Pulmonary, Sleep, and Critical Care Updates

Update in Acute Lung Injury and Critical Care 2010

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In this Update, we provide an overview of selected studies published in 2010 in the *American Journal of Respiratory and Critical Care Medicine* and other journals focusing on novel findings on acute lung injury (ALI) and its more severe form, the acute respiratory distress syndrome (ARDS). We attempt to highlight key articles that advanced our understanding on clinical and basic aspects of critical illness.

ADVANCES IN UNDERSTANDING THE PATHOGENESIS OF ALI

Risk Factors, Early Diagnosis, and Prevention of ALI

Preventing the development of ALI is a significant focus of research; however, we are limited by our inability to anticipate which patients are likely to develop ALI. A single-center observational study reported an ALI prediction model, the Lung Injury Prediction Score (LIPS), incorporating the risk factors: high-risk trauma, high-risk surgery, aspiration, sepsis, shock, pneumonia, and pancreatitis, as well as risk modifiers, such as alcohol abuse, hypoalbuminemia, tachypnea, oxygen supplementation, chemotherapy, obesity, and diabetes (1). Another multicenter observational cohort study of 5,584 patients in 22 hospitals showed that ALI was rarely present at the time of initial emergency department evaluation. Instead, ALI appeared to develop over a period of hours to days in 6.8% of at risk patients. The occurrence of ALI varied according to predisposing conditions, and the LIPS model predicted which patients might develop ALI early in the course of their illness. Development of ALI significantly increased the risk of in-hospital death, further stressing the importance of preventive strategies (2).

According to the World Health Organization (Geneva, Switzerland), annual influenza epidemics result in about 3 to 5 million cases of severe illness, and about 250,000 to 500,000 deaths. In 2009, the outbreak of the novel H1N1 influenza (also known as influenza A or H1N1/09) pandemic presented enormous challenges in health care worldwide. An inception-cohort study enrolling 337 adult patients described epidemiology,

clinical features, outcomes, and mortality predictors in patients with confirmed, probable, and suspected viral pneumonia caused by H1N1 admitted to 35 intensive care units with acute respiratory failure requiring mechanical ventilation in Argentina (3). Fortunately, the H1N1-associated morbidity and mortality turned out to be significantly lower than in previous pandemics (4, 5).

Adverse effects of therapeutic modalities on patients with malignancies may lead to complications resulting in acute respiratory failure, the leading reason for intensive care unit admission among this patient population, carrying a high mortality rate. Because outcomes are worse when the cause of respiratory failure remains unidentified, early and effective diagnostics are essential. A multicenter randomized controlled trial compared safety and efficacy of noninvasive tests with or without fiberoptic bronchoscopy and bronchoalveolar lavage (BAL) in the early diagnosis of acute respiratory failure. Interestingly, noninvasive diagnostic tests alone provided the diagnosis in most of these patients (6). However, because etiologic diagnosis was obtained by fiberoptic bronchoscopy and BAL in 18% of the patients enrolled, and the invasive diagnostics were not associated with a higher risk of complications and intubation rate, the authors suggested that this procedure should be used in addition to noninvasive tests if feasible, early after intensive care unit (ICU) admission (6). Another study established that early continuous positive airway pressure in patients with hematological malignancies presenting with early changes in respiratory variables reduced the need for ventilatory support and thus may represent a preventive measure in this patient population (7).

An example of a potentially preventable form of ALI is transfusion-related acute lung injury (TRALI), representing the most common cause of transfusion-associated mortality. Therefore, identifying the antigens that are frequently associated with severe TRALI is of clinical importance. Studies have characterized human neutrophil alloantigen (HNA)-3a, which is responsible for numerous fatal TRALI cases. The studies demonstrated that HNA-3a arises from a nucleotide polymorphism in the choline transporter-like protein-2 gene. The resulting variation at amino acid position 154 determines the reactivity of the protein with HNA-3a-specific antibodies (8, 9). Another study described the biological mechanism of HLA class II antibody-induced TRALI (10). Thus, implementing novel screening measures should lead to a significant reduction of TRALI cases.

