Pulmonary and Critical Care Updates

Update on Acute Lung Injury and Critical Care Medicine 2009

Michael A. Matthay^{1,2,3} and Steven Idell⁴

¹Department of Medicine, ²Department of Anesthesia, and ³Cardiovascular Research Institute, University of California, San Francisco, San Francisco, California; and ⁴Texas Lung Injury Institute, University of Texas Health Science Center at Tyler, Tyler, Texas

This article reviews selected contributions published in 2009 regarding the epidemiology, clinical course, pathogenesis, and treatment of acute lung injury (ALI). Articles in critical care medicine that relate to multiorgan failure are also included. Research on epidemiology and genetic contributions to ALI have opened several promising areas for future studies to establish the environmental and genetic factors that influence its development and outcomes. Novel discoveries have been made on the likely role of platelets and lymphocytes in the pathogenesis and resolution of ALI. Animal and clinical studies have provided new insights regarding the mechanisms that initiate and sustain ALI and the value of both biological and clinical factors for predicting outcome in ALI. Based on pre-clinical studies, cell-based treatment for ALI, acute renal failure, and septic shock represents a new direction that may eventually have clinical value for therapy of critically ill patients with organ failure. The results of a multicenter randomized trial demonstrated that mortality in critically ill patients was not altered by high- compared with low-intensity renal replacement therapy. In another large randomized trial, tight glucose control worsened mortality in critically ill patients compared with conventional control.

Because the topic is broad, our comments are restricted to a subset of a number of highly meritorious publications, although we included citations for several other articles published in 2009. We primarily focused on discoveries regarding epidemiology, definitions, genetics, clinical course, pathogenesis, and new treatments, including publications from both clinical and experimental studies.

EPIDEMIOLOGY OF ALI

Little is known about the influence of race and ethnicity on mortality from ALI. A retrospective cohort study of patients enrolled in the Acute Respiratory Distress Syndrome (ARDS) Network trials was performed on 2,362 mechanically ventilated patients (1,715 white, 449 African-American, and 198 Hispanic). African-American and Hispanic patients with ALI had a significantly higher risk of death compared with white patients. The increased risk was associated with increasing severity of illness

at presentation for African Americans, but this association was not observed among Hispanics (1). This study will stimulate further research to understand the mechanistic basis for the racial and ethnic disparities in mortality from ALI, including both environmental and genetic factors.

Two articles addressed the issue of whether mortality from ALI and ARDS has decreased. In one report, the authors performed a literature review and concluded that mortality had decreased before 1994, but that there was no significant trend for reduced mortality since 1994. Although this review included many articles, the interpretation was complicated because of a heterogeneous mix of patients. As the authors themselves indicate, their analyses included patients with mild ALI as well as more severe ARDS (2). In contrast to this report, another study evaluated mortality among patients with ALI in clinical trials conducted at ARDS Network centers. This analysis included 2,451 mechanically ventilated patients with ALI enrolled in ARDS Network randomized trials between 1996 and 2005 (3). Mortality was 35% in 1996 and declined during each subsequent year to a low of 26% in 2005. After adjustment for demographic and clinical covariates, including lower tidal volume ventilation and severity of illness, the temporal trend for a decline in mortality persisted ($P = 0.0002$). Thus, the results from this study support the conclusion that advances in critical care, aside from just lung-protective ventilation, decreased mortality in ALI.

CLINICAL DEFINITIONS AND EARLY DIAGNOSIS OF ALI

Current definitions of ALI or ARDS require the patient to be intubated and ventilated. However, most patients have ALI before intubation and mechanical ventilation. If it were possible to identify patients with ALI before the need for mechanical ventilation, it would be possible to intervene earlier with therapies that could potentially reduce the need for positive pressure ventilation and conceivably improve mortality because treatment could be administered at an earlier phase of ALI. To address this issue, one group evaluated 100 patients admitted to the emergency department with bilateral chest radiographic opacities that were not explained by volume overload or cardiac failure. There were 100 patients who met these criteria and 33 who progressed to develop ALI during subsequent hospitalization. By multivariate analysis of clinical predictors, only an initial oxygen requirement greater than 2 L/min coupled with the presence of bilateral opacities predicted progression to ALI. A clinical diagnosis of early ALI was 73% sensitive and 79% specific for progression to ALI (4). In another study investigators used automatic electronic tools that screened for patients with a ratio of arterial oxygen saturation and the fraction of inspired oxygen below certain cutoffs in conjunction with a report of a chest radiograph with bilateral infiltrates or edema. With this approach, the authors found that they could identify patients with

(Received in original form February 11, 2010; accepted in final form February 12, 2010)

Support by grants NHLBI R37 HL51856, NHLBI R01 HL51854, and NIAID P01 A1053194 (M.A.M.) and NHLBI P01 HL076406 and NHLBI XO-1NS063898 (S.I.).

Correspondence and requests for reprints should be addressed to Michael A. Matthay, M.D., University of California San Francisco, 505 Parnassus Avenue, M917, San Francisco, CA 94143-0624. E-mail: michael.matthay@ucsf.edu

Am J Respir Crit Care Med Vol 181, pp 1027–1032, 2010

DOI: 10.1164/rccm.201001-0074UP

Internet address: www.atsjournals.org

ALI at the time of hospital admission, a process that allowed identification of patients with lung injury at an earlier phase (5).

GENETICS AND ALI

A number of studies reported associations between a variety of single nucleotide polymorphisms and clinical outcomes in ALI. An excellent review of this topic was published (6). This review summarized most of the candidate genes that have been associated with ALI, acknowledging those studies that have been replicated in independent populations, with a particular focus on specific pathways for which candidate genes so far can be clustered. An insightful editorial comment on this review article was also published (7).

