Cincinnati Children's

2015 Research Annual Report

Critical Care Medicine

RESEARCH AND TRAINING DETAILS

Click to view members

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

Download Report in PDF Format Visit Critical Care Medicine

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

Wheeler DS, Whitt JD, Lake M, Butcher J, Schulte M, **Stalets E**. A Case-Control Study on the Impact of Ventilator-Associated Tracheobronchitis in the PICU. *Pediatr Crit Care Med.* 2015 Jul;16(6):565-71.

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.

Basu RK, **Wong HR**, Krawczeski CD, **Wheeler DS**, Manning PB, Chawla LS, Deverajan P, Goldstein SL. Combining functional and tubular damage biomarkers improves diagnostic precision for acute kidney injury after cardiac surgery. *J Am Coll Cardiol.* 2014 Dec 30;64(25):2753-62.

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 post-operative 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.

Young SM, Liu S, Joshi R, Batie MR, Kofron M, Guo J, Woods JC, **Varisco BM**. Localization and stretch-dependence of lung elastase activity in development and compensatory growth. *J Appl Physiol (1985).* 2015 Apr 1;118(7):921-31.

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 homogenous 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.

Kaplan J, Nowell M, **Chima R**, **Zingareli B**. Pioglitazone reduces inflammation through inhibition of NF-kappa B in polymicrobial sepsis. *Innate Immunity.* 2014 Jul;20(5):519-28.

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

1. Alobaidi R, Basu RK, Goldstein SL, Bagshaw SM. **Sepsis-associated acute kidney injury**. *Semin Nephrol*. 2015; 35:2-11.

2. Atkinson SJ, Cvijanovich NZ, Thomas NJ, Allen GL, Anas N, Bigham MT, Hall M, Freishtat RJ, Sen A, Meyer K, Checchia PA, Shanley TP, Nowak J, Quasney M, Weiss SL, Banschbach S, Beckman E, Howard K, Frank E, Harmon K, Lahni P, Lindsell CJ, Wong HR. **Corticosteroids and pediatric septic shock outcomes: a risk stratified analysis**. *PLoS One*. 2014; 9:e112702.

3. Basu RK, Donaworth E, Siroky B, Devarajan P, Wong HR. **Loss of matrix metalloproteinase-8 is associated with worsened recovery after ischemic kidney injury**. *Ren Fail*. 2015; 37:469-75.

4. Basu RK, Kaddourah A, Terrell T, Mottes T, Arnold P, Jacobs J, Andringa J, Goldstein SL, Prospective Pediatric AKIRG. **Assessment of Worldwide Acute Kidney Injury, Renal Angina and Epidemiology in critically ill children (AWARE): study protocol for a prospective observational study**. *BMC Nephrol*. 2015; 16:24.

5. Basu RK, Wong HR, Krawczeski CD, Wheeler DS, Manning PB, Chawla LS, Devarajan P, Goldstein SL. **Combining functional and tubular damage biomarkers improves diagnostic precision for acute kidney injury after cardiac surgery**. *J Am Coll Cardiol*. 2014; 64:2753-62.

6. Brady PW, Zix J, Brilli R, Wheeler DS, Griffith K, Giaccone MJ, Dressman K, Kotagal U, Muething S, Tegtmeyer K. **Developing and evaluating the success of a family activated medical emergency team: a quality improvement report**. *BMJ Qual Saf*. 2015; 24:203-11.

7. Chima RS, Ortega R, Connor CW. **Melodic algorithms for pulse oximetry to allow audible discrimination of abnormal systolic blood pressures**. *J Clin Monit Comput*. 2014; 28:597-603.

8. Dandoy CE, Davies SM, Hirsch R, Chima RS, Paff Z, Cash M, Ryan TD, Lane A, El-Bietar J, Myers KC, Jodele S. **Abnormal echocardiography 7 days after stem cell transplantation may be an early indicator of thrombotic microangiopathy**. *Biol Blood Marrow Transplant*. 2015; 21:113-8.

9. Guan S, Guo C, Zingarelli B, Wang L, Halushka PV, Cook JA, Fan H. **Combined treatment with a CXCL12 analogue**

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

10. Jodele S, Davies SM, Lane A, Khoury J, Dandoy C, Goebel J, Myers K, Grimley M, Bleesing J, El-Bietar J, Wallace G, Chima RS, Paff Z, Laskin BL. **Diagnostic and risk criteria for HSCT-associated thrombotic microangiopathy: a study in children and young adults**. *Blood*. 2014; 124:645-53.

11. Kaplan J, Nowell M, Chima R, Zingarelli B. **Pioglitazone reduces inflammation through inhibition of NF-kappaB in polymicrobial sepsis**. *Innate Immun*. 2013; 20:519-528.

