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Predicting Mortality in Patients with Acute Lung Injury

Acute lung injury (ALI) and the acute respiratory distress syndrome (ARDS) are common disorders estimated to affect nearly 200,000 people per year in the United States alone (1). Despite improvements in supportive care, the overall mortality rate for these patients continues to hover near 40% (2). In King County, Washington, Rubenfeld and coworkers reported that the incidence of ARDS was twice as high in patients over 74 compared with patients between 60 and 64 years of age, and that older patients who developed the syndrome were significantly more likely to die (1). Therefore, the incidence of ALI/ARDS and its associated mortality are likely to rise as the population ages, particularly in the developed world.

Novel therapies identified through bench and clinical research and translated to clinical practice have led to substantial improvements in ICU care in the past decade. Advances in imaging and laboratory diagnostics have dramatically improved our ability to identify and treat primary causes of critical illness, reducing diagnostic procedure-related morbidity and mortality. New antimicrobials and vasoactive agents, more effective therapies to prevent stress ulcer and venous thromboembolism, and a variety of new agents to treat other complications of critical illness effectively reduce the risk of ICU-related complications. In addition, we have learned to better use the resources available to us in the ICU. Positive pressure ventilation strategies designed to prevent ventilator-induced lung injury, interruptions in sedation, improved fluid management, limitation of empiric antibiotic usage, strategies to prevent ventilator-associated pneumonia, and the use of protocols and checklists to ensure consistent patient care delivery have all improved the supportive care of patients with ALI/ARDS (3–8).

Given these and other research-driven improvements in supportive care, it is surprising that the crude mortality in most studies conducted in patients with ARDS remains relatively constant (2). One possible explanation is that the lack of change represents a true success as our ICUs fill with older patients with more co-morbidities. Even if this is true, it is clear that for a significant proportion of patients with ALI/ARDS, even the best supportive therapy is not enough. For these patients, novel therapies designed to interrupt ongoing lung injury or promote healing lung that investigators have identified as effective in preclinical or phase II trials may improve outcomes (9). Therefore, when testing potentially toxic new therapies investigators need biomarkers to identify subsets patients with ARDS at a higher risk of death, as the risk-to-benefit profile in these patients is more likely to be favorable. Investigators have frequently examined bronchoalveolar lavage fluid to identify predictive biomarkers, as the procedure can be done safely, is often performed as part of routine clinical care, and can reveal valuable insight into the severity of damage to the alveolar membrane (5, 10).

The low-density lipoprotein receptor-related protein (LRP-1) is a large endocytic receptor that is expressed in many tissues, including the lung (11). LRP-1 recognizes more than 30 different ligands with varying affinity, facilitating their cellular uptake

via endocytosis (11). In the low pH of the endosome, a conformational change in the structure in LRP-1 causes it to release the ligand, which can be recycled or degraded in the lysosome (12). In this issue of the *Journal*, Wygrecka and colleagues (pp. 438) found that the levels of soluble LRP-1 (sLRP-1) were increased in patients with ARDS compared with a control group of spontaneously breathing subjects or mechanically ventilated patients with cardiogenic pulmonary edema (13). The BAL levels of sLRP-1 were positively correlated with APACHE II scores and were significantly higher in patients who died from ARDS compared with those who survived. BAL fluid from patients with ARDS induced sLRP release from lung fibroblasts (but not epithelial cells or macrophages) through a mechanism that required TNF- α and membrane type-1 matrix metalloproteinase. The investigators went on to show that sLRP-1 inhibited the uptake of matrix metalloproteinases-2 and -9, which might enhance tissue injury. In support of this hypothesis they found that BAL fluid levels of MMP-2 and -9, and the basement membrane protein laminin, were positively correlated with the levels of sLRP-1 in the patients with ARDS.

