical studies, cataloguing beneficial effects on IL CD62L, Beta integrin CD116, the down regulation of PMN/endothelial cell interaction through CD116 CD62L decrease in PMN chemotaxis, increase lymphocyte function, reduction of endothelial cell permeability and improved organ function alterations in cellular signaling and increase in IL10 productivity by macrophages.

Hypertonic Saline Dextran (HSD) has been shown to be safe and effective in eight clinical trials. In recent experiments in the Sunnybrook, University of Toronto lab, normal saline was shown to up-regulate flow inflammatory lymphocytes. This did not occur with HSD. HSD blinded the inflammatory response to LPS stimulus, enhanced serum-soluble L selectin, inhibited LPS-induced and spontaneous increases in TNF alpha. IL 10 was shown to go up dramatically. The alpha adrenergic inflammatory response to shock found with normal saline was not present with Hypertonic Saline Dextran.

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This excellent body of science was further supplemented by a paper contributed by four of the leading scientists involved in research on hypertonic fluid resuscitations (Kramer, Wade, Dubick, and Atkins). George Kramer provided an overview of state of the science on a small volume, hyperosmolar, hyperoncotic resuscitation fluids, and HBOCs. He also noted his recent work on closed-loop resuscitation systems. Eighty-two trials with 7.5% solutions have been conducted, all under powered for survival in shock, but clearly showing that the solution provides early, fast, effective volume replacement and vasodilation with immunomodulation and a mortality decrease of 4.3% when used as HSD. HSD has been shown to be particularly beneficial in head injury and penetrating injury.

It was clear from these discussions that work will continue on optimizing resuscitation fluids. It is indeed fitting that the first injury related, multi-center trial to come from NIHLB/USAMRMMC collaboration will focus on HSD (? HS) resuscitation. This 10-center clinical consortium, jointly funded by the National Institute of Health and the US Army MRMC, will eventually provide rapid translational research for the basic sciences devoted to resuscitation, hemostasis and other injury-related research. It is a much needed and urgently required effort that will allow adequate powering and rapid accumulation of appropriate patient populations.

Dr. Pang Shek stressed the considerable value of this effort which he has been promoting for a number of years, stressing that within 5 years substantial results are likely to be able to be taken to the point of wounding provider. Dr. Shek also discussed the NATO Response Force, launched in November 2002 wherein there is a need for a rapid response within 5 days for 30 days – “first force in and out” and thus the urgent need for interoperable medical support systems for such a force.

The ceremonial signing of this agreement occurred at the closing session of the first day of this joint NATO/ATACCC meeting.

Other cutting edge resuscitation strategies included:

Vasopressin. Summarizing many years of research funded by the Office of Naval Research, Landry specified the effects of this drug in cardiogenic, septic and late phase (vasodilatory) hemorrhage shock.

Proctor, from the University of Miami also ONR funded, presented data from a fluid percussion, TBI model with shock showing benefits in terms of fluid needs, ICP and cerebral compliance, but expressing some concerns about decreased cardiac index and possible bowel ischemia in this non-vasodilated shock model.

- Another exciting adjuvant is Trans Sodium Crocetin, which improves O₂ consumption in shock by changing the O₂ diffusivity by alterations in the structure of water. This tantalizing animal data will hopefully soon result in human tests by Gainer’s lab at UVA.
- Other promising adjuvants presented at the meeting included a world-class summary of the use of complement inhibitor APT070. The use of which would merely require a change in labeling in this already FDA-approved drug.
- A number of papers gave the state of the art on HBOCs. Bovine polymerized hemoglobin (HBOC-201) is being studied in animal models by the Naval Medical Research Center who reported on its hemodynamic, coagulation and immunological effects compared with Hextend® and controls, in hemorrhagic shock models in swine for both controlled and uncontrolled hemorrhage. Kramer and Dubick also updated us on the use of the competing Polyheme®. These oxygen-carrying colloids appear to reduce the need for volume but may still have some issues in terms of nitric oxide

scavenging and increased systemic and pulmonary vascular resistance; though nothing like as bad as those that were found in the Baxter product some years ago. Polyheme® and Hextend® were also studied by Sondeen at the ISR with respect to prolonging resuscitation and preventing “pop-the-clot” rebleeding.

HBOC’s are on the verge of being part of a therapeutic armamentarium but their precise role in the treatment of early shock management remains a little unclear and requires to be defined. Questions also remain regarding the appropriateness of shock models without tissue damage and the complexities and variabilities in uncontrolled hemorrhage shock states.

Hemostasis. This topic is receiving substantial attention from many researchers and is producing results which can be near term fielded. Particularly exciting was the evident interlinkage and crosswalk between immunology and coagulation which is providing a fertile and important field of research focus.

