Critical Care Medicine

RESEARCH AND TRAINING DETAILS

Faculty: 11
Research Students: 3
Support Personnel: 17
Direct Annual Grant Support: $1,320,975
Peer Reviewed Publications: 24

CLINICAL ACTIVITIES AND TRAINING

Clinical Staff: 10
Clinical Fellows: 15
Other Students: 2
Inpatient Encounters: 10,195

Research Highlights

Dr. Raj Basu served as co-principal investigator of the largest-to-date prospective study of
acute kidney injury in critically ill children

Dr. Raj Basu served as co-principal investigator, along with Dr. Stuart Goldstein from the Center for Acute Care Nephrology, for the largest-to-date prospective study of acute kidney injury in critically ill children. The Assessment of Worldwide AKI in Pediatrics, Renal Angina and Epidemiology (AWARE) study (Clinical Trials: NCT 01987921) enrolled over 5200 patients from 32 individual sites across four continents and 11 countries. The study captured data on all children admitted to the intensive care unit from admission through 28 days, focusing on the epidemiology and associated outcomes of acute kidney injury. Urine was captured on over 600 patients for biomarker analyses. The preliminary results of the AWARE study confirm findings from small, single-center findings: AKI is common (11% of all patients), and patients with AKI suffer worse hospital outcome (increased length of stay, prolonged mechanical ventilation, higher rates of mortality) compared to patients without AKI. The initial protocols for this study have already been published in the *BMC Nephrology* journal, and the preliminary analyses will soon be submitted for review.

**Significant Publications**


Hospital-acquired infections increase morbidity, mortality, and charges in the PICU. Following implementation of a quality improvement bundle directed at ventilator-associated pneumonia in our PICU in 2005, we observed an increase in ventilator-associated tracheobronchitis coincident with the near-elimination of ventilator-associated pneumonia. The impact of ventilator-associated tracheobronchitis on critically ill children has not been previously described. Accordingly, we conducted a retrospective case control study, with institutional review board approval, of 77 consecutive cases of ventilator-associated tracheobronchitis admitted to our PICU from 2004-2010. We matched each case with a control based on the following criteria (in rank order): age range (< 30 d, 30 d to 24 mo, 24 mo to 12 yr, > 12 yr), admission Pediatric Risk of Mortality III score +/- 10, number of ventilator days of control group (> 75% of days until development of ventilator-associated tracheobronchitis), primary diagnosis, underlying organ system dysfunction, surgical procedure, and gender. We successfully matched 45 of 77 ventilator-associated tracheobronchitis patients with controls. There were no significant differences in age, gender, diagnosis, or Pediatric Risk of Mortality III score between groups. Ventilator-associated tracheobronchitis patients had a longer PICU length of stay (median, 21.5 d; interquartile range, 24 d) compared to controls (median, 18 d; interquartile range, 17 d), although not statistically significant (p = 0.13). Ventilator days were also longer in the ventilator-associated tracheobronchitis patients (median, 17 d; IQR, 22 d) versus control (median, 10.5 d; interquartile range, 13 d) (p = 0.01). There was no significant difference in total hospital length of stay (54 d vs 36 d; p = 0.69). PICU mortality was higher in the ventilator-associated tracheobronchitis group (15% vs 5%; p = 0.14), although not statistically significant. There was an increase in both median PICU charges ($197,393 vs $172,344; p < 0.05) and hospital charges ($421,576 vs $350,649; p < 0.05) for ventilator-associated tracheobronchitis patients compared with controls. CONCLUSIONS: Ventilator-associated tracheobronchitis is a clinically significant hospital-acquired infection in the PICU and is associated with longer duration of mechanical ventilation and healthcare costs, possibly through causing a longer PICU length of stay.


The prediction and diagnosis of acute kidney injury (AKI)can be made more precise using novel biomarkers. Traditional diagnosis relies on changes in serum creatinine and/or urine output, both non-specific for type, duration, severity, or reversibility of injury. Novel biomarkers may be more specific for injury phenotype – particularly functional (glomerular) or tubular damage associated AKI. The 10 Acute Dialysis Quality Initiative consensus meeting
recommended using a combination of novel biomarkers to refine AKI classification. We were the first group to operationalize this recommendation, comparing the predictive ability of a combination of biomarkers: functional (cystatin C) and tubular damage (neutrophil gelatinase associated lipocalin-NGAL) versus the status quo (changes in serum creatinine) for granular details of AKI. In nearly 350 patients following cardiopulmonary bypass surgery, the combination of cystatin C/NGAL demonstrated vastly superior performance compared to creatinine for the ability to identify AKI phenotype, (i.e., duration, severity, and reversibility of injury). Notably, these biomarkers were measured and results assessed two hours after initiation of bypass, on average almost six-eight hours earlier than the first postoperative serum creatinine measurement. We conclude that utilization of novel biomarkers, used in combination, offers an increased ability to identify discrete characteristics of AKI (and earlier) – information that may be beneficial for immediate management, supportive care, and even targeted therapy.


