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- 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 Infection
- Rib Fracture Management
- Crash Injury Research and Engineering Network (CIREN)
- Massive Transfusion after Severe Injury

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AWARDS

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Based on a strong interest in trauma and critical care, my research has focused on injury prevention, important clinical questions regarding patient management, and elucidation of 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 Maier and 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. To address the injury prevention side of the equation, I have recently become the local Principal Investigator (PI) for the Crash Injury Research and Engineering Network (CIREN), which collects detailed data regarding the biomechanics of injury associated with motor vehicle crashes. These data will allow us to make recommendations regarding automobile design and crash test parameters that will translate into a reduction in occupant injury. I am also working with the Department of Defense to define the optimal management strategies for injured patients requiring massive transfusion.

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. In 2005 we 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 included mortality, infectious complications, multiple organ dysfunction, and long-term neurological function for patients with traumatic brain injury. We 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 U.S. and Canada and a data coordinating center based at the University of Washington (PI: Gerald Van Belle; Co-PIs: Graham Nichol, Eileen Bulger). The Seattle and King County Medic One programs, along with Airlift Northwest, represent 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. With this group, we recently completed two Phase III trials of hypertonic resuscitation in the prehospital environment. One trial focused on patients with hypovolemic shock, and the other on those with severe traumatic brain injury without shock. Both of these trials have closed and do not show any improvement in outcome with this therapeutic strategy. In collaboration with investigators from the University of Toronto and Harvard University, we are continuing to explore the immunologic response in patients from these trials to better understand the influence of hypertonicity on the innate and cellular immune response (PI: Eileen Bulger).

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 next turned our attention to the impact of prehospital ventilation on outcome following TBI. Hyperventilation may lead to cerebral vasoconstriction and thus impair cerebral blood flow. Hypoventilation may lead to cerebral vasodilation and thus raise intracranial pressure. Hyperventilation has been reported to be a common problem following prehospital intubation. We have undertaken a

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Prehospital Airway Management and 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 is that of patients 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,

series of studies aimed at defining the optimal ventilation strategy for injured patients. For trauma patients intubated in the prehospital setting, those with an arrival arterial pCO_2 between 30-35mmHg demonstrated improved outcomes, which was most marked for those with severe TBI (*J Trauma* 2007). Further studies have examined the impact of correcting patients into a target range in the Emergency Department (ED); our current studies are examining the utility of end tidal CO_2 monitoring for this patient population, both in the field and in the ED (*J Trauma* 2008). Taken together, these studies will allow us to design an optimal ventilation strategy for these patients early after injury.

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 United States 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 emergency medical services (EMS) system design is critical to interpreting the various studies in the literature and to designing future multicenter 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 in a recently completed prospective, randomized trial of high dose enteral vitamins E and C vs. placebo in the surgical intensive care unit (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 developed an animal model of ARDS and demonstrated that both PAF-AH and hypertonic saline, when given intravenously, dramatically down-regulate alveolar macrophage activation in response to inflammatory stimuli.

Management of Necrotizing Soft Tissue Infection

Harborview Medical Center (HMC) serves as a regional referral center for patients with severe necrotizing soft tissue infection, and as a result has seen a 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 five-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 (Anaya et al., *Surg Infections*, 2009). We have also worked 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 rate 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 (*Acute Pain* 2008). We plan to use the results of this survey to stimulate the generation of guidelines for the use of thoracic epidural analgesia after injury.

Crash Injury Research and Engineering Network (CIREN)

The Harborview Injury Prevention and Research Center houses one of eight national CIREN centers supported by the National Highway Transportation and Safety Administration. These centers collect detailed injury and crash investigation data following motor vehicle crashes to identify the forces responsible for injury. Some of our current research projects include: examining mechanisms of injury associated with renal injuries, patterns of injury associated with misuse of child restraints, the impact of seat back position on outcome following frontal crashes, the relationship between obesity and lower extremity fractures, the cost of spinal cord injuries associated with rollover collisions, and the development of prehospital triage guidelines.

Massive Transfusion after Severe Injury

With support from the Department of Defense, we are currently participating in a multicenter prospective observational trial of massive transfusion in trauma patients. This dataset will then be used to design an interventional, randomized controlled trial to determine the optimal ratio of packed red blood cells to fresh frozen plasma and platelets for resuscitation of these patients.

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