It is well known that extracellular superoxide dismutase (EC-SOD) is a potent antioxidant that plays an important role in protecting the lung against oxidant-mediated injury. In an interesting study, investigators sequenced the EC-SOD promoter and gene to determine genetic variation and linkage disequilibrium patterns in two separate patient populations with infection-associated ALI. The results indicated that a GCCT haplotype of EC-SOD was associated with a reduced duration of mechanical ventilation and reduced mortality (8).

Higher plasma and pulmonary edema fluid levels of plasminogen-activator inhibitor 1 (PAI-1) have been associated with increased mortality in patients with pneumonia and ALI. The 4G allele of the 4G/5G polymorphism of the PAI-1 gene has been associated with higher PAI-1 levels and an increased incidence of hospitalizations for pneumonia. In a study of 111 patients, the 4G allele of the 4G/5G polymorphism in the PAI-1 gene was associated with fewer ventilator-free days and increased mortality in hospitalized patients with severe pneumonia (9). In pediatric patients with ALI, higher plasma levels of PAI-1 were associated with increased mortality and fewer ventilator-free days in ALI (10). Another study reported that genetic polymorphisms of peptidase inhibitor 3 (elafin) were associated with increased risk of developing ARDS, especially with extrapulmonary injury (11). Patients with these single nucleotide polymorphisms had lower elafin levels in the plasma, which might reduce host defense against neutrophil elastase-mediated injury. There is a rapidly growing interest in the genetic factors that influence the development and severity of ALI, including both candidate gene strategies as well as genome-wide association studies.

PATHOGENESIS OF ALI IN HUMAN STUDIES

The study of the pathogenetic and prognostic value of plasma and airspace protein biomarkers for ALI and sepsis has become an area of active research over the past decade. Several new studies identified additional potential pathways that may influence the severity and outcomes of ALI.

Other investigators reported that the Decoy Receptor 3 (DcR3) discriminated survivors and nonsurvivors in both a primary patient cohort and as well as in a 59-patient validation study. Plasma levels of DcR3 were independently associated with 28-day mortality as well as multiple organ dysfunction and ventilator dependence. Plasma DcR3 levels were superior to the prognostic value provided by measurement of tumor necrosis factor (TNF)- α or IL-6 (12). In another study, investigators reported elevated levels of biologically active 20S proteasome, a multicatalytic proteinase, in the bronchoalveolar lavage fluid of patients with ARDS compared with other inflammatory lung disease and normal patients. The authors speculated that the origin of the alveolar proteasome in ARDS could be the alveolar epithelium (13).

In a novel combined experimental and clinical study, extracellular histones were found to be important mediators of death and sepsis (14). There is evidence that extracellular histones are released in response to inflammatory challenge and contribute to endothelial dysfunction, organ failure, and death in mice. Interestingly, activated protein C (APC) cleaves histones and reduces their toxicity.

Assessment of the prognostic and pathogenetic value of biomarkers provided new insights in patients with ALI. However, a single biomarker alone is not likely to be robust enough to provide major prognostic value. To test the potential prognostic value of multiple plasma biomarkers, 549 patients from an ARDS Network trial were studied for their potential relationship to clinical outcomes. Clinical variables (Acute Physiology and Chronic Health Evaluation III, organ failures, age, underlying cause of lung injury, alveolar-arterial oxygen difference, and plateau airway pressure) predicted mortality with an area under the receiver operating curve of 0.82. A combination of both the clinical predictors and the eight biomarkers had an area under the curve of 0.85, significantly greater than the clinical predictors alone. The best performing biomarkers were IL-8 and SP-D, supporting the concept that acute inflammation and alveolar epithelial injury are important pathogenetic pathways in lung injury (15).

There is new interest in genomic classification to enhance diagnosis and treatment of patients with ALI. In one study, the investigators studied 13 patients with ALI from sepsis and 20 patients with sepsis alone, and then did microarrays on peripheral blood samples. Although this was a small study, the authors found that an eight-gene expression profile was associated with ALI and an internal validation revealed that the gene signature was able to distinguish patients with ALI and sepsis from patients with sepsis alone with 100% accuracy and a positive predictive value of 100% (16). The use of classification models to develop gene expression profiles for patients with early and established lung injury may have pathogenetic and prognostic value.

The mechanisms by which procoagulant or antifibrinolytic pathways participate in the pathogenesis of ALI have been a topic of major interest for several years. In one study, ARDS edema fluid had higher concentrations of microparticles that were enriched for tissue factor and appeared to originate at least in part from the alveolar epithelium. Thus, alveolar epithelial-derived microparticles are a potential source of tissue factor procoagulant activity in the airspaces of patients with ARDS (17). A thoughtful commentary on this topic and its basic science and clinical significance was also published. This commentary emphasized that microparticles in the airspaces of the injured lung may be biologically active, probably reflect more than just cellular debris, and may reflect several cellular sources, including injured alveolar epithelial cells (18).

PATHOGENESIS OF ALI IN ANIMAL STUDIES

A large number of experimental studies published in 2009 address novel mechanisms of lung injury. Due to space limitations, we cannot discuss all of these interesting studies. We highlight a few of the studies and then provide references to several more. One excellent article examined the role of neutrophils in transepithelial migration. This review has important implications for ALI (19).

New work suggests that lymphocytes may play an important role in the resolution of endotoxin-induced ALI in mice (20). Using both knockout mice and adoptive transfer methods, this group found that Tregs (a subset of CD4⁺ lymphocytes expressing CD25 as well as the transcription factor Forkhead box protein 3) were essential for the timely resolution of lung injury.

An excellent editorial summarized work in this new area (21). Other investigators studied the role of lymphocytes and subsets in a model of hemorrhagic shock followed by peritoneal sepsis and reported evidence that lymphocytes control neutrophil recruitment via IL-10 (22). In another focus on resolution of lung injury, there is additional evidence that the nuclear factor- κ B pathway in macrophages contributes substantively to the severity and duration of lung inflammation (23).