12. Liu S, Cimprich J, Varisco BM. **Mouse pneumonectomy model of compensatory lung growth**. *J Vis Exp*. 2014; .

13. Moler FW, Silverstein FS, Holubkov R, Slomine BS, Christensen JR, Nadkarni VM, Meert KL, Clark AE, Browning B, Pemberton VL, Page K, Shankaran S, Hutchison JS, Newth CJ, Bennett KS, Berger JT, Topjian A, Pineda JA, Koch JD, Schleien CL, Dalton HJ, Ofori-Amanfo G, Goodman DM, Fink EL, McQuillen P, Zimmerman JJ, Thomas NJ, van der Jagt EW, Porter MB, Meyer MT, Harrison R, Pham N, Schwarz AJ, Nowak JE, Alten J, Wheeler DS, Bhalala US, Lidsky K, Lloyd E, Mathur M, Shah S, Wu T, Theodorou AA, Sanders RC, Jr., Dean JM, Investigators TT. **Therapeutic hypothermia after out-of-hospital cardiac arrest in children**. *N Engl J Med*. 2015; 372:1898-908.

14. Samraj RS, Stalets EL. **Pediatric Longitudinal Clivus Fracture: Survival With Minimal Morbidity**. *J Intensive Care Med*. 2014; .

15. Shibata AR, Troster EJ, Wong HR. **Glucocorticoid Receptor Expression in Peripheral WBCs of Critically Ill Children**. *Pediatr Crit Care Med*. 2015; 16:e132-40.

16. Sweeney TE, Shidham A, Wong HR, Khatri P. **A comprehensive time-course-based multicohort analysis of sepsis and sterile inflammation reveals a robust diagnostic gene set**. *Sci Transl Med*. 2015; 7:287ra71.

17. Weiss SL, Cvijanovich NZ, Allen GL, Thomas NJ, Freishtat RJ, Anas N, Meyer K, Checchia PA, Shanley TP, Bigham MT, Fitzgerald J, Banschbach S, Beckman E, Howard K, Frank E, Harmon K, Wong HR. **Differential expression of the nuclear-encoded mitochondrial transcriptome in pediatric septic shock**. *Crit Care*. 2014; 18:623.

18. Wheeler DS, Robble MA, Hebron EM, Dupont MJ, Ebben AL, Wheeler RA. **Drug predictive cues activate aversion-sensitive striatal neurons that encode drug seeking**. *J Neurosci*. 2015; 35:7215-25.

19. Wheeler DS, Whitt JD, Lake M, Butcher J, Schulte M, Stalets E. **A Case-Control Study on the Impact of Ventilator-Associated Tracheobronchitis in the PICU**. *Pediatr Crit Care Med*. 2015; 16:565-71.

20. Wong HR, Cvijanovich NZ, Anas N, Allen GL, Thomas NJ, Bigham MT, Weiss SL, Fitzgerald J, Checchia PA, Meyer K, Shanley TP, Quasney M, Hall M, Gedeit R, Freishtat RJ, Nowak J, Shekhar RS, Gertz S, Dawson E, Howard K, Harmon K, Beckman E, Frank E, Lindsell CJ. **Developing a clinically feasible personalized medicine approach to pediatric septic shock**. *Am J Respir Crit Care Med*. 2015; 191:309-15.

21. Wong HR, Liu KD, Kangelaris KN, Lahni P, Calfee CS. **Performance of interleukin-27 as a sepsis diagnostic biomarker in critically ill adults**. *J Crit Care*. 2014; 29:718-22.

22. Wong HR, Walley KR, Pettila V, Meyer NJ, Russell JA, Karlsson S, Shashaty MG, Lindsell CJ. **Comparing the prognostic performance of ASSIST to interleukin-6 and procalcitonin in patients with severe sepsis or septic shock**. *Biomarkers*. 2015; 20:132-5.

23. Young SM, Liu S, Joshi R, Batie MR, Kofron M, Guo J, Woods JC, Varisco BM. **Localization and stretch-dependence of lung elastase activity in development and compensatory growth**. *J Appl Physiol (1985)*. 2015; 118:921-31.

24. Zhai H, Brady P, Li Q, Lingren T, Ni Y, Wheeler DS, Solti I. **Developing and evaluating a machine learning based algorithm to predict the need of pediatric intensive care unit transfer for newly hospitalized children**. *Resuscitation*. 2014; 85:1065-71.

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 Tegtmeyer, 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

Grant and Contract Awards		Annual Direct

Alder, M

Host Response to Trauma Research Training Program

National Institutes of Health(University of Cincinnati)

GM008478	7/1/2014-6/30/2016	$45,432

Chima, R

Heart and Lung Failure - Pediatric Insulin Titration Trial

National Institutes of Health(Children's Hospital Boston)

U01 HL107681	7/1/2011-6/30/2016	$15,400

Approaches and Decisions for Acute Pediatric TBI (ADAPT) Trial

National Institutes of Health(University of Pittsburgh)

U01 NS081041	7/1/2013-6/30/2018	$29,121

Kaplan, J

Sweat Patch for Quantification of Lactate in Critically Ill Patients

University of Cincinnati

UL1 TR000077	7/1/2014-6/30/2015	$30,900

Poynter, S

Multi-Center Trial of Limiting PGY 2&3 Resident Work Hours in ICU

National Institutes of Health(Brigham & Women's Hospital)

