

# Eileen Bulger, M.D.



- HYPERTONIC RESUSCITATION FOR BLUNT TRAUMA
- PREHOSPITAL AIRWAY MANAGEMENT & TREATMENT FOR TRAUMATIC BRAIN INJURY
- IMMUNOMODULATION OF THE ALVEOLAR MACROPHAGE
- THE CYTOKINE PROFILE OF BURN PATIENTS RECEIVING PLASMAPHERESIS
- RIB FRACTURE MANAGEMENT
- VARIATIONS IN THE CARE OF HEAD INJURED PATIENTS
- THE USE OF ANABOLIC STEROIDS IN THE CHRONICALLY VENTILATED SURGICAL PATIENT

## AWARDS

### American Association for the Surgery of Trauma

- Wyeth-Ayer Research Scholarship Award, 2001
- John H. Davis Research Scholarship Award, 2002

### American College of Surgeons

- Committee on Trauma Competition, Best Basic Science Paper 1995 & 1999, Finalist 1996
- Washington State Chapter Henry N. Harkins Resident Paper Competition, 2nd place (1994)
- Helen and John Schilling Resident Research Symposium, First Place (2000)
- Seattle Surgical Society Award

### Shock Society

- Young Investigator Award, Finalist (1996)

## FUNDING

### American Association for the Surgery of Trauma Research Scholarship

### Brain Trauma Foundation

### Clinical Nutrition Research Unit, University of Washington

- Pilot & Feasibility Award

### Medic One Foundation

### National Institutes of Health

### Washington State Council of Firefighters

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, 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. Nicole Gibran seeks to explore the cytokine physiology associated with the response to plasmapheresis in the severely burned patient. Additional clinical trials address the pain management options for patients with rib fractures, the use of anabolic steroids during critical illness and variability in the care of patients with traumatic brain injury.

### 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 are embarking on a clinical trial to answer these questions. We will randomize patients to receive 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 is ARDS within 28 days. Secondary outcomes include mortality, infectious complications, multiple organ dysfunction, and long term neurologic function for patients with traumatic brain injury. We intend to enroll 400 patients over a 2.5 year time period. Without the support of the Seattle/King County Medic One program and Airlift Northwest, this study would not be possible. It is our hope that the lessons learned from this trial will support a multi-center trial of hypertonic resuscitation in the future.

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The NIH has recently released a request for applications to establish a clinical research consortium to conduct multi-center trials for the acute resuscitation of both cardiac arrest and traumatic injury. They have committed \$43 million over 5 years, toward funding seven regional clinical centers and a data coordinating center to conduct these studies. With the support of the Medic One Program, Dr Peter Kudenchek (Principal Investigator) and myself and Dr Tom Rea (Co-PIs) are submitting an application for Harborview Medical Center to be a regional clinical center within this consortium. If funded, this will provide the infrastructure and support to conduct a number of clinical trials with the large patient population available from multiple centers.

#### **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. In addition, in collaboration with Drs. Jerry Jurkovich and Fred Rivara, co-PIs on the National Study of Costs and Outcome for Trauma (NSCOT), we have been utilizing data collected from 14 geographic regions in the US to assess the variability in prehospital care provided to victims of traumatic injury. 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.

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 this in mind we have initiated a project supported by the Brain Trauma Foundation to investigate the relationship between prehospital interventions and outcome following TBI. We are currently in the process of linking prehospital data from the Seattle Fire Dept and King County EMS to trauma registry data from Harborview Medical Center to address these issues.

#### **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 Dept of Bioengineering we have recently 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.

### The Cytokine Profile of Burn Patients Receiving Plasmapheresis

Burn mortality has dramatically decreased over the past twenty years due to improvements in ICU management and better skin coverage. However, patients with large burns still face a high mortality during the first 48 hours of resuscitation. Severe burn injury is associated with a systemic inflammatory response which results in increased capillary permeability. As a result, these patients require a massive fluid resuscitation.

Several formulas have been developed to help estimate the fluid requirements during the first 24 hours, however, some patients, especially those with large, deep burns or inhalation injury, exceed these estimates and thus have evidence of ongoing inflammation which is not self-limiting. These patients have a higher mortality. Anecdotal experience suggests that these patients benefit from a plasma exchange which results in cessation of the capillary leak and decreased fluid requirements after therapy. In collaboration with Dr. Nicole Gibran, we are investigating the cytokine profile and degree of oxidative stress of these patients, both before and after plasmapheresis, to better define the mechanism responsible for the clinical improvement seen with this therapy.