Based on experimental studies, a major contribution of platelets in the pathogenesis of ALI has been established. In a mouse study, platelets played a critical role in neutrophil-mediated lung injury from acid instillation or antibody-mediated transfusion-associated lung injury (24). Another group that used elegant imaging methods also identified an important role for platelets through interactions with neutrophils in lung and organ injury (25). Also, a comprehensive review of platelets and their role in ALI, thrombosis, and lung inflammation was published (26).

Investigators addressed the role of coagulation factor components on lung injury from sepsis and other clinically relevant injuries (27). In a novel study, others found that increased local expression of coagulation factor Xa contributes to the fibrotic response in human and mouse lung injury, a potentially important pathway after ALI (28). Also, factor Xa may represent an important activator of PAR1. In another study, investigators studied uPAR expression because of its central role in neutrophil recruitment. This group determined that endotoxin-mediated uPAR expression is mediated through tyrosine phosphorylation of phosphoglycerate kinase and heterogeneous nuclear ribonucleoprotein (29).

There has been considerable research recently that demonstrates that noninfectious stimuli signal through Toll-like receptors. In one study, oxidant-Toll-like receptor interactions were shown to be important in both *in vitro* and *in vivo* mouse studies (30).

One group reported that endothelin-1 activates the endothelin B receptor that generates nitric oxide, resulting in reduced alveolar fluid clearance because of Na,K-ATPase down-regulation (31). In a bleomycin model of ALI and fibrosis, blockade of insulin-like growth factor improved survival and reduced fibrosis (32). Other investigators reported a role for IL-6 in reducing lung injury (33–35).

Several other studies have provided new insights into the pathogenesis and potential new therapeutic approaches to lung injury (36–48).

CLINICAL OBSERVATIONS

A major issue in patients with ALI and other critical care patients is management of antimicrobial therapy in an intelligent and organized approach. In an excellent perspective article on this topic, investigators established that managing antimicrobial therapy involves a multifaceted approach that attempts to combat the emergence of resistance, improve clinical outcomes, and control costs by improving the use of antibiotics. Clinical decision support systems, biomarker-derived treatment algorithms, and improved knowledge regarding the different components of antimicrobial therapy represent advances that have been made in this direction. However, further work is needed in this area (49).

In another study that focused on the value of specialty versus general intensive care units (ICUs), investigators conducted a retrospective cohort study, analyzing patients admitted to 124 ICUs from 2002 through 2005. With adjustments for important confounders, there were no significant differences in risk-adjusted mortality between general versus ideal specialty ICUs

for all conditions other than pneumonia. In fact, risk-adjusted mortality was significantly greater for patients admitted to nonideal specialty critical care units. Thus, the authors conclude that investment in ICU specialization may not improve mortality (50). It has been speculated that there are significance differences in patterns of critical care use in different countries. In a recent study evaluating the use of hospital and intensive care services during terminal hospitalizations in England and the United States, investigators found that 50% of all hospital deaths involve intensive care in the United States compared with only 10% in England. The greatest limitations on intensive care during terminal hospitalizations in England occur among elderly and medical patients (51). It has been more recently appreciated that delirium is a major, more widespread problem in critically ill patients than had been previously recognized. In a prospective cohort study, 340 consecutive admissions in patients 60 years of age or older were studied. The investigators found that the number of days of delirium that older patients experienced during ICU admission is significantly associated with mortality up to 1 year after admission controlling for severity of illness (52).

There are new radiographic and nuclear medicine methods that may play a role in diagnosis or guide therapy for patients with ALI. Neutrophilic inflammation plays an important role in the pathogenesis of ALI. In one study, investigators used positron emission tomography with ^{18}F -fluoro-2-deoxy-D-glucose to image cellular metabolism in patients with ALI. The goal was to assess the magnitude and regional distribution of inflammatory metabolic activity in the lungs of patients with ALI. Metabolic activity, presumably primarily from neutrophils, was markedly increased across the entire lung density spectrum and was not restricted to regions with the lowest aeration. Thus, denser collapsed or consolidated areas of the lung imaged by chest radiograph or CT scanning probably do not reflect the extent of inflammation in ALI (53).

The relationship of physical examination to measurements of central venous pressure, fluid output, and central venous oxygen saturation was evaluated in 500 patients who were part of the ARDS Network Fluid and Catheter Treatment Trial. Physical examination findings including capillary refill time greater than 2 seconds, mottling of the extremities, or cool extremities had a low sensitivity and a low positive predictive value for cardiac index and mixed venous oxygen saturation. There were some correlations that were statistically significant but not clinically useful (54).

Finally, there has been a great deal of concern regarding the pandemic of H1N1 viral pneumonia leading to severe ALI and death in particularly susceptible patients, including pregnant women, patients older than 70 years of age, and patients with immunosuppressive illnesses (55, 56).

TREATMENT OF ACUTE LUNG INJURY: EXPERIMENTAL STUDIES

The open lung strategy aims to reopen (recruit) nonaerated lung areas in patients with ALI/ARDS to minimize alveolar hyperinflation in the limited area of normally aerated tissue. However, this goal implies that nonaerated portions of the lung, once recruited, would resume mechanical properties similar or equal to those of the neighboring collapsed or consolidated lung. However, the results of one experimental study challenged this hypothesis (57). Further, in a model of mechanically ventilated pigs, other investigators found that alveolar recruitment was not protective against alveolar hyperinflation, because recruited lung tissue has mechanical properties that are different from those of the surrounding collapsed or consolidated

lung (58). The significance of this work was well discussed in a related commentary (59).