Synthesis and remodeling of the lung matrix is necessary for lung growth and development. Because cyclic negative force is applied to developing lung tissue during the respiratory cycle, we hypothesized that stretch is a critical regulator of lung matrix remodeling. By using quantitative image analysis of whole-lung and whole-lobe elastin in situ zymography images, we demonstrated that elastase activity increased two-fold during the alveolar stage of postnatal lung morphogenesis in the mouse. Remodeling was restricted to alveolar walls and ducts and was nearly absent in dense elastin band structures. In the mouse pneumonectomy model of compensatory lung growth, elastase activity increased three-fold, peaking at 14 days post-pneumonectomy and was higher in the accessory lobe compared with other lobes. The accessory lobe experiences greater post-pneumonectomy compensatory lung growth than the other lobes. Remodeling during normal development and during compensatory lung growth was different with increased major airway and pulmonary arterial remodeling during development but not regeneration, and with homogeneous remodeling throughout the parenchyma during development, but remodeling increased only in subpleural regions during compensatory lung growth. Left lung wax plombage prevented increased elastase activity during compensatory lung growth. To test whether the adult lung retains an innate capacity to remodel elastin, we developed a confocal microscope-compatible stretching device. In ex vivo adult mouse lung sections, lung elastase activity increased exponentially with strain and in peripheral regions of lung more than in central regions. Our study demonstrates that lung elastase activity is stretch-dependent and supports a model in which externally applied forces influence the composition, structure, and function of the matrix during periods of alveolar septation.


There are few therapies that improve outcomes in patients with sepsis. Preclinical work in our laboratory demonstrates that the nuclear receptor peroxisome proliferator-activated receptor-gamma (PPARg) is involved in the regulation of sepsis-induced inflammation. PPARg expression is downregulated in various tissues during sepsis and this downregulation is associated with poor survival. The insulin sensitizing thiazolidinedione drug, pioglitazone, is a specific PPARg agonist and reduces pro-inflammatory responses in patients with type 2 diabetes and coronary artery disease, and may be beneficial in sepsis. Polymicrobial sepsis was induced in mice and mice received an intraperitoneal injection of vehicle or pioglitazone at 1 h and 6 h after CLP. Mice were sacrificed at various time points after sepsis. In sepsis, vehicle-treated mice had hypoglycemia, increased lung injury and increased lung neutrophil infiltration. Pro-inflammatory plasma cytokines were increased, but the plasma adipokine, adiponectin, was decreased in vehicle-treated septic mice. This corresponded with inhibitor kB (I kappa B alpha) protein degradation and an increase in NF-kappa B activity in lung. Pioglitazone treatment improved plasma glucose and adiponectin levels, and decreased pro-inflammatory cytokines. Lung IkBa protein expression increased and corresponded with a decrease in
NF-kappa B activity in the lung from pioglitazone-treated mice. We conclude that pioglitazone reduces the inflammatory response in polymicrobial sepsis in part through inhibition of NF-kappa B and may be a novel therapy in sepsis.

Liu S, Cimprich J, Varisco BM. *Mouse pneumonectomy model of compensatory lung growth*. *J Vis Exp*. 2014 Dec 17;(94). In humans, disrupted repair and remodeling of injured lung contributes to a host of acute and chronic lung disorders which may ultimately lead to disability or death. Injury-based animal models of lung repair and regeneration are limited by injury-specific responses making it difficult to differentiate changes related to the injury response and injury resolution from changes related to lung repair and lung regeneration. However, use of animal models to identify these repair and regeneration signaling pathways is critical to the development of new therapies aimed at improving pulmonary function following lung injury. The mouse pneumonectomy model utilizes compensatory lung growth to isolate those repair and regeneration signals in order to more clearly define mechanisms of alveolar re-septation. This publication describes our technique for performing mouse pneumonectomy and sham thoracotomy. This technique may be utilized in conjunction with lineage tracing or other transgenic mouse models to define molecular and cellular mechanism of lung repair and regeneration.

### Division Publications


and antibiotics improves survival and neutrophil recruitment and function in murine sepsis. *Immunology.* 2015; 144:405-411.


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**Faculty, Staff, and Trainees**

**Faculty Members**

**Hector Wong, MD**, Professor  
**Leadership** Director of the Division of Critical Care Medicine  
**Research Interests** Septic shock; genomics; biomarkers.

**Ranjit Chima, MD, FAAP**, Associate Professor  
**Leadership** Associate Medical Director, Destination Excellence; Chair of the Central Line Committee  
**Research Interests** Bone marrow transplantation-associated critical illness; ECLS glucose homeostasis.

**Lesley Doughty, MD**, Associate Professor  
**Leadership** Fellowship Director  
**Research Interests** Sepsis; viral infections; mechanical ventilation.