- Recombinant rFVIIa. One of the hottest topics in the whole arena of combat casualty care is the great promise shown by rFVIIa in patients with severe hemorrhage. Dr. Uri Martonovits, the father of rFVIIa use in this domain (the drug was originally created for hemophilia), gave the conference participants an overview of its use in combat casualty care, identifying roles not only for adjuvant use in patients with serious and uncontrolled hemorrhage, but also emerging potential value in patients with intracerebral hematoma from traumatic brain injury and the hemorrhagic consequences of primary blast injury to the lung. Dr. Martonovits deliberately extrapolated the value as being more likely with early use to the point that he suggested that in the future it might be given as a prophylaxis for high risk Special Forces missions.
- Sandro Rizoli reported on a subset of patients from the recently completed controlled trial of use of rFVIIa in severe hemorrhage conducted in a number of European countries, South Africa and Singapore, identified as those who received coagulation factors in the presence of massive transfusion. Dr. Rizoli reported the reduced need of red blood cells and fresh frozen plasma and platelets in those receiving rFVIIa when compared with placebo controls. He also pointed to a trend towards reduction in multiple organ failure and ARDS but no impact on death. Lively discussion identified concerns with respect to:
 - the operational definition of patients by using coagulation factor administration as both a dependant & independant variable
 - disappointment that there was no reduction in death from hemorrhage
 - concerns about cost effectiveness in that the cost of drug administration far outweighed the savings in administering blood products.

Despite these concerns there was general approbation regarding the fact that a controlled trial had been conducted, the difficulties of which in this patient population cannot be underestimated, and the fact that the good safety record had caused the FDA to withdraw their clinical hold on the use of this exciting and extremely promising drug.

Tourniquets. This topic continues to be the focus of lively discussion and debate. The surgeon’s perspective was ably presented by Dr. Pillgram-Larsen who emphasized the value of compression dressings and urged the limitation of tourniquets to the tactical environment. This approach indeed comports with the pleas of the point of wounding care medics who continue to find value in a tourniquet, but would wish an improved

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design. It was somewhat stunning to see a recent picture from Iraq with sticks used to tighten cloth tourniquets—a technology that has been around for centuries. The failure of the one-handed tourniquet to do the job has provoked substantial effort at the ISR to identify the requirements for optimum tourniquet. A later presentation on technologies from Dr. McEven & Inkpen (from one of the leading companies that makes tourniquets for use in surgery) elaborated on optimal tourniquet designs and their efforts to transport lessons learned in tourniquet use in surgical practice (some 20,000 users per day in the US) to the point of wounding care provider. As surgeons we do not see those that die from lack of tourniquet use in the field. There have been at least 8 such incidents in Operation Iraqi Freedom.

Dressings. Many researchers have been developing and evaluating a large number of dressings with hemostatic or other worthy attributes. The Army Hemostatic Research program has tested some eleven dressings with further evaluation on three.

- Martineau (DRDC) presented data on a bi-layer wound dressing. The hydrogel layer prevented drying of the wound and a foam layer provided effective drug delivery. This absorbable, flexible, strong, non-adherent dressing showed promise for both burns and other wounds.
- A formidable array of research from the US Army Institute of Surgical Research presented a comprehensive research program addressing controlled and uncontrolled hemorrhage. These include the hemostasis research program (Ryan), evaluating compressible hemorrhage and strategies to strengthen clot formation using rFVIIa and to manage resuscitation to prevent the “pop-the-clot” phenomena that occurs as the systolic pressure recovers above 90 mmHg, (Sondeen) thus reducing the problems associated with re-bleeding as a consequence of successful initial resuscitation. Dubick gave an overview of the hypotensive research strategies using Hespan, Hextend® and bovine polymerized hemoglobin in controlled and uncontrolled hemorrhage models. This joint Army/Navy program was particularly focused on issues of uncontrolled hemorrhage.
- A structured set of research strategies for non compressible, uncontrolled hemorrhage was presented by both Drs. Sondeen and Kheirabadi. The latter exposed a number of experiments using foam and other agents to induce clotting in closed intra-abdominal hemorrhage. These interesting results are yet to yield a product worthy of clinical consideration but this important research line continues.
- Martini, also from the ISR, presented an elegant and important series of experiments in hemorrhagic shock swine identifying the impact of acidosis and hypothermia individually and collectively on coagulation and thus unveiling separate and complementary strategies for addressing this vexing clinical problem.

Monitoring & Diagnosis. A number of works were presented on cutting-edge techniques for monitoring shock states including two papers from the University of Minnesota on cellular energetics and near-infrared spectroscopy to discriminate between likely and unlikely survivors.

Trans-dermal non-invasive monitoring of glucose and lactose was presented using a micro-fluid electro-chemical chip with a wireless transmission range of up to 100 meters. This small monitor could be placed on the individual soldier and function up to 2 hours. Another soldier-centric monitor was the capacitance-coupled ECG monitor which provided ECG trace without skin contact. Other research work discussed the Armored Ballistic Impact Protection System for intended use with the Future Force Warrior together with some very preliminary data. A conceptual presentation arrayed the set of sensors that could be used in the Future Force Warrior detecting vital signs and providing data on the environment for both monitoring and decision support for the medic.

