Bridging the chasm between bench and bedside: translational research in acute lung injury

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The gap between clinical practice and scientific discovery, often referred to as the gap between the bench and the bedside, is a huge void in some disease processes. Translational research is often focused on bridging that gap. Acute lung injury (ALI) is an excellent example of how critical that bridging can be. ALI presents unique challenges to clinicians and scientists. On the clinical side, the diagnosis is somewhat nonspecific. Individuals with identified clinical risk factors that have a specified level of impaired oxygenation, a consistent chest radiograph, and no clinical evidence of left ventricular failure have ALI (2). No biopsies are required to confirm the diagnosis, and, despite years of looking, there is no specific biomarker that makes the diagnosis. Thus the diagnosis is, in part, based on a subjective assessment by the clinician caring for the patient. The situation is further complicated by the observations that patients with ALI are not homogeneous. The incidence of ALI as well as the morbidity and mortality from the syndrome depends on the individual’s clinical risk factor as well as numerous preexisting and comorbid factors including age, gender (11), ethnicity (11), alcohol abuse (12), diabetes (10), and probably others as yet unidentified. In addition, studies are increasingly showing that measures previously considered to be part of routine care, such as mechanical ventilation, can actually enhance the pulmonary inflammatory process and further contribute to morbidity and mortality (1, 4, 13). Designing clinical trials that take all these factors into account can be challenging.

The barriers for the basic scientist can seem equally daunting. Although it often seems relatively easy to create ALI in an animal model or to evaluate a potential mechanism of injury in an in vitro system, translating the important discoveries from those studies into therapeutic interventions that improve patient outcome has been frustrating. This is in part because it is difficult to replicate the clinical scenario either in vitro or even in animal models. However, observations both at the bench and the bedside have captured the interest of scientists on each side and have led to important contributions. For example, it was noticed in clinical studies that alcohol abuse was associated with an increased incidence of ALI and mortality from the syndrome. This observation has led to extensive basic and clinical research on the impact of alcohol in pulmonary inflammation (9). These studies have significantly contributed to our understanding of the pathogenesis of ALI and have been important in the development of the concept that therapeutic interventions targeted to specific groups of patients with ALI may be appropriate to consider. This collaborative bedside-bench approach is an exciting effort.

The five call for papers articles published in this issue of AJP–Lung Cellular and Molecular Physiology represent the bench-bedside spectrum of studies in ALI. Each one of them contributes to new knowledge to the field and opens doors for additional studies from the other side of the bench-bedside spectrum. The study by Bowler and colleagues (3) utilized a new technique, proteomics, to analyze the proteins in pulmonary edema fluid and plasma from 16 patients with ALI and 12 normal subjects. They confirmed previous observations that pulmonary edema fluid in ALI is rich in plasma proteins and made the novel observation that many of the proteins were modified posttranslation. These observations could lead directly to numerous basic and clinical studies. As the authors indicate, variables such as age and mechanical ventilation could impact on their results. This could be addressed by a study from a larger clinical patient population carefully controlled for those clinical variables such as ventilation, age, gender, clinical risk factor, etc., that are known to influence morbidity and mortality. Studies designed to identify the state of plasma and lung proteins in specific animal models of ALI could help identify which proteins have evidence of posttranslational modification and what the relative level of importance is of each of the proteins identified. Even more basic studies could further elaborate on the mechanism of posttranslational modification of these proteins.

Ishizaka and colleagues (5) also used a novel technique, bronchoscopic microsampling, to study the pathogenesis of ALI in patients. This group analyzed the levels of a lung epithelial cell marker, KL-6, in both the plasma and epithelial lining fluid from patients with ALI and found an association between KL-6 levels in these fluids and mortality. The cut-off values for KL-6 predictive of mortality were fairly specific and sensitive. This trial was small, and the patients were heterogeneous, but this novel finding now begs to be expanded to a larger, more defined patient population to see whether KL-6 can be used as a biomarker in clinical ALI. Furthermore, the investigators performed additional in vitro studies showing that cytokines stimulated the release of KL-6 from alveolar type II cells and that these cells were a likely source of KL-6 in the pulmonary edema fluid. Stimulated epithelial cells were the likely source of the KL-6 but whether proliferating and/or injured epithelial cells contributed is not definitively known but could be important in the consideration of potential therapeutic interventions. This question could be answered with animal models of ALI.

The study by Krupa and colleagues (6) was stimulated by their previous finding that the IL-8 in the lungs of patients with ALI is complexed with IL-8 autoantibodies and that there is an association between level of these complexes and mortality. They took this clinical observation back to the bench in the study published here. Through a series of experiments, the authors have elegantly demonstrated that these anti-IL-8:IL-8 complexes are proinflammatory. These complexes are chemotactic for neutrophils, and this activity is mediated by FC R11a. This now invites a study in patients with ALI to determine
whether these mechanisms of activity of these complexes occur in vivo.

Clinical trials have confirmed that low tidal volume ventilation improves clinical outcomes, but the mechanisms by which low tidal volumes are protective are still being identified. Morisaka and colleagues (8) have shown that large tidal volumes are associated with the upregulation of CD14 on alveolar macrophages. In animals treated with LPS, large tidal volumes were associated with an increase in epithelial-alveolar permeability and an increase in TNF in the plasma. These studies in aggregate suggest that large tidal volume ventilation “sensitizes” alveolar macrophages to LPS by upregulation of CD14. This finding immediately invites further studies to confirm that large tidal volumes upregulate CD14 on alveolar macrophages in humans. If that occurs, and there is no reason to think that it would not, the potential for improved outcomes in patients is tremendous. For example, all patients who require prolonged mechanical ventilation are at risk for infections such that the response to infections may be magnified if they have been ventilated with larger tidal volumes and CD14 is upregulated. Similarly, one of the major clinical risk factors for ALI is sepsis. Perhaps patients with sepsis should be ventilated with low tidal volumes even before they develop ALI. Identifying whether this upregulation of CD14 is a homogeneous response could also be important. It is likely that there is genetic variability in the extent of the upregulation such that this mechanism of ventilator-associated lung injury may be more important in some patients than in others. This could be explored in animal models. In vitro models could further elaborate on how mechanical stress results in this upregulation.

β2-Adrenergic agonists enhance alveolar fluid clearance, a process that is impaired in ALI. A number of mechanisms whereby these agonists enhance fluid clearance have been studied and identified. Maris and colleagues (7) expand this knowledge by demonstrating that salmeterol inhibits LPS-induced neutrophil influx into the lungs of mice, probably by reducing the expression of CD11 on the surface of the neutrophils. Not only is alveolar fluid clearance impaired in ALI, neutrophil-mediated injury is often considered to be a hallmark of the syndrome. Thus the study by Maris and colleagues suggests yet another reason that β-agonists could be therapeutically beneficial in ALI and encourages the initiation of a large clinical trial as well as additional in vitro and in vivo studies to elaborate the mechanism of the decreased neutrophil influx.

These five studies have each made distinct contributions to our understanding of ALI. That expansion of our knowledge, alone, makes them important. In aggregate, they also make an important contribution that should not be overlooked. By representing the spectrum of research from bench to bedside (and back), they encourage the generation of ideas for additional studies that depend on the collaboration of clinical and basic scientists to bridge the gap between them. In the subways in London one is always advised, “Mind the gap.” Perhaps that should be the mantra for ALI research.

REFERENCES