**Jennifer Kaplan, MD, MS**, Associate Professor  
**Research Interests** Sepsis; obesity; inflammation.

**Sue E. Poynter, MD, MEd**, Associate Professor  
**Leadership** Medical Director Division of Respiratory Care; Associate Director Pediatric Residency Training Program  
**Research Interests** Medical education; residency and fellowship training.

**Erika Stalets, MD, MS**, Assistant Professor  
**Leadership** Medical Director Pediatric Intensive Care Unit  
**Research Interests** Quality improvement; patient safety; sepsis.

**Ken Tegtmeier, MD**, Professor  
**Leadership** Chair Code Committee  
**Research Interests** Multimedia medical education.

**Rajit Basu, MD**, Assistant Professor  
**Leadership** Co-Director Center for Acute Care Nephrology  
**Research Interests** Phenotype and recognition of kidney injury; end of life care.

**Derek S. Wheeler, MD, MMM, FAAP, FCCP, FCCM**, Associate Professor  
**Leadership** Chief of Staff; Chair of Clinical Affairs  
**Research Interests** Patient safety; healthcare administration.

**Basilia Zingarelli, MD, Ph.D.**, Professor  
**Leadership** Director, Basic Science Research  
**Research Interests** Sepsis; hemorrhage and ischemia and reperfusion injury.

**Brian Varisco, MD**, Assistant Professor  
**Research Interests** Mechanisms of lung development, repair and regeneration.

**Edward Cooper, MD**, Assistant Professor
Trainees
- William Hanna, MD, PL-7, University of Kentucky College of Medicine
- Danielle Webster, MD, PL-7, University of Missouri - Kansas City
- Matthew Alder, MD, PL-6, University of Alabama School of Medicine
- Theodore DeMartini, MD, PL-6, University of Texas Medical Branch
- Hammad Ganatra, MD, PL-5, Aga Khan Medical College
- Yu Inata, MD, PL-5, Osaka City University
- Laura Kitzmiller, MD, PL-5, Wayne State University School of Medicine
- Travis Langner, MD, PL-6, University of Kansas School of Medicine
- Mary Sandquist, MD, PL-5, Ohio State University College of Medicine
- Claire Stewart, MD, PL-5, Ohio State University College of Medicine
- Aaron Gardner, MD, PL-8, St. George's University
- Itay Ayalon, MD, PL-6, Sackler School of Medicine
- Zachary Berrens, MD, PL-5, University of Cincinnati College of Medicine
- Saul Flores, MD, PL-9, Universidad Mayor de San Andres
- Dzmitry Matsiukevich, MD, PL-5, Gomel State Medical Institute

Grants, Contracts, and Industry Agreements

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| Current Year Direct                                | $1,320,975 |

| Total                                             | $1,320,975 |
For 20 years, scientific research into septic shock has tried to determine how best to identify, diagnose and treat the potentially life-threatening infection, which can quickly overwhelm the body’s immune system. But researchers have been limited by the disease’s non-specific spectrum of symptoms and treatment results that vary from patient to patient.

The editors of the *American Journal of Respiratory and Critical Care Medicine* describe a finding by Hector Wong, MD, Director of the Division of Critical Care Medicine, as a new approach that “might help shift this impasse for children with septic shock.”

Published Feb. 1, 2015, the study reports success at identifying subclasses of septic shock in individual patients based on gene expression patterns linked to their immune system responses and glucocorticoid receptor signaling. The RNA-quantifying gene expression method also has the potential to rapidly generate clinical data, possibly within 8 to 10 hours. This could become a valuable advantage for a disease that can progress from diagnosis to death in a matter of days or hours. Septic shock has a mortality rate of 40-60 percent in adults and 25 percent in children.

Knowing a patient’s specific disease subclass for septic shock can potentially aid therapeutic decisions. Corticosteroids — a standard protocol for septic shock treatment that works through the glucocorticoid receptor — can be life saving for many patients. However, this study shows that steroids are associated with a four-fold increase in mortality within one subclass of septic shock patients. Having a gene-based classification method for septic shock patients will help doctors quickly identify which patients should not receive steroid therapy, Wong says.

Information from gene expression also holds hope of more personalized medicine approaches for treating septic shock. Doctors may one day be able to use the patient’s own personalized medicine approaches to treat the disease, or to link symptom-specific drugs to the patient’s symptom-based subclass in hopes of a greater chance of survival, Wong says.

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**Genetic Expression Method Allows Doctors to Rapidly Identify Subclasses of Septic Shock**

PUBLISHED FEB. 1, 2015

*American Journal of Respiratory and Critical Care Medicine*

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These composite gene expression mosaics show the mean expression values for 100 subclass-defining genes based on NanoString-derived expression data. Red intensity correlates with increased gene expression, and blue intensity correlates with decreased gene expression. Examples 1 and 2 were allocated to subclass A; examples 3 and 4 were allocated to subclass B. Compared to subclass B, those in subclass A had a higher mortality rate and a more complicated course, including higher median PRISM scores, lower total white blood cell and absolute neutrophil counts, and higher absolute lymphocyte counts.

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