Some work has been focused on the extrapulmonary effects of mechanical ventilation in ALI. In one study in mice, investigators found that mechanical ventilation can interact with acute kidney injury to cause changes in lung function through mechanisms that involve neutrophils (60). An excellent commentary on this topic was also published (61).

There has been a longstanding interest in the potential to reduce lung injury by blocking specific mediators that play an important role in acute lung inflammation. In a mouse model, investigators found that blocking 12-HETE production provided a survival benefit in acid-induced lung injury. CDC, the 12/15-LO inhibitor used in this study, was effective when given as a pretreatment; however, high doses of CDC are required to inhibit 12/15-LO so more specific and effective pharmacologic inhibitors need to be developed to be tested in patients with ALI (62).

Based on the work cited above, strategies to alter platelet function may have value in treating ALI. There is evidence that antiplatelet therapy, including aspirin, reduces the severity of experimental lung injury (24).

Based on preclinical studies, there has been a rapidly growing interest in the potential of cell-based therapy for the treatment of ALI. Mesenchymal stem cells (MSC) can be isolated from several tissues, including bone marrow, placenta, cord blood, and adipose tissue. Primarily because of their paracrine effects, MSC can limit organ injury or enhance repair. In one report, investigators found that administration of allogeneic bone-marrow derived human MSC effectively reversed severe endotoxin-induced pulmonary edema and lung injury in an *ex vivo* perfused human lung preparation. Secretion of keratinocyte growth factor by the MSC was responsible for 80% of the protective effect (63). Two other recent articles provided evidence that MSC or the cultured medium effectively reduced perinatal hyperoxic lung injury in newborn rodents (64, 65). Another group reported the value of microvesicles isolated from MSC for reversing experimentally induced acute renal failure (66). Finally, intravenous MSC reduced mortality in a mouse model of peritoneal sepsis, primarily through PGE-2 mediated reprogramming of alveolar macrophages that resulted in high levels of the antiinflammatory cytokine IL-10 in the MSC-treated mice (67).

TREATMENT OF ACUTE LUNG INJURY AND OTHER CRITICAL ILLNESSES: CLINICAL STUDIES

Extracorporeal membrane oxygenation therapy (ECMO) for severe respiratory failure from ALI/ARDS has been primarily used as rescue therapy. Investigators in the United Kingdom assessed the potential value of ECMO for the treatment of severe lung injury and respiratory failure (CESAR trial). The study was designed as a pragmatic trial to determine if referral to a major specialty center with protocolized ARDS care that included ECMO was superior to care in specialty centers without protocolized care and without access to ECMO. There was a small significant benefit of ECMO therapy in the 57 of 90 patients who received ECMO compared with 90 patients allocated to conventional management (63 vs. 47%; $P = 0.03$). The results indicate that that referral in the United Kingdom to a regional center that specializes in care for patients with ALI, including lung-protective ventilation, is of value. This study did not establish the superiority or the efficacy of ECMO for ALI (68).

ECMO has also been used on an anecdotal basis as a rescue therapy for patients with severe ARDS from H1N1 influenza pneumonia. In one recent report, ECMO was used for rescue therapy in Australia and New Zealand with an overall 21%

mortality rate in this group. However, there was no control group, thus no conclusions can be made about the value of ECMO therapy for severe viral pneumonia from influenza without prospective randomized trials (69).

There has been considerable interest in the possibility that therapy with statins might improve clinical outcomes from sepsis and ALI. Investigators treated volunteers either with placebo or 40 mg or 80 mg of simvastatin for 4 days before the inhalation of 50 μ g of aerosolized endotoxin. Pretreatment with simvastatin reduced endotoxin-induced alveolar neutrophilia, myeloperoxidase, TNF- α , and matrix metalloproteinases 7, 8, and 9. Thus, this clinical study paves the way for further therapeutic evaluation of statins in patients with ALI (70).

Although there is some evidence that surfactant therapy may be effective in pediatric patients with ALI, surfactant therapy has not yet been shown to be effective in adult patients with ALI. In another trial of surfactant for adult patients with ALI, 418 patients were randomized to either usual care or usual care plus direct instillation of exogenous natural porcine surfactant HL10. There was no difference in mortality in the control versus the treated group. There was even a trend toward increased adverse effects with surfactant therapy (71).

There has been discussion regarding the potential benefits of early goal-directed therapy, corticosteroids, recombinant human APC, tight glucose control, and lung-protective strategies for patients with sepsis and lung injury. In a large cohort of adult patients with severe sepsis from 77 ICUs, compliance with therapeutic goals (central venous pressure ≥ 8 mm Hg for persistent hypotension despite fluid resuscitation and/or lactate > 36 mg/dl, central venous oxygen saturation $\geq 70\%$ for persistent hypotension, blood glucose $\geq$ normal but < 150 mg/dl, and inspiratory plateau pressure < 30 cm H₂O for mechanically ventilated patients), early broad-spectrum antibiotics, fluid challenge, low-dose steroids, and APC were evaluated. Using propensity scores, the results show that early administration of broad-spectrum antibiotics and administration of APC in the most severely ill patients reduced mortality (72). A new, prospective randomized double-blind trial is being performed to test the efficacy of APC therapy for sepsis (PROWESS Shock Trial). While awaiting the results of this new trial, investigators and clinicians should read the recently published excellent discussion of the issues that pertain to the clinical use of APC for severe sepsis (73).

Although there have been several negative trials regarding the value of glucocorticoids for treating early or late ALI, some clinicians believe that steroid therapy may still have value for the treatment of ALI. There are no major new results in this area in 2009 but more data should be available in the near future.

The potential therapeutic value of high- versus low-intensity continuous renal replacement therapy for acute renal failure in 1,508 critically ill patients was tested in a multicenter trial. The results showed that there was no difference in the high- versus low-intensity continuous renal replacement therapy with an equivalent 90-day mortality of 45% in both groups (74).