Interestingly, a study conducted in Olmsted County, Minnesota, over an 8-year period described a significant decrease in the incidence of ARDS (from 82.4 to 38.9 per 100,000 person-years) (11). Because a decline in hospital-acquired ARDS rather than the number of cases on admission was observed, the authors hypothesized that preventing second hits leading to ARDS in the ICU, such as ventilation with high tidal volumes, multiple blood transfusions, plasma transfusion from potentially alloimmunized donors, delayed antibiotic treatment, and goal-

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directed resuscitation in septic patients, was responsible for the fall in incidence density (11). Thus, perhaps advances in preventive measures explain why the incidence of ARDS was significantly decreased.

Genetics, Genomics, Proteomics, and Metabolomics

Several studies have reported associations between single nucleotide polymorphisms and clinical outcomes in patients with sepsis and ALI susceptibility. In a two-stage case-control study followed by a nested case-control design in two independent populations, the commonly occurring *FAS* haplotype, including *FAS*_{21541T} and *FAS*_{9325A}, was associated with ALI susceptibility (12). However, no association between *FAS* genotypes and mortality was observed, suggesting that this common genetic variation in *FAS* may primarily influence susceptibility to ALI as opposed to severity (12). Another study described the *CysGlyGln* haplotype of the β_2 -adrenergic receptor gene (*ADRB2*), which has been associated with altered responses to adrenergic agonists, on outcome in septic shock. Patients with the AA genotype of *ADRB2* rs1042717, homozygotes for the *CysGlyGln* haplotype, required higher norepinephrine dose, had higher heart rates, developed more often organ dysfunction, and displayed increased 28-day mortality in both cohorts (13).

Simultaneous alterations of various molecular pathways, by affecting inflammation and alveolo-capillary barrier dysfunction, can lead to ALI. Thus, high-throughput genomic and proteomic analysis studies have been proposed to identify new molecular pathways. One study identified dysregulation of 16 proteins including down-regulation of apolipoprotein (Apo) A-I, the major protein component of the high-density lipoprotein, in BAL from patients with idiopathic lung fibrosis and from a mouse model of bleomycin-induced ALI. Importantly, administration of Apo A-I to mice reduced the bleomycin-induced lung inflammation and partially rescued the ALI phenotype, suggesting a pathogenic role for Apo A-I in lung injury (14).

Metabolomics, a novel approach that, by measuring metabolites and end products of specific cellular processes, may reveal pathology, has emerged as an alternative to proteomics with the potential for discovery of novel biomarkers and pathogenic factors of ALI. Using high-resolution nuclear magnetic resonance spectroscopy for metabolite fingerprinting in plasma samples from patients with sepsis-induced ALI, four metabolic networks have been identified that might be associated with changes in oxidative status, energy balance, apoptosis, and barrier function, the hallmarks of sepsis and ALI (15, 16). Understanding the interactions of pathways involved in the pathogenesis of ALI will certainly be advanced by systems biology; however, interpretation of the complex data generated by “omics” can be challenging (17).

NOVEL THERAPEUTIC APPROACHES AND OUTCOME

Advances in ALI Therapy

Several studies assessed novel therapeutic approaches for patients with ALI. A multicenter, open-label randomized controlled trial enrolling 348 critically ill patients with elevated lactate levels on ICU admission assessed the effects of lactate monitoring and the objective to decrease lactate by 20% or more per 2 hours for the initial 8 hours of ICU stay. Surprisingly, despite an aggressive treatment algorithm, reduction of lactate was not faster when compared with control group therapy and yet the treatment protocol to decrease lactate serum levels resulted in a significant reduction in the risk of hospital death, leading to a 9.6% absolute reduction in hospital

mortality and reduced short-term organ failure, earlier weaning from the ventilator, and subsequent earlier discharge from the ICU (18).

