Eileen Bulger, M.D.

- Hypertonic Resuscitation for Blunt Trauma
- Prehospital Airway Management & Treatment for Traumatic Brain Injury
- National Variability in Prehospital Care following Injury
- Immunomodulation of the Alveolar Macrophage
- Management of Necrotizing Soft Tissue Infections
- Rib Fracture Management

AWARDS

American Association for the Surgery of Trauma
- Wyeth-Ayerst Research Scholarship Award
- John H. Davis Research Scholarship Award
- Peter C. Cannizaro Award 2004

FUNDING

American Association for the Surgery of Trauma Research Scholarship
Brain Trauma Foundation
Medic One Foundation
National Institutes of Health

Based on a strong interest in trauma and critical care, my research has focused on addressing important clinical questions regarding patient management, and elucidating the cellular biology of the systemic inflammatory response. My clinical research has focused on the prehospital care of patients following traumatic injury, including airway management and fluid resuscitation strategies. My laboratory efforts, in collaboration with Dr. Ronald V. Maier & Dr. Joseph Cuschieri, have focused on the immunomodulation of the alveolar macrophage, which plays a key role in the development of the acute respiratory distress syndrome (ARDS). In addition, a collaborative study with Dr. Avery Nathens seeks to explore the predictors of poor outcome following necrotizing soft tissue infection. Additional clinical trials address the pain management options for patients with rib fractures and the development of clinical care guidelines for these patients.

Hypertonic Resuscitation for Blunt Trauma

An evolving body of evidence suggests that resuscitation with hypertonic fluids following injury may improve outcome. The potential benefits of hypertonic resuscitation include more rapid restoration of tissue perfusion, preservation of cerebral perfusion while lowering intracranial pressure for brain-injured patients, and modulation of the inflammatory response at the time of reperfusion, thus lessening the subsequent development of inflammatory organ injury such as ARDS. With the support of the National Heart, Lung, and Blood Institute of the NIH, we have embarked on clinical trials to answer these questions. We recently closed a local trial in which randomized patients received either hypertonic saline/dextran (HSD) or lactated ringers as their first resuscitation fluid, administered by the paramedics at the scene of the injury.

The primary outcome variable was ARDS-free survival within 28 days. Secondary outcomes include mortality, infectious complications, multiple organ dysfunction, and long term neurological function for patients with traumatic brain injury. We have subsequently used the lessons learned from this trial to design a multicenter trial to be conducted by the Resuscitation Outcomes Consortium (ROC). The ROC involves 10 clinical centers in the US and Canada and a data coordinating center based at the University of Washington (PI: Al Halstrom; Co-PIs: Graham Nichol, Eileen Bulger). The Seattle and King County Medic One programs are one of the regional clinical centers (PI: Peter Kudenchuk; Co-PIs: Tom Rea and Eileen Bulger).

The ROC, which is supported by the NIH, Department of Defense and Canadian Institute for Health Research is charged to conduct prehospital clinical trials of promising therapies for both cardiac arrest and life threatening trauma. The proposed trial of hypertonic resuscitation will enroll nearly 6000 patients in a three arm trial of HSD, hypertonic saline without dextran and normal saline as the initial resuscitation fluid for a hypovolemic shock cohort and a traumatic brain injury cohort. These trials are designed as definitive Phase III trials to determine the efficacy of this resuscitation strategy. Investigators from three of the clinical centers including Seattle, San Diego, and Toronto have also submitted an

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R01 application to conduct detailed studies of the immuno-inflammatory response of patients enrolled in the clinical trial (PI: Bulger).

Prehospital Airway Management & Treatment for Traumatic Brain Injury

Currently supported by two grants from the Medic One Foundation, we have been investigating the airway management strategies employed in Seattle, with a particular focus on the management of patients with anatomy or injuries that make endotracheal intubation particularly challenging. We have reported that with the aid of paralytic agents to facilitate intubation, the Seattle Medic One program has the highest success rate for intubation in the literature at 98.4% and the lowest surgical airway rate at 1.1%. (*J Emerg Med*, 2002). We have subsequently established a prospective data collection process to allow us to track the impact of different airway management strategies on patient outcome.