Finally, there has been considerable uncertainty regarding the value of tight glucose control for critically ill patients. A large multicenter randomized trial of intensive versus conventional glucose control was performed in 6,104 critically ill patients. The results showed that tight glucose control (81–108 mg/dl) increased mortality compared with that of patients with a conventional blood glucose target of 180 mg/dl or less. This increased mortality did not become apparent until after day 20 so the mechanistic connection between glucose control and outcome is not clear (75). The incidence of severe hypoglycemia (blood glucose level ≤ 40 mg/dl) occurred in 6.8% of patients undergoing intensive control compared with 0.5% of the patients undergoing conventional control ($P < 0.0001$).

Conflict of Interest Statement: M.A.M. has no financial relationship with a commercial entity that has an interest in the subject of this manuscript. S.I. has received lecture fees from Brahms (\$5,001–\$10,000); industry-sponsored grants from Attenuon, LLC (\$10,001–\$50,000); \$1001–\$5000 from Williams and Wilkins Publishers, up to \$1,000 from Hodder Arnold Publishers, and up to \$1,000 from Wolters Kluwer Publishers; consultancy fees from NIH (up to \$1,000); and sponsored grants from NIH (over \$100,000), FAMRI (over \$100,000), and U.S. Army (\$10,001–\$50,000).