Wygrecka and coworkers have identified one important mechanism by which LRP-1 might contribute to the pathophysiology of ARDS. In addition, LRP-1 has been shown to regulate the activity of platelet-derived growth factor and transforming growth factor- β 1, promote the clearance of Factor VIII, modulate the activity of the fibrinolytic system by binding with the urokinase-type plasminogen activator, contribute to the tPA-mediated increase in blood-brain barrier permeability after stroke, promote focal adhesion disassembly, and enhance cell migration, all of which may be important in the development and resolution of ALI (11). In addition, LRP-1 plays an important role in the phagocytosis of apoptotic cells and foreign particles. For example, Gardai and colleagues reported that in the lung LRP-1 interacts with surfactant proteins-A and -D to promote phagocytosis and induce inflammation in response to foreign particles or damaged cells (14). Further study will be required to determine the predominant mechanism(s) by which LRP-1 might contribute to the pathogenesis of ALI/ARDS.

Before it can be used to direct treatment, a biomarker must be shown to have a high sensitivity, specificity, and positive and negative predictive value for the predicted outcome; be reproducible outside of the institution or laboratory in which it was developed; demonstrate biological plausibility; and be validated in a cohort of patients independent from the original cohort (15). Substantial further investigation is required before bronchoalveolar lavage fluid levels of sLRP-1 can be used as a biomarker to identify patients at risk of death from ARDS. However, the findings of Wygrecka and coworkers add to those conducted by other investigators who collectively have identified an array of physiologic and laboratory parameters to improve our ability to identify patients at high risk of death earlier in their clinical course (16). Rigorous prospective examination of their utility as clinical prediction tools may open the door for the use of active pharmacologic or biological interventions to prevent ALI/ARDS-associated mortality.

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Baseline Values and Short Serial Change A “Road Map” for a Poor Early Outcome in Idiopathic Pulmonary Fibrosis

The selection of an optimal primary endpoint in idiopathic pulmonary fibrosis (IPF) pharmaceutical studies has proved problematic. Mortality, the ideal definition of outcome, is essentially impracticable, and no surrogate for mortality has been wholly satisfactory. It is generally accepted, based on a number of studies of pulmonary function trends against mortality (1–3), that serial change in the forced vital capacity (FVC) is the most accurate endpoint that is currently available. However, despite the poor average outcome in IPF, the prevalence of declines in FVC by at least 10% from baseline, traditionally viewed as a marker of significant change, has been much lower than expected in pharmaceutical studies (4). The evaluation of change in FVC as a continuous variable has also caused difficulty, as there is no consensus as to whether treatment effects of less than 10% are clinically significant. However, the goal of achieving an average FVC treatment effect of 10% in IPF studies lasting 1 year is problematic. In placebo arms, average FVC declines have been significantly lower than 10% (5, 6). As such, validation of the clinical significance of thresholds for average FVC decline of less than 10% is urgently required.

In this issue of the *Journal*, du Bois and colleagues (pp. 459) have attempted the ambitious goal of creating a “road map” for the identification of likely progression of IPF (7), based upon analyses of the combined treatment and placebo arms of two large pharmaceutical studies (5, 8). The authors have shown that on multivariate analysis, factors independently

predictive of mortality are age, the baseline severity of FVC, the occurrence of admissions to hospital, and serial FVC trends including, crucially, “marginal” declines of 5 to 10%. Plainly, an accurate index would be highly desirable in routine practice and this report does provide an important starting point. As complex multivariate models are not always robust when subsequently tested, confirmation is required in a separate cohort: the number of deaths in the current study was too low to allow split sample testing. Furthermore, re-evaluation in a large “all-comers” cohort would allow the index to be tested in key patient subgroups not evaluated in the current study.

Pharmaceutical populations are necessarily subject to major selection bias with the exclusion of subgroups of patients with advanced disease or significant comorbidity. It is likely, also, that patients with more rapidly progressive IPF encountered in clinical practice (9, 10) are underrepresented. Rapid progression must necessarily limit the window of opportunity to satisfy severity-based entry criteria. Furthermore, patients and enrolling clinicians may be less likely to accept placebo-controlled evaluation when disease is overtly highly progressive. In the proposed index, there is no specific surrogate for pulmonary hypertension, a malignant prognostic determinant that is frequent in advanced disease but also occurs when interstitial disease is less advanced. This deficiency might be addressed by the inclusion in the model of baseline DL_{CO} levels or major serial changes in six minute walk data, recently shown by this group to