U01 HL111478	9/15/2012-5/31/2017	$293,464

Varisco, B

Chymotrypsin Like Elastase-1 Links Alveolar and Microvascular Growth

Parker B. Francis Fellowship Program

	7/1/2014-6/30/2017	$50,000

Lung Regeneration Following Posterior Spinal Fusion

Scoliosis Research Society

	1/1/2015-12/31/2016	$5,000

Wheeler, D

Therapeutic Hypothermia after Cardiac Arrest

National Institutes of Health(University of Michigan)

U01 HL094345	9/1/2009-2/28/2014	$1,213

Wong, H

Stratification of Pediatric Septic Shock

National Institutes of Health

R01 GM099773	8/7/2012-6/30/2016	$243,861

Novel Diagnostic and Stratification Tools for Septic Shock

National Institutes of Health

R01 GM108025	5/1/2014-2/28/2018	$330,185

Zingarelli, B

Role of Eicosanoids in Shock

National Institutes of Health(Medical University of South Carolina)

R01 GM027673	7/1/2012-3/31/2016	$22,128

PPARgamma and PPARgamma Agonists in Septic Shock

National Institutes of Health

R01 GM067202	9/14/2012-6/30/2016	$254,271
	Current Year Direct	**$1,320,975**
	Total	**$1,320,975**

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

Hector Wong, MD

RESEARCH AND TRAINING DETAILS

Faculty	11
Research Students	3
Support Personnel	17
Direct Annual Grant Support	$1.3M
Peer Reviewed Publications	24

Wong HR, Cvijanovich NZ, Anas N, Allen GL, Thomas NJ, Bigham MT, Weiss SL, Fitzgerald J, Checchia PA, Meyer K, Shanley TP, Quasney M, Hall M, Gedeit R, Freishtat RJ, Nowak J, Shekhar RS, Gertz S, Dawson E, Howard K, Harmon K, Beckman E, Frank E, Lindsell CJ. Developing a clinically feasible personalized medicine approach to pediatric septic shock. *Am J Respir Crit Care Med.* 2015;191(3):309-315.

PUBLISHED FEB. 1, 2015
American Journal of Respiratory and Critical Care Medicine

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.

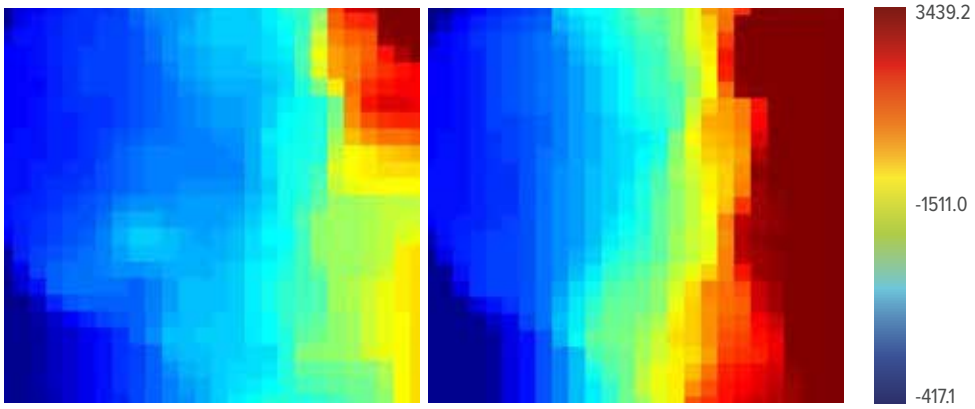
The editors of the *American Journal of Respiratory and Critical Care Medicine* describe a finding by Hector Wong, MD, Director of the Division of Critical Care Medicine, as a new approach that "might help shift this impasse for children with septic shock."

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.

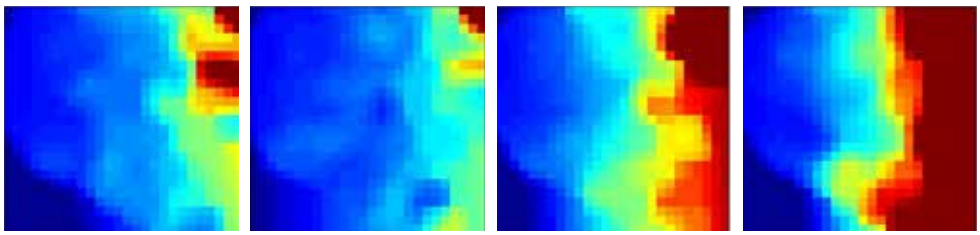
Knowing a patient's specific disease subclass for septic shock can potentially aid therapeutic decisions. Corticosteroids — a standard protocol for septic shock treatment that works through the glucocorticoid receptor — can be life saving for many patients. However, this study shows that steroids are 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 adaptive immune responses 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.

A



B



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.

This study shows that steroids are associated with a four-fold increase in mortality within one subclass of septic shock patients.