

# Eileen Bulger, M.D.



- IMMUNOMODULATION OF THE ALVEOLAR MACROPHAGE
- THE CYTOKINE PROFILE OF BURN PATIENTS RECEIVING PLASMAPHERESIS
- PRE-HOSPITAL MANAGEMENT OF THE DIFFICULT AIRWAY
- RIB FRACTURE MANAGEMENT
- VARIATIONS IN THE CARE OF HEAD INJURED PATIENTS
- THE USE OF ANABOLIC STEROIDS IN THE CHRONICALLY VENTILATED SURGICAL PATIENT

#### AWARDS:

##### 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/ Wyeth-Ayerst Research Scholarship

##### Clinical Nutrition Research Unit, University of Washington

- Pilot & Feasibility Award

##### Medic One Foundation

##### Northwest Burn Foundation

##### 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 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. On the clinical front, I have been interested in the pre-hospital management of the difficult airway, impact of rib fractures in the elderly, variations in the care of head injured patients, the use of anabolic steroids in the ICU.

#### 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. We are currently exploring the intracellular signaling pathways interrupted during this process and have extended these studies to animal models of ARDS. PAF AH has recently been studied in a phase II clinical trial for trauma and septic patients at risk for ARDS with encouraging results. The PAF AH treated group was found to have a significant decrease in 28 day mortality, the development of ARDS, and length of ICU stay compared to placebo controls.

#### The Cytokine Profile of Burn Patients Receiving Plasmapheresis

Burn mortality has dramatically decreased over the past twenty years due to improvements in ICU manage-

ment 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.

#### Pre-hospital Management of the Difficult Airway

The introduction of endotracheal intubation to the pre-hospital arena in the 1970s has resulted in definitive airway control for the majority of critically ill and

the pre-hospital use of paralytic agents to facilitate endotracheal intubation in the combative patient or one with significant muscular spasm.

The Seattle Medic One program has been on the forefront of advanced field care by providing training and access to the techniques of surgical airway access and extensive experience with the pre-hospital use of paralytic agents since 1970. This experience provides the opportunity for a population based study of the indications for pre-hospital intubation and the use of paralytic agents. We have recently completed an analysis of all pre-hospital intubations in Seattle over the past three years with detailed investigation regarding the management of the "difficult airway patients." In addition, we are collecting prospective data for every prehospital intubation event. Our goal is to optimize the field management of these complex 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

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injured patients, leading to a significant improvement in morbidity and mortality. There remain, however, patients who have a "difficult airway" in that they can not be successfully intubated by conventional techniques.

These include patients with prohibitive head and neck habitus or anatomy such as trauma patients with significant facial and neck injuries and medical patients with severe upper airway inflammation or obstruction. These are patients in whom orotracheal or nasotracheal intubation, with or without the use of chemical paralysis, is impossible to accomplish. Successful definitive airway control for these patients requires advanced surgical airway access techniques: cricothyroidotomy, tracheostomy, or retrograde intubation. There also remains considerable controversy in the literature concerning

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. 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 hyper-metabolic 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 believe that post-surgical or trauma patients who require a prolonged period of mechanical ventilation (>7 days) may benefit from oxandrolone therapy. To test this hypothesis we are currently enrolling patients in prospective, randomized, blinded trial of oxandrolone vs. placebo in this patient population.

In addition to the clinical arm of this trial, we are simultaneously investigating the effect of anabolic agents on monocyte function, *in vitro*, and receiving circulating monocyte samples from the patients in this study to evaluate their activation status.

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RELATED PUBLICATIONS:

1. Hoyt DB, Bulger EM, Knudson MM et al. Death in the Operating Room: An analysis of a multi-center experience. *J Trauma* 37: 426-432, 1994.
2. Bulger EM, Garcia I, Maier RV. The differential effects of the membrane antioxidant, vitamin E on macrophage activation. *Surgical Forum*. 47:92-95, 1996.
3. Bulger EM, Smith DG, Maier RV, Jurkovich GJ. Fat embolism syndrome: A ten year review. *Archives of Surgery* 132:435-439, 1997.
4. Bulger EM, Helton WS, Clinton CM, Roque RP, Garcia I, Maier RV. Enteral vitamin E supplementation inhibits the cytokine response to endotoxin. *Archives of Surgery* 132:1337-1341, 1997.
5. Bulger EM, Garcia I, Maier RV. Dithiocarbamates enhance tumor necrosis factor- $\alpha$  production by rabbit alveolar macrophages, despite inhibition of NF- $\kappa$ B. *Shock* 9 (6): 397-405, 1998
6. Bulger EM, Arneson MA, Mock CM, Jurkovich GJ. Rib Fractures in the Elderly, *J Trauma* 48(6): 1040-1046, 2000.
7. Bulger EM, Arbabi S, Garcia I, Maier RV: The macrophage response to endotoxin requires platelet activating factor. *Shock*, 17(3):173-179, 2002.
8. Bulger EM, Garcia I, Maier RV: Intracellular antioxidant activity is necessary to modulate the macrophage response to endotoxin. *Shock*, 18(1):58-63, 2002.

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DEPARTMENT CO-INVESTIGATORS:

**Michael K. Copass, M.D. / Joseph Cuschieri, 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. / Charles Mock, M.D., M.P.H. / Avery B. Nathens, M.D., Ph.D.**

OTHER CO-INVESTIGATORS:

**Frederick T. Rivara, M.D., M.P.H.;** UW Department of Pediatrics and HIPRC Director

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