References

- Erickson SE, Shlipak MG, Martin GS, Wheeler AP, Ancukiewicz M, Matthay MA, Eisner MD. National Institutes of Heart, Lung, and Blood Acute Respiratory Distress Syndrome Network. Racial and ethnic disparities in mortality from acute lung injury. *Crit Care Med* 2009;37:1–6.
- Phua J, Badia JR, Adhikari NK, Friedrich JO, Fowler RA, Singh JM, Scales DC, Stather DR, Li A, Jones A, *et al.* Has mortality from acute respiratory distress syndrome decreased over time? A systematic review. *Am J Respir Crit Care Med* 2009;179:220–227.
- Erickson SE, Martin GS, Davis JL, Matthay MA, Eisner MD, National Institutes of Heart, Lung and Blood Acute Respiratory Distress Syndrome Network. Recent trends in acute lung injury mortality: 1996–2005. *Crit Care Med* 2009;37:1574–1579.
- Levitt JE, Bedi H, Calfee CS, Gould MK, Matthay MA. Identification of early acute lung injury at initial evaluation in an acute care setting prior to the onset of respiratory failure. *Chest* 2009;135:936–943.
- Ahmed A, Kojicic M, Herasevich V, Gajic O. Early identification of patients with or at risk of acute lung injury. *Neth J Med* 2009;67:268–271.
- Gao L, Barnes KC. Recent advances in genetic predisposition to clinical acute lung injury. *Am J Physiol Lung Cell Mol Physiol* 2009;296:L713–L725.
- Gong MN. Gene association studies in acute lung injury: replication and future direction. *Am J Physiol Lung Cell Mol Physiol* 2009;296:L711–L712.
- Arcaroli JJ, Hokanson JE, Abraham E, Geraci M, Murphy JR, Bowler RP, Dinarello CA, Silveira L, Sankoff J, Heyland D, *et al.* Extracellular superoxide dismutase haplotypes are associated with acute lung injury and mortality. *Am J Respir Crit Care Med* 2009;179:105–112.
- Sapru A, Hansen H, Ajayi T, Brown R, Garcia O, Zhuo H, Wiemels J, Matthay MA, Wiener-Kronish J. 4G/5G polymorphism of plasminogen activator inhibitor 1 gene is associated with mortality in intensive care unit patients with severe pneumonia. *Anesthesiology* 2009;110:1086–1091.
- Sapru A, Curley MA, Brady S, Matthay MA, Flori H. Elevated Pai-1 is associated with poor clinical outcomes in pediatric patients with acute lung injury. *Intensive Care Med* 2010;36:157–163.
- Tejera P, Wang Z, Zhai R, Su L, Sheu CC, Taylor DM, Chen F, Gong MN, Thompson BT, Christiani DC. Genetic polymorphisms of peptidase inhibitor 3 (elafin) are associated with acute respiratory distress syndrome. *Am J Respir Cell Mol Biol* 2009;41:696–704.
- Chen CY, Yang KY, Chen MY, Chen HY, Lin MT, Lee YC, Perng RP, Hsieh SL, Yang PC, Chou TY. Decoy receptor 3 levels in peripheral blood predict outcomes of acute respiratory distress syndrome. *Am J Respir Crit Care Med* 2009;180:751–760.
- Sixt SU, Adamzik M, Spyrcak D, Saul B, Hakenbeck J, Wohlschlaeger J, Costabel U, Kloss A, Giesebrecht J, Dahmann B, *et al.* Alveolar extracellular 20S proteasome in patients with acute respiratory distress syndrome. *Am J Respir Crit Care Med* 2009;179:1098–1106.
- Xu J, Zhang X, Pelayo R, Monestier M, Ammollo CT, Semeraro F, Taylor FB, Esmon NL, Lupu F, Esmon CT. Extracellular histones are major mediators of death in sepsis. *Nat Med* 2009;15:1318–1321.
- Ware LB, Koyama T, Billheimer DD, Wu W, Bernard GR, Thompson BT, Brower RG, Standiford TJ, Martin TR, Matthay MA, *et al.* Prognostic and pathogenetic value of combining clinical and biochemical indices in patients with acute lung injury. *Chest* 2010;137:288–296.
- Howrylak JA, Dolinay T, Lucht L, Wang Z, Christiani DC, Sethi JM, Xing EP, Donahoe MP, Choi AM. Discovery of the gene signature for acute lung injury in patients with sepsis. *Physiol Genomics* 2009;37:133–139.
- Bastarache JA, Fremont RD, Kropski JA, Bossert FR, Ware LB. Procoagulant alveolar microparticles in the lungs of patients with acute respiratory distress syndrome. *Am J Physiol Lung Cell Mol Physiol* 2009;297:L1035–L1041.
- Zimmerman GA. Thinking small, but with big league consequences: Procoagulant microparticles in the alveolar space. *Am J Physiol Lung Cell Mol Physiol* 2009;297:L1033–L1034.
- Zemans RL, Colgan SP, Downey GP. Transepithelial migration of neutrophils: mechanisms and implications for acute lung injury. *Am J Respir Cell Mol Biol* 2009;40:519–535.
- D'Alessio FR, Tsushima K, Aggarwal NR, West EE, Willett MH, Britos MF, Pipeling MR, Brower RG, Tuder RM, McDyer JF, *et al.* CD4+CD25+Foxp3+ Tregs resolve experimental lung injury in mice and are present in humans with acute lung injury. *J Clin Invest* 2009;119:2898–2913.
- Pietropaoli A, Georas SN. Resolving lung injury: a new role for tregs in controlling the innate immune response. *J Clin Invest* 2009;119:2891–2894.
- Venet F, Chung CS, Huang X, Lomas-Neira J, Chen Y, Ayala A. Lymphocytes in the development of lung inflammation: A role for regulatory CD4+ T cells in indirect pulmonary lung injury. *J Immunol* 2009;183:3472–3480.
- Han W, Joo M, Everhart MB, Christman JW, Yull FE, Blackwell TS. Myeloid cells control termination of lung inflammation through the NB-κB pathway. *Am J Physiol Lung Cell Mol Physiol* 2009;296:L320–L327.
- Looney MR, Nguyen JX, Hu Y, Van Ziffle JA, Lowell CA, Matthay MA. Platelet depletion and aspirin treatment protect mice in a two-event model of transfusion-related acute lung injury. *J Clin Invest* 2009;119:3450–3461.
- Hidalgo A, Chang J, Jang JE, Peired AJ, Chiang EY, Frenette PS. Heterotypic interactions enabled by polarized neutrophil microdomains mediate thromboinflammatory injury. *Nat Med* 2009;15:384–391.
- Bozza FA, Shah AM, Weyrich AS, Zimmerman GA. Amicus or adversary: Platelets in lung biology, acute injury, and inflammation. *Am J Respir Cell Mol Biol* 2009;40:123–134.
- Ding BS, Hong N, Christofidou-Solomidou M, Gottstein C, Albelda SM, Cines DB, Fisher AB, Muzykantov VR. Anchoring fusion thrombomodulin to the endothelial lumen protects against injury-induced lung thrombosis and inflammation. *Am J Respir Crit Care Med* 2009;180:247–256.
- Scotton CJ, Krupiczkoj MA, Konigshoff M, Mercer PF, Lee YC, Kaminski N, Morser J, Post JM, Maher TM, Nicholson AG, *et al.* Increased local expression of coagulation factor X contributes to the fibrotic response in human and murine lung injury. *J Clin Invest* 2009;119:2550–2563.
- Bhandary YP, Velusamy T, Shetty P, Shetty RS, Idell S, Cines DB, Jain D, Bdeir K, Abraham E, Tsuruta Y, *et al.* Post-transcriptional regulation of urokinase-type plasminogen activator receptor expression in lipopolysaccharide-induced acute lung injury. *Am J Respir Crit Care Med* 2009;179:288–298.
- Paul-Clark MJ, McMaster SK, Sorrentino R, Sriskandan S, Bailey LK, Moreno L, Ryffel B, Quesniaux VF, Mitchell JA. Toll-like receptor 2 is essential for the sensing of oxidants during inflammation. *Am J Respir Crit Care Med* 2009;179:299–306.
- Comellas AP, Briva A, Dada LA, Butti ML, Trejo HE, Yshii C, Azzam ZS, Litvan J, Chen J, Lecuona E, *et al.* Endothelin-1 impairs alveolar epithelial function via endothelial ETB receptor. *Am J Respir Crit Care Med* 2009;179:113–122.
- Choi JE, Lee SS, Sunde DA, Huizar I, Haug KL, Thannickal VJ, Vittal R, Plymate SR, Schnapp LM. Insulin-like growth factor-I receptor blockade improves outcome in mouse model of lung injury. *Am J Respir Crit Care Med* 2009;179:212–219.
- Kolliputi N, Waxman AB. Il-6 cytoprotection in hyperoxic acute lung injury occurs via pi3k/akt-mediated bax phosphorylation. *Am J Physiol Lung Cell Mol Physiol* 2009;297:L6–L16.
- Wolters PJ, Wray C, Sutherland RE, Kim SS, Koff J, Mao Y, Frank JA. Neutrophil-derived IL-6 limits alveolar barrier disruption in experimental ventilator-induced lung injury. *J Immunol* 2009;182:8056–8062.
- Waxman AB, Kolliputi N. Il-6 protects against hyperoxia-induced mitochondrial damage via Bcl-2-induced bak interactions with mitochondria. *Am J Respir Cell Mol Biol* 2009;41:385–396.
- Wadgaonkar R, Patel V, Grinkina N, Romano C, Liu J, Zhao Y, Sammani S, Garcia JG, Natarajan V. Differential regulation of sphingosine kinases 1 and 2 in lung injury. *Am J Physiol Lung Cell Mol Physiol* 2009;296:L603–L613.
- Abolhassani M, Guais A, Chaumet-Riffaud P, Sasso AJ, Schwartz L. Carbon dioxide inhalation causes pulmonary inflammation. *Am J Physiol Lung Cell Mol Physiol* 2009;296:L657–L665.
- Carnesecchi S, Deffert C, Pagano A, Garrido-Urbani S, Metrailler-Ruchonnet I, Schappi M, Donati Y, Matthay MA, Krause KH, Barazzzone Argiroffo C. NADPH oxidase-1 plays a crucial role in