The use of neuromuscular blocking agents in patients with ALI remains controversial and might be associated with muscle weakness. A multicenter, double-blind study randomly assigned 340 patients with severe ARDS to receive either cisatracurium besylate or placebo for 48 hours and evaluated clinical outcomes. Although the rate of ICU-acquired paresis remained unchanged, there was a significant reduction in mortality at 28 days in the cisatracurium besylate group when compared with the placebo group (23.7 vs. 33.3%, respectively) (19).

Intensive insulin therapy in critically ill patients represents another area of controversy. Unlike in adult ICU patients (reviewed in Reference 20), a prospective randomized trial in severely burned pediatric patients showed that intensive insulin therapy was associated with improved morbidity (21).

Determinants of ALI Outcome

A number of clinical studies focused on mechanisms that may influence outcomes in ALI. Analysis of tissue biopsies from deceased ICU patients revealed an increased number of newly formed adipocytes, which appeared to have an increased ability to take up and metabolize glucose and store triglycerides. Because hyperglycemia and dyslipidemia are associated with increased mortality in critical illness, the authors hypothesized that this adaptive response may be protective (22). Another study observed that survival of critically ill patients was associated with early activation of mitochondrial biogenesis, which may counteract mitochondrial protein depletion, thereby maintaining energetic status, whereas in nonsurvivors these responses appeared to be impaired (23, 24). A secondary analysis of 501 patients in the Fluids and Catheters Treatment Trial (FACTT) confirmed that pulmonary vascular dysfunction is common in patients with ALI, representing an independent risk factor associated with poor outcomes (25).

Another study evaluated the effects of prior vasopressor requirement on outcomes in patients who received resuscitation after cardiopulmonary arrest in an ICU. The study identified 49,656 adult patients within the National Registry of Cardiopulmonary Resuscitation with an overall survival rate to hospital discharge of 15.9%. Patients who required vasopressors before cardiopulmonary resuscitation were less likely to survive than those who did not (9.3 vs. 21.2%, respectively) (26). These data should help clinicians to inform consent for this procedure; however, one trial suggested that disclosing prognosis to surrogate decision-makers in the ICU and reaching physician-surrogate concordance about prognosis can be challenging (27).

A substudy of the Awakening and Breathing Controlled Trial enrolling 180 mechanically ventilated patients randomized to daily spontaneous awakening trials with spontaneous breathing trials or to sedation per usual care and daily spontaneous breathing trials resulted in similar cognitive, psychological, and quality of life outcomes 3 and 12 months after hospital discharge (28).

Optimizing Intensive Care Delivery and Clinical Trials in ALI

The current organization of critical care delivery is evolving, and new models are being studied. A population-based retrospective cohort study of 107,324 patients admitted to 112 Pennsylvania ICUs showed that multidisciplinary care and high-intensity physician staffing were associated with significant reductions in the odds of death (29). There have been different voices suggesting alternative organizational models for intensive care, comparing advantages and potential pitfalls of 24/7

coverage, tiered regionalization, telemedicine, and quality improvement through regional outreach, checklists, and protocol-driven care (30–37).

The ICU environment generates a high risk of iatrogenic events. An observational prospective multicenter cohort study in 70 ICUs reported 1,192 medical errors, 15.4% of which led to adverse events with clinical consequences. Furthermore, having two or more adverse events was an independent risk factor for ICU mortality, indicating an urgent need to develop error prevention programs (38). The relationship between organization of critical care and optimization of health care delivery as well as future clinical research were also the focus of a multidisciplinary workshop convened by the National Heart, Lung, and Blood Institute (Bethesda, MD) (39).