### 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%.

One of the key strategies in the management of these patients involves the ability to obtain adequate pain control to optimize pulmonary status. To further investigate the issues surrounding pain management for these patients, we are currently enrolling patients into a prospective, randomized trial of thoracic epidural vs. intravenous narcotics. A preliminary analysis of this data suggests that the use of epidural analgesia decreased the subsequent rate of pneumonia and shortens the duration of mechanical ventilation. We hope to use this data to develop an optimal management strategy for these patients.

### Variations in the Care of Head Injured Patients

In 1995 the Brain Trauma Foundation compiled a series of evidenced-based guidelines for the care of the head injured patient. That same year, a survey of the clinical management of the head injured patient, nationwide, revealed considerable variation in care.

In this study we sought to determine the current status of variations in care, since these guidelines have been widely distributed, with a particular focus on the controversy surrounding intracranial pressure monitoring. We have analyzed data from 34 academic trauma centers of the University HealthSystem Consortium regarding the management of patients with severe brain injury (GCS < 8). Centers were classified as "aggressive" if they placed intracranial pressure monitors in more than 50% of those patients meeting the Brain Trauma Foundation guidelines for monitoring. We have found that management at "aggressive" centers is associated with a significant reduction in mortality.

### The Use of Anabolic Steroids in the Chronically Ventilated Surgical Patient

Multisystem traumatic injury results in a hypermetabolic state which leads to a stress-induced catabolism and the accelerated breakdown of protein stores. If this process continues unchecked it results in loss of lean body mass which can lead to muscle weakness and depression of the immune response, making the patient more susceptible to infectious complications. Weakness of the respiratory musculature can inhibit ventilator weaning and lack of protein leads to significant impairment in wound healing. These complications are observed with a loss of

only 10-15% of lean body mass. A loss of lean body mass greater than 40% is usually fatal due to infectious complications.

Recognition of these concerns has led to an appropriate emphasis on early nutritional support including replacement of protein losses. Despite this approach, however, several studies have shown that aggressive nutritional support alone does not prevent substantial body protein loss during the catabolic state of severe illness. As a result, attention has turned to the development of adjuvant nutritional therapies which when administered, in conjunction with aggressive protein support, will help reverse the catabolic state. These include the use of recombinant human growth hormone and anabolic steroids.

Oxandrolone is an oral anabolic steroid with enhanced anabolic activity and minimal androgenic activity when compared to testosterone. In chronically malnourished patients including renal dialysis patients, COPD patients, and HIV patients, anabolic steroids, in

combination with an enhanced protein diet, have been shown to significantly improve lean body mass and muscle strength. In burn patients, oxandrolone use has been improvements in lean body mass and strength training during the rehabilitation phase.

Based on these studies, oxandrolone has achieved FDA approval as an adjunctive therapy to promote weight gain after extensive surgery, chronic infections, and severe trauma. Despite this approval, this agent has not been well studied in the acute trauma population. We hypothesized that post-surgical or trauma patients who require a prolonged period of mechanical ventilation (>7 days) may benefit from oxandrolone therapy. We have recently completed a prospective, randomized controlled trial of oxandrolone in this population and although we demonstrated improvement in the nutritional parameters for patients given oxandrolone we were unable to identify any improvement in clinical outcome.

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#### RELATED PUBLICATIONS

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3. Bulger EM, Garcia I, Maier RV. Dithiocarbamates enhance tumor necrosis factor-production by rabbit alveolar macrophages, despite inhibition of NF-B. *Shock*, 1998; 9(6):397-405.
4. Bulger EM, Arneson MA, Mock CM, Jurkovich GJ. Rib Fractures in the Elderly. *J Trauma*, 2000; 48(6):1040-1046.
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6. Bulger EM, Garcia I, Maier RV. Intracellular antioxidant activity is necessary to modulate the macrophage response to endotoxin. *Shock*, 2002; 18(1):58-63.
7. 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*, 2002; 30 (8): 1870-1876.
8. Bulger EM, Copass MK, Maier RV, Larsen J, Knowles J, Jurkovich GJ. An analysis of advanced prehospital airway management. *J Emerg Med*, 2002; 23:183.
9. 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*, 2003; 20:17-22.
10. Bulger EM, Garcia I, Maier RV. Induction of heme-oxygenase 1 inhibits the proinflammatory response of endothelial cells. In press, *Surgery*, 2003.

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#### DEPARTMENT CO-INVESTIGATORS

Michael K. Copass, M.D. / Iris Garcia / Nicole S. Gibran, M.D. / David Gourlay, M.D. / Sandra Jelacic / Gregory J. Jurkovich, M.D. / Ronald V. Maier, M.D. / Avery B. Nathens, M.D., Ph.D., MPH / Daniel Sabbath / Kristen Staudenmeyer, M.D.

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