- hyperoxia-induced acute lung injury in mice. *Am J Respir Crit Care Med* 2009;180:972-981.
39. El Kebir D, Jozsef L, Pan W, Wang L, Petasis NA, Serhan CN, Filep JG. 15-epi-lipoxin A4 inhibits myeloperoxidase signaling and enhances resolution of acute lung injury. *Am J Respir Crit Care Med* 2009;180:311-319.
  40. Iyer SS, Jones DP, Brigham KL, Rojas M. Oxidation of plasma cysteine/cystine redox state in endotoxin-induced lung injury. *Am J Respir Cell Mol Biol* 2009;40:90-98.
  41. Kantrow SP, Shen Z, Jagneaux T, Zhang P, Nelson S. Neutrophil-mediated lung permeability and host defense proteins. *Am J Physiol Lung Cell Mol Physiol* 2009;297:L738-L745.
  42. Lorne E, Zhao X, Zmijewski JW, Liu G, Park YJ, Tsuruta Y, Abraham E. Participation of mammalian target of rapamycin complex 1 in toll-like receptor 2- and 4-induced neutrophil activation and acute lung injury. *Am J Respir Cell Mol Biol* 2009;41:237-245.
  43. Marshall HE, Potts EN, Kelleher ZT, Stamler JS, Foster WM, Auten RL. Protection from lipopolysaccharide-induced lung injury by augmentation of airway s-nitrosothiols. *Am J Respir Crit Care Med* 2009;180:11-18.
  44. Matt U, Warszawska JM, Bauer M, Dietl W, Mesteri I, Doninger B, Haslinger I, Schabbauer G, Perkmann T, Binder CJ, et al. Bbeta(15-42) protects against acid-induced acute lung injury and secondary pseudomonas pneumonia in vivo. *Am J Respir Crit Care Med* 2009;180:1208-1217.
  45. Mayer K, Kiessling A, Ott J, Schaefer MB, Hecker M, Henneke I, Schulz R, Gunther A, Wang J, Wu L, et al. Acute lung injury is reduced in fat-1 mice endogenously synthesizing n-3 fatty acids. *Am J Respir Crit Care Med* 2009;179:474-483.
  46. Munoz NM, Meliton AY, Meliton LN, Dudek SM, Leff AR. Secretory group V phospholipase A2 regulates acute lung injury and neutrophilic inflammation caused by lps in mice. *Am J Physiol Lung Cell Mol Physiol* 2009;296:L879-L887.
  47. Reddy NM, Suryanarayana V, Yates MS, Kleeberger SR, Hassoun PM, Yamamoto M, Liby KT, Sporn MB, Kensler TW, Reddy SP. The triterpenoid CDDO-imidazolide confers potent protection against hyperoxic acute lung injury in mice. *Am J Respir Crit Care Med* 2009;180:867-874.
  48. Zmijewski JW, Lorne E, Zhao X, Tsuruta Y, Sha Y, Liu G, Abraham E. Antiinflammatory effects of hydrogen peroxide in neutrophil activation and acute lung injury. *Am J Respir Crit Care Med* 2009;179:694-704.
  49. Lawrence KL, Kollef MH. Antimicrobial stewardship in the intensive care unit: Advances and obstacles. *Am J Respir Crit Care Med* 2009;179:434-438.
  50. Lott JP, Iwashyna TJ, Christie JD, Asch DA, Kramer AA, Kahn JM. Critical illness outcomes in specialty versus general intensive care units. *Am J Respir Crit Care Med* 2009;179:676-683.
  51. Wunsch H, Linde-Zwirble WT, Harrison DA, Barnato AE, Rowan KM, Angus DC. Use of intensive care services during terminal hospitalizations in England and the United States. *Am J Respir Crit Care Med* 2009;180:875-880.
  52. Pisani MA, Kong SY, Kasl SV, Murphy TE, Araujo KL, Van Ness PH. Days of delirium are associated with 1-year mortality in an older intensive care unit population. *Am J Respir Crit Care Med* 2009;180:1092-1097.
  53. Bellani G, Messa C, Guerra L, Spagnoli E, Foti G, Patroniti N, Fumagalli R, Musch G, Fazio F, Pesenti A. Lungs of patients with acute respiratory distress syndrome show diffuse inflammation in normally aerated regions: A [18F]-fluoro-2-deoxy-D-glucose PET/CT study. *Crit Care Med* 2009;37:2216-2222.
  54. Grissom CK, Morris AH, Lanken PN, Ancukiewicz M, Orme JF Jr, Schoenfeld DA, Thompson BT. National Institutes of Heart, Lung and Blood Acute Respiratory Distress Syndrome Network. Association of physical examination with pulmonary artery catheter parameters in acute lung injury. *Crit Care Med* 2009;37:2720-2726.
  55. Echevarria-Zuno S, Mejia-Arangure JM, Mar-Obeso AJ, Grajales-Muniz C, Robles-Perez E, Gonzalez-Leon M, Ortega-Alvarez MC, Gonzalez-Bonilla C, Rascon-Pacheco RA, Borja-Aburto VH. Infection and death from influenza A H1N1 virus in Mexico: a retrospective analysis. *Lancet* 2009;374:2072-2079.
  56. Jamieson DJ, Honein MA, Rasmussen SA, Williams JL, Swardlow DL, Biggerstaff MS, Lindstrom S, Louie JK, Christ CM, Bohm SR, et al. H1N1 2009 influenza virus infection during pregnancy in the USA. *Lancet* 2009;374:451-458.
  57. Mertens M, Tabuchi A, Meissner S, Krueger A, Schirrmann K, Kertzsch U, Pries AR, Slutsky AS, Koch E, Kuebler WM. Alveolar dynamics in acute lung injury: Heterogeneous distension rather than cyclic opening and collapse. *Crit Care Med* 2009;37:2604-2611.