MEDIATORS, BIOMARKERS, AND EXPERIMENTAL THERAPIES OF SEPSIS AND ALI

Several reports focused on mechanisms of sepsis and ALI. For example, on sepsis cytoplasmic accumulation of myeloid nuclear differentiation antigen was impaired, which contributed to delayed neutrophil apoptosis, thereby resulting in sustained inflammation (40). Another report provided evidence that phosphoinositide-3 kinase (PI3K)- γ , a key regulator of leukocyte recruitment, plays an important role in the pathogenesis of sepsis. Genetic inhibition of PI3K- γ improved survival, reduced multiorgan damage, and limited bacterial decompartmentalization in cecal ligation and perforation-induced sepsis (41). In the same sepsis model, hydrogen sulfide restored impaired neutrophil migration and reduced bacteremia and lung injury via a K_{ATP}^+ channel-dependent mechanism, thereby increasing survival (42). Also, an agonist of the transcription factor peroxisome proliferator-activated receptor (PPAR)- β/δ attenuated organ dysfunction and inflammation and improved sepsis survival in mice by activation of the serine/threonine protein kinase Akt and inhibition of glycogen synthase kinase-3 β and nuclear factor- κ B (43). Similarly, insulin-like growth factor-1 protected gastrointestinal barrier function in a pneumonia model of sepsis (44).

Role of Inflammation and Innate Immunity in ALI

Inflammation plays a central role in the pathogenesis of ALI. Thus, it is perhaps not surprising that the majority of the proposed mediators of ALI and the potential therapeutic approaches focus on modulating inflammation. For example, it has been reported that trauma may lead to systemic inflammation via the release of mitochondrial damage-associated molecular patterns dysregulating immunity. Damage-associated molecular patterns behaved similarly to microbial pathogen-associated molecular patterns, perhaps because mitochondria were evolutionarily derived from bacteria (45). Interestingly, targeting receptors for advanced glycation end-products, which recognize pathogen-associated molecular patterns, protected against hyperoxia-induced lung injury (46). Also, NF-E2-related factor-2 (Nrf2) has been proposed as a master regulator of antioxidant responses, and PPAR γ as a key effector molecule in the Nrf2-mediated protection against hyperoxic lung injury (47, 48).

One study showed that activation of the inflammasome and subsequent secretion of proinflammatory cytokines were initiated by K^+ efflux through the purinergic P2X7 receptor in alveolar macrophages, leading to alveolar epithelial injury on hyperoxia (49). Interestingly, ATP released from pulmonary epithelial cells on bleomycin-induced ALI was identified as an endogenous danger signal that via the P2X7 receptor/pannexin-1 axis led to injury (50). Another study defined a role for the proinflammatory neuropeptide, substance P, in the pathogenesis of burn-induced

ALI, which was attenuated in preprotachykinin-A gene-deficient mice, which encodes substance P (51). Also, an antiinflammatory and potentially therapeutic role for milk fat globule epidermal growth factor-8, which is known to attenuate inflammation by enhancing apoptotic cell clearance, was proposed in ALI secondary to ischemia-reperfusion injury of the gut (52). An article described a protective function for the antiinflammatory mediator resolvin E1 in experimental ALI caused by acid aspiration and subsequent bacterial challenge (53). Tissue inhibitor of metalloproteinase-3 was proposed to mediate resolution of inflammation after ALI in a bleomycin-induced mouse model (54). In the same model of ALI, surfactant protein A also appeared to reduce inflammation and apoptosis, thereby improving epithelial integrity (55). Also, the neuronal guidance protein netrin-1, which serves as a negative guidance cue for leukocyte migration and holds antiinflammatory potential, was repressed during ALI, contributing to injury, and administration of exogenous netrin-1 attenuated experimental ALI in an adenosine 2B receptor-dependent manner (56). A protective role for adenosine signaling through the adenosine 2B receptor was also proposed in endotoxin-induced ALI (57). An interesting article described the development of a new animal model for malaria-induced ALI to explore pathogenesis and treatment options (58). Another study characterized the effects of apelin, a potent vasodilator and angiogenic factor, in a neonatal rat model of ALI and found that apelin reduced pulmonary inflammation, fibrin deposition, and right ventricular hypertrophy via a nitric oxide synthase-dependent mechanism (59).