Refinements in triage have been taken very seriously by researchers. A number of posters presented data on sequential analysis of vital signs. Perhaps the most interesting work in this arena comes from the Institute of Surgical Research where continuous prehospital vital signs monitoring in patients has yielded valuable insights into the changes in pulse volume and pulse pressure in early pre-hypotensive shock states. There appears to be little doubt that measurement of the RR interval and information on pulse pressure or pulse volume could substantially improve the ability to detect individuals who are bleeding prior to hypotension developing and thus obviate severe shock states being taken as the threshold for action. In theory, such information could be coupled with time between injury and the identification of sub-clinical shock thresholds, enabling prognostication of the time interval available before definitive therapy must be available and aiding in the titration of resuscitative and coagulation therapies that lengthen this window of opportunity in tactical settings.

The end user (medic) requests for simple, reliable wireless vital signs monitor was heard by Commander Peter Rhee who presented a demonstration of a wireless COTS system that could be made available now and monitor a number of patients at level 1, 2, 3 facilities. Other monitors presented included systems directed at non-invasive monitoring for brain blood flow. A number of others connected sensor suites to decision-support systems to help in triage and treatment decisions. There were at least three solid attempts to integrate vital signs monitoring and ventilator functions. Ultimately these systems will provide closed-loop care with ventilation being driven by end-tidal CO₂ and/or compliance, oxygen saturation providing closed-loop direction of FI_{O2} and measures of shock state guiding intravenous and transfusion therapy. Such devices would ameliorate the risk associated with transfer of patients between level 2 and 3 and would be of particular value in patients that have had damage control therapy at level 2 requiring definitive care at level 3 capabilities.

Researchers also presented data on predictive blood gas analysis for patients needing strategic air evacuation.

Wounds -Fracture Healing

- In Operation Iraqi Freedom, as in all wars in the past 150 years, limb and soft tissue injuries predominate. With increasing interoperability a small light radio-lucent, non-magnetic, low-cost external fixator is sorely needed. NATO has issued a STAMAG for such a transport fixator. New designs responsive to this were presented.
- A number of leading researchers with decades of expertise presented technologies to improve wound healing including photodynamic therapy and low-energy photonic therapy (LEPT). With open fractures constituting the majority of fractures occurring in combat, delayed healing and non-union as result of infection. An antimicrobial bone graft demonstration identified that such technologies were available and indeed could be shortly deployed to address these problems.
- Important contributions were heard on pain management with both basic science research for a morphine replacement and data on use of nasal Ketamine and the Fentanyl lollypop.
- One paper presented the use of training simulators identified substantial skill decrement on performance under stress situations.

The Marine Combat Trauma Registry emphasized the value of systematic data collection in identifying the epidemiology, severity of injury and outcomes of injury and actual workload at various levels of care.

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Observations and Conclusions

A substantial number of excellent scientific papers were presented many from world leaders in their domain and all of which had direct short or long-term bearing on combat casualty care. Outstanding science on hemostasis, shock research and resuscitation was dominant but important and cutting-edge presentations on technologies and monitoring with rationale solutions for existing problems were also offered. The Program Committee did an outstanding job in providing a meeting at which any person interested in this domain could obtain substantial information and value.

Had time permitted on an already very full schedule, topics of interest that would have had a ready audience include:

- Trauma Registries & Trauma Systems. Contemporary aggregated data on a valid denominator can provide us with information on the epidemiology, severity and nature of wounds and outcome. This would allow for identification of roles of various medical care resources in different phases of combat and more effectively matched need and resources in planning. There have been over 7,000 US casualties in Operation Iraqi Freedom and 935 deaths—every single one of which has received a complete autopsy. Registry data is being collected by the United States Navy and Marines, United States Army and the British Army. Information from these data would surely help guide and prioritize research and primary, secondary and tertiary tactics, techniques and technologies of injury prevention. It would provide a better understanding of systems of care needed and it would thus provide a substrate for precision implementation of the trauma systems that Colonel Holcomb advises us to implement. Trauma registries have played a substantial role in the civilian sector for the past twenty years and are sorely needed for combat settings.
- The use of IED's has been a dominant factor during the insurgency phase of Operation Iraqi Freedom with different tactics and use in combination with small arms causing devastating injuries. The known availability of infantry mobile TBX and the likely use of such weapons mandate a focus on explosive injuries, particularly primary and tertiary blast with a view to protection, prevention, deflection and definitive treatment.
- Problems associated with the medical resourcing-accurate and effective matching need with available resources and the failure of the logistic train to adequately supply and re-supply were noted, but few solutions offered.
- There needs to be a structured approach to transatlantic collaboration.

Recommendations

- More Joint Meetings
- More multi-national presentations at such joint meetings, particularly from research labs in Europe.
- Future focus to include:
 - The scientific basis (evidence) for combat and expeditionary injury care
 - Epidemiology and patterns of severity of injury and databases on the battlefield and post maneuver expeditionary force trauma systems
 - Blast injury research to characterize the scope and nature of primary blast injury in a context of secondary, tertiary, and quaternary injury in contemporary tactics. This particular topic would have significant crosswalk value to civilian terrorist issues.

- Develop a database using “portal” system to catalog available research and opportunities for collaboration.
- Surgical infection and morbidity with a view to developing multinational clinical trials on primary, secondary, tertiary prevention approaches to the morbidity sequelae of combat injury