Among injured patients, the group that may benefit the most from early airway control and resuscitation are those with traumatic brain injury (TBI). It has been well established that hypoxia and hypotension contribute to the development of secondary brain injury and worsen outcome following TBI. A single episode of prehospital hypotension has been associated with a two-fold increase in the incidence of adverse outcome (severely disabled, vegetative, or dead) following severe brain injury. With the support of the Brain Trauma Foundation we recently completed a study investigating the relationship between prehospital interventions and outcome following TBI. We identified that patients undergoing prehospital intubation facilitated by neuromuscular blocking agents actually had a better outcome than those intubated without these medications (*J Trauma* 2005). We are now collaborating with the national experts in this area to draft a position paper regarding the prehospital management of the airway for patients with severe traumatic brain injury. In addition, we are collecting additional data to assess the impact of prehospital hyperventilation on outcome in this patient population.

National Variability in Prehospital Care following Injury

In collaboration with Drs. Jerry Jurkovich and Fred Rivara, co-PIs on the National Study of Costs and Outcome for Trauma (NSCOT), we have utilized data collected from 14 geographic regions in the US to assess the variability in prehospital care provided to victims of traumatic injury. We have identified substantial variability in prehospital care among the regions including: prehospital intubation (5-48%), use of neuromuscular blocking agents or sedatives to facilitate intubation (0-100%), surgical airway access (0.1-3.5%), peripheral and central intravenous access (22-95%), and needle thoracentesis (0-5%). Intubation success rates averaged 94% in patients receiving neuromuscular blocking agents vs. 67% for those who did not ($p < 0.001$). This variability persisted even when patients were stratified based on their injury severity and physiology. Understanding this national variability in care and EMS system design is critical to interpreting the various studies in the literature and to designing future multi-center trials.

Immunomodulation of the Alveolar Macrophage

ARDS is a process of acute inflammatory lung injury, which affects a diverse array of surgical and medical patients. The etiology of this process is thought to involve an excessive overexpression of the inflammatory response, leading to the destruction of host tissue. The alveolar macrophage is a key cell in the coordination of this response. Our laboratory has focused on all aspects of this response using endotoxin as a prototypic inflammatory stimulant. In previous studies we have demonstrated that treatment of alveolar macrophages with certain antioxidants, in vitro, results in significant inhibition of the macrophage cytokine response. This work was extended to an *in vivo* model of enteral Vitamin E supplementation in rats with similar results and a recently completed prospective, randomized trial of high dose enteral Vitamin E and C vs. placebo in the surgical ICU.

Recently we have also investigated the use of platelet activating factor acetylhydrolase (PAF AH) *in vitro*. PAF is a pro-inflammatory lipid mediator which has been implicated in several animal models of lung

injury. PAF AH is the endogenous enzyme for PAF metabolism. These studies have demonstrated profound inhibition of cytokine production by macrophages treated with PAF AH prior to and following LPS stimulation. With the support of the American Association for the Surgery of Trauma Research Scholarship, we have developed an animal model of ARDS and have begun to test promising modulators of macrophage activation in this model. We have demonstrated that both PAF-AH and hypertonic saline, when given intravenously, dramatically down-regulate alveolar macrophage activation in response to inflammatory stimuli.

In collaboration with Dr. Pat Stayton in the Department of Bioengineering, we have secured NIH funding to test a novel intracellular drug delivery system as a means to modulate alveolar macrophage activation, in vivo. We will utilize our established model of ARDS to test the delivery of antisense IRAK and iNOS to alveolar macrophages and the impact of this therapy on subsequent cytokine production.

Management of Necrotizing Soft Tissue Infection

Harborview Medical Center serves as a regional referral center for patients with severe necrotizing soft tissue infection and as a result has seen dramatic increase in the number of these cases over the past several years. In an effort to define the morbidity and mortality of this population, we undertook a retrospective review of our experience over a 5 year period (Anaya et al, *Arch Surg* 2005). In this review we identified clinical predictors of mortality and limb loss based on data available at the time of patient admission. In a subsequent study we incorporated data from patients treated at the University of Texas in Houston and developed a clinical prediction rule which was internally validated. We are also working with the Surgical Infection Society to generate evidence-based guidelines for the management of these patients.