  58. Grasso S, Stripoli T, Sacchi M, Trerotoli P, Staffieri F, Franchini D, De Monte V, Valentini V, Pugliese P, Crovace A, et al. Inhomogeneity of lung parenchyma during the open lung strategy: a computed tomography scan study. *Am J Respir Crit Care Med* 2009;180:415-423.
  59. Hubmayr RD. Another look at the opening and collapse story. *Crit Care Med* 2009;37:2667-2668.
  60. Dodd OJ, Hristopoulos M, Scharfstein D, Brower R, Hassoun P, King LS, Becker P, Liu M, Wang W, Hassoun HT, et al. Interactive effects of mechanical ventilation and kidney health on lung function in an in vivo mouse model. *Am J Physiol Lung Cell Mol Physiol* 2009;296:L3-L11.
  61. Liu KD. Impact of acute kidney injury on lung injury. *Am J Physiol Lung Cell Mol Physiol* 2009;296:L1-L2.
  62. Zarbock A, Distasi MR, Smith E, Sanders JM, Kronke G, Harry BL, von Vietinghoff S, Buscher K, Nadler JL, Ley K. Improved survival and reduced vascular permeability by eliminating or blocking 12/15-lipoxygenase in mouse models of acute lung injury (ALI). *J Immunol* 2009;183:4715-4722.
  63. Lee JW, Fang X, Gupta N, Serikov V, Matthay MA. Allogeneic human mesenchymal stem cells for treatment of E. coli endotoxin-induced acute lung injury in the ex vivo perfused human lung. *Proc Natl Acad Sci USA* 2009;106:16357-16362.
  64. van Haften T, Byrne R, Bonnet S, Rochefort GY, Akabutu J, Bouchentouf M, Rey-Parra GJ, Galipeau J, Haromy A, Eaton F, et al. Airway delivery of mesenchymal stem cells prevents arrested alveolar growth in neonatal lung injury in rats. *Am J Respir Crit Care Med* 2009;180:1131-1142.
  65. Aslam M, Baveja R, Liang OD, Fernandez-Gonzalez A, Lee C, Mitsialis SA, Kourembanas S. Bone marrow stromal cells attenuate lung injury in a murine model of neonatal chronic lung disease. *Am J Respir Crit Care Med* 2009;180:1122-1130.
  66. Bruno S, Grange C, Deregis MC, Calogero RA, Saviozzi S, Collino F, Morando L, Busca A, Falda M, Bussolati B, et al. Mesenchymal stem cell-derived microvesicles protect against acute tubular injury. *J Am Soc Nephrol* 2009;20:1053-1067.
  67. Nemeth K, Leelahavanichkul A, Yuen PS, Mayer B, Parmelee A, Doi K, Robey PG, Leelahavanichkul K, Koller BH, Brown JM, et al. Bone marrow stromal cells attenuate sepsis via prostaglandin E(2)-dependent reprogramming of host macrophages to increase their interleukin-10 production. *Nat Med* 2009;15:42-49.
  68. Peek GJ, Mugford M, Tiruvoipati R, Wilson A, Allen E, Thalanany MM, Hibbert CL, Truesdale A, Clemens F, Cooper N, et al. Efficacy and economic assessment of conventional ventilatory support versus extracorporeal membrane oxygenation for severe adult respiratory failure (CESAR): A multicentre randomised controlled trial. *Lancet* 2009;374:1351-1363.
  69. Australia and New Zealand Extracorporeal Membrane Oxygenation Influenza Investigators, Davies A, Jones D, Bailey M, Beca J, Bellomo R, Blackwell N, Forrest P, Gattas D, et al. Extracorporeal membrane oxygenation for 2009 influenza A(H1N1) acute respiratory distress syndrome. *JAMA* 2009;302:1888-1895.
  70. Shyamsundar M, McKeown ST, O'Kane CM, Craig TR, Brown V, Thickett DR, Matthay MA, Taggart CC, Backman JT, Elborn JS, et al. Simvastatin decreases lipopolysaccharide-induced pulmonary inflammation in healthy volunteers. *Am J Respir Crit Care Med* 2009;179:1107-1114.
  71. Kesecioglu J, Beale R, Stewart TE, Findlay GP, Roubey JJ, Holzapfel L, Bruins P, Steenken EJ, Jeppesen OK, Lachmann B. Exogenous natural surfactant for treatment of acute lung injury and the acute respiratory distress syndrome. *Am J Respir Crit Care Med* 2009;180:989-994.
  72. Ferrer R, Artigas A, Suarez D, Palencia E, Levy MM, Arenzana A, Perez XL, Sirvent JM. Edusepsis Study G. Effectiveness of treatments for severe sepsis: a prospective, multicenter, observational study. *Am J Respir Crit Care Med* 2009;180:861-866.
  73. Toussaint S, Gerlach H. Activated protein C for sepsis. *N Engl J Med* 2009;361:2646-2652.
  74. Investigators RRTS, Bellomo R, Cass A, Cole L, Finfer S, Gallagher M, Lo S, McArthur C, McGuinness S, Myburgh J, et al. Intensity of continuous renal-replacement therapy in critically ill patients. *N Engl J Med* 2009;361:1627-1638.
  75. Investigators N-SS, Finfer S, Chittock DR, Su SY, Blair D, Foster D, Dhingra V, Bellomo R, Cook D, Dodek P, et al. Intensive versus conventional glucose control in critically ill patients. *N Engl J Med* 2009;360:1283-1297.