Several studies focused on the modulation of innate immunity in the context of ALI. One study described the small GTPase Rab10 as a key regulator of cellular trafficking of Toll-like receptor-4, which plays an important role in inflammatory responses, thereby modulating disease severity of LPS-induced ALI (60). A regulatory role for pentraxin-3 in inflammation has long been recognized and the underlying mechanisms were now described, showing that pentraxin-3 is released from activated leukocytes and attenuated neutrophil recruitment at sites of inflammation (61). An interesting study provided insights into the mechanisms of methicillin-resistant *Staphylococcus aureus* infection-induced ALI by identifying the central role of Pantone-Valentine leukocidin, a pore-forming toxin that targets polymorphonuclear leukocytes, in the pathogenesis of the disease (62). Also, urokinase-type plasminogen activator increased tissue factor expression and tissue factor-dependent coagulation appeared to promote fibrin deposition in the airways, leading to barrier dysfunction and lung fibrosis (63). Interestingly, urokinase-type plasminogen activator also decreased the phagocytosis of apoptotic neutrophils by alveolar macrophages, which may enhance the severity of ALI (64).

Restoring Alveolo-Capillary Barrier Integrity

Restoration of alveolo-capillary barrier integrity plays an important role in the resolution of ALI and patient recovery. Neutrophil α -defensins, the pore-forming proteins that assist in killing of phagocytosed bacteria, contributed to epithelial injury in acid aspiration-induced ALI via a low-density lipoprotein-related receptor-dependent mechanism (65). Another report suggested a transcriptional role of Krüppel-like factor-4 in maintaining adherens junctions by regulating vascular endothelial cadherin expression and improving endothelial barrier dysfunction on inflammatory stimuli (66). Also, the Abl tyrosine kinase was proposed as a regulator of the multifunctional cytoskeletal protein, nonmuscle myosin light chain kinase, in maintaining endothelial barrier function (67). Repair of the injured endothelial barrier requires cellular regeneration and

reannealing of junctional complexes. Endothelial cell-restricted disruption of the forkhead box protein (Fox) M1 demonstrated a novel role of this transcription factor in mediating barrier repair through the control of β -catenin (68).

Apoptosis, Degradation, Proliferation, and Progenitor and Stem Cells in ALI

Several reports focused on cell proliferation and cell therapy in the context of ALI. One study identified oxidant-mediated apoptotic pathways as important contributors to the development of ALI, specifically the conditional loss of proapoptotic Bcl-2 family members BAX and BAK in the lung epithelium prevented hyperoxia-induced alveolar epithelial cell death, ameliorated lung injury, and prolonged survival (69). In a hyperoxia-induced ALI model, chitinase-like proteins breast regression protein-39 and YKL-40 were shown as key regulators of injury and epithelial apoptosis (70). Another report documented apoptosis of splenic and circulating lymphocytes in a murine model of endotoxin-induced ALI, which was further augmented by the infusion of soybean oil-based, and to a lesser extent by olive oil-based, emulsions, which may be of relevance for patients with ALI requiring parenteral nutrition (71). Interestingly, during the repair response of ALI, cytokine macrophage migration-inhibitory factor was highly expressed, which protected from apoptosis, but also led to increased proliferation in orthotopic tumors injected after the acute phase of injury (72).

Experimental insights provide evidence that bone marrow progenitor cells can incorporate into the lung. A study in patients requiring extracorporeal membrane oxygenation for life support found that hematopoietic, mesenchymal, and epithelial cell progenitors were mobilized into the circulation, suggesting that progenitor cell mobilization may be a mechanism of nonresident progenitor cell recruitment to injured tissues (73).

Significant progress has been made on mesenchymal stem cell research. An excellent review discussed advances in this exciting area (74). Mesenchymal stem cells appeared to reduce inflammation while enhancing bacterial clearance, and improved survival in experimental sepsis (75). Furthermore, allogeneic human mesenchymal stem cells were shown to restore epithelial protein permeability in cultured human alveolar type II cells, possibly via paracrine mechanisms involving secretion of angiopoietin-1 (76). Also, when alveolar type II cells derived from human embryonic stem cells were transplanted into rodent lungs subjected to bleomycin-induced ALI, the transplanted cells behaved like normal alveolar type II cells and differentiated into alveolar type I epithelial cells, leading to increased survival (77).

The previously described novel mediators, experimental therapies, and organizational models of care delivery may ultimately translate into effective therapeutic approaches for the treatment of ALI, leading to better outcomes.

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