Rib Fracture Management

Rib fractures are a common injury in the blunt trauma population and are often under-appreciated in the setting of multiple injuries. The elderly are particularly susceptible to complications resulting from rib fractures and underlying pulmonary injury. We recently reviewed all patients > age 65 admitted to HMC with rib fractures over the past ten years and compared these to a cohort of younger patients. Of note, there was a nearly linear increase in mortality and complication rates associated with increasing rib fracture number in the elderly group. An elderly patient with only 3-4 rib fractures had a 19% mortality and a 31% rate of pneumonia. For an elderly patient with > 6 rib fractures, mortality was 33% with a pneumonia rate of 51%.

The key strategy in the management of these patients involves the ability to obtain adequate pain control to optimize pulmonary status. To determine the best pain management strategy for these patients we undertook a prospective, randomized trial of thoracic epidural vs. intravenous narcotics. We demonstrated that epidural analgesia decreased the rate of nosocomial pneumonia and shortened the duration of mechanical ventilation (*Ann Surg* 2005). In recognition of the ongoing controversy regarding the indications and contraindications for epidural placement in multiply injured patients, we next conducted a survey of pain service directors at all Level 1 trauma centers in the United States. We plan to use the results of this survey to stimulate the generation of guidelines for the use of thoracic epidural analgesia after injury.

RELATED PUBLICATIONS

1. Bulger EM, Nathens AB, Rivara FP, Moore M, MacKenzie EJ, Jurkovich GJ. Management of Severe Head Injury: Institutional Variations in Care and Effect on Outcome. Critical Care Medicine 30 (8): 1870-1876, 2002.
2. Bulger EM, Copass MK, Maier RV, Larsen J, Knowles J, Jurkovich GJ. An analysis of advanced prehospital airway management. J Emerg Med 23:183- , 2002.
3. Bulger EM, Gourlay D, Cuschieri J, Jelacic S, Staudenmeyer K, Garcia I, Maier RV. Platelet Activating Factor Acetylhydrolase inhibits alveolar macrophage activation, in vivo. Shock 20:17-22, 2003.
4. Bulger EM, Garcia I, Maier RV. Induction of heme-oxygenase 1 inhibits the proinflammatory response of endothelial cells. Surgery 134:146-52, 2003.
5. Bulger EM, Edwards T, Klotz P, Jurkovich GJ. Epidural analgesia improves outcome following multiple rib fractures. Surgery 136(2): 426-30, 2004
6. Bulger EM, Jurkovich GJ, Farver CL, Klotz P, Maier RV. Oxandrolone dose not improve outcome for chronically ventilated surgical patients. Annals of Surgery 240(3):472-8, 2004.
7. Anaya D, McMahon K, Nathens AB, Sullivan S, Foy H, Bulger EM. Predictors of Mortality and Limb Loss in Necrotizing Soft Tissue Infections. Archives of Surgery 140:151-157, 2005.
8. Bulger EM, Copass MK, Sabath D, Maier RV, Jurkovich GJ. The use of Neuromuscular Blocking Agents to Facilitate Prehospital Intubation does not Impair Outcome following Traumatic Brain Injury, J. Trauma, 58 (4):718-724, 2005.
9. Pickens J, Copass MK, Bulger EM. Trauma Patients Receiving CPR: Predictors of Survival. J Trauma, 58(5):951-958, 2005.
10. Staudenmeyer K, Maier RV, Jelacic S, Bulger EM. Hypertonic saline modulates innate immunity in a model of systemic inflammation. Shock 23 (5): 459-463, 2005.

DEPARTMENT CO-INVESTIGATORS

Daniel Anaya, M.D. / Michael K. Copass, M.D. / Joseph Cuschieri, M.D. / Hugh Foy, M.D. / Iris Garcia / Sandy Hanson, R.N. / Gregory J. Jurkovich, M.D. / Ronald V. Maier, M.D. / Avery B. Nathens, M.D., Ph.D., M.P.H. / Daniel Sabath

OTHER CO-INVESTIGATORS

Thomas Edwards, M.D.; UW Department of Anesthesiology / **Mickey Eisenberg, M.D.;** UW Department of Emergency Medicine / **Al Halstrom, Ph.D.;** UW Department of Biostatistics / **Peter Kudenchuck, M.D.;** UW Department of Cardiology / **Graham Nichol, M.D.;** UW Department of Medicine / **Thomas Rea, M.D.;** UW Department of Medicine / **Frederick T. Rivara, M.D., M.P.H.;** UW Department of Pediatrics / **Patrick Stayton, Ph.D.;** UW Department of Bioengineering