NIH Public Access
Author Manuscript

Biomarkers in acute lung injury: Are we making progress?

Sushma K. Cribbs, MD and **Greg S. Martin, MD, MSc**

Acute lung injury (ALI) and its severe form, acute respiratory distress syndrome (ARDS), continue to be significant challenges to the critical care physician. First described in 1967, ALI/ ARDS is characterized by the onset of clinically significant hypoxemia and diffuse bilateral pulmonary infiltrates. A clinically devastating and life threatening syndrome, it continues to carry a mortality of 40% – 50%, and is an important cause of pulmonary and non-pulmonary morbidity in patients who survive hospitalization. (1)

For four decades, the search has continued for useful diagnostic and prognostic biomarkers that will guide us as critical care physicians to precisely distinguish ALI/ARDS from other disorders and to portend disease progression. The identification of such a biomarker would allow for improved clinical decision-making, knowledgeable family discussions, and better utilization of healthcare resources. Unfortunately, this search has been hindered by the inherent heterogeneity of the disease along with the consistent lack of correlation between biochemical markers, pathophysiologic variables and clinical outcomes.

ALI/ARDS instigates a myriad of cellular and molecular cascades that result in circulating inflammatory and prothrombotic mediators; pathophysiologic disturbances that may be important determinants of mortality. With improved understanding of pathophysiology, many biomarkers have been assessed for diagnostic or prognostic capability, such as inflammatory mediators such as interleukin-1β [IL-1β] (2,3) and tumor necrosis factor-α [TNF-α] (4), which can be detected in the distal airspaces of the lung in ALI/ARDS patients. Most recently investigators have documented the influence of the coagulation system in ALI/ARDS, with levels of IL-8, ICAM-8, plasminogen activator inhibitor-1 and protein C being predictive of clinical outcomes. (5,6) We have also evaluated markers of endothelial injury (von Willebrand factor), (7,8) epithelial injury, (receptor for advanced glycation end-products [RAGE] (9) and surfactant protein-D [SP-D]), (10) stem cells, (11) and physiologic measures such as pulmonary dead space fraction (12) or extravascular lung water. (13,14)

This issue of *Critical Care Medicine* includes an important hypothesis-generating article by Mauri and his colleagues (15). The authors report the results of an observational study of pentraxin 3 (PTX3) as a marker of severity and as an outcome predictor in ALI/ARDS patients. They enrolled 21 patients with ALI/ARDS, measured plasma PTX3, C-reactive protein (CRP), and other inflammatory markers at various time points, and correlated these results to multiple measures of disease severity and organ dysfunction including lung injury score (LIS), sequential organ failure assessment (SOFA), and simplified acute physiology score II (SAPS II). The authors made several novel observations: 1) Plasma PTX3 levels were elevated in patients with ALI/ARDS for the first week, which then decreased and stabilized until ICU discharge. In contrast, CRP levels remained consistently elevated throughout the ICU stay; 2) PTX3 level was the only parameter examined that was consistently and significantly different between survivors and non-survivors; 3) PTX3 levels correlated with parameters of lung injury and organ dysfunction; 4) PTX3 levels were elevated in either blood or bronchoalveolar lavage fluid for patients with a documented infection.

Using analytical tools to assess biological parameters can provide researchers with an opportunity to gain a mechanistic understanding of disease processes. In 2001, the NIH adopted

the definition of a biomarker as "…an indicator of normal biologic processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention." (16) The authors of this study have begun to study an interesting idea will PTX3 levels help predict which ALI/ARDS patients will die? PTX3, a newly discovered acute phase protein, is expressed locally in response to a variety of infectious and inflammatory stimuli and plays a key role in innate immunity (17,18). Unlike its cousin, CRP, PTX3 gene expression is induced by TNF-α and IL-1β in an assortment of human tissue cells, including fibroblasts and epithelial cells (17). Increased levels of PTX3 have been found in a number of sepsis and ALI animal models, correlating with lung injury severity (19), and in some cases mortality (20), suggesting that PTX3 may play a role in the pathogenesis of ARDS.

A biomarker that indicates pathogenic processes and is involved in molecular pathways will guide researchers in further understanding intricate disease mechanisms, so that novel therapeutic interventions may be developed. Applying criteria publicized by the McMaster group (21), we can assess the value of PTX3 as a biomarker in ALI/ARDS. Accordingly, there was a representative inception cohort of ALI/ARDS patients, with the primary cause being pneumonia; however, the small sample from a single ICU setting limits generalizability. Objective outcome criteria were used and included standards for measuring organ dysfunction (LIS, SOFA, SAPS II) and survival, although adjustment for extraneous prognostic factors was not performed. Despite PTX3 being the only parameter statistically different between survivors and non-survivors, it is likely that other parameters would also differ with a larger study population. In addition, the numerical differences seen with age, SOFA and SAPS II scores may be clinically (if not statistically) significant. Because of these limitations, the different PTX3 levels seen between ALI/ARDS survivors and non-survivors should be interpreted with caution.

Nevertheless, despite these limitations, this work on PTX3 represents an important development in our understanding of ALI/ARDS the exploration of a novel prognostic and potentially pathophysiologic biomarker in a patient population that continues to suffer a high mortality. Because PTX3 may play an important role in host defense and contribute to the pathogenesis of ALI/ARDS, it may be a critical biochemical marker to improve our understanding of ALI/ARDS pathophysiology, to help us accurately identify ALI/ARDS patients, and to predict outcomes. Further study is needed to corroborate these hypotheses, with sufficient numbers of patients to account for both relevant biomarker parameters as well as clinical data that is available at the bedside for prognostic purposes (such as organ dysfunctions or severity of illness scores). While biomarker exploration may have scientific value in isolation, the combination of biological data with clinical information is necessary for biomarkers to have clinical utility. This combined approach is the standard for future biomarker studies. With our recent advances in understanding both pathophysiology of ALI/ARDS and technological advances in biomarker identification, we are optimistic that a clinically and scientifically useful biomarker is not far over the horizon.

Reference List

1. Ware LB, Matthay MA. The acute respiratory distress syndrome. N Engl J Med 2000;342:1334–1349. [PubMed: 10793167]

2. Donnelly SC, Strieter RM, Reid PT, et al. The association between mortality rates and decreased concentrations of interleukin-10 and interleukin-1 receptor antagonist in the lung fluids of patients with the adult respiratory distress syndrome. Ann Intern Med 1996;125:191–196. [PubMed: 8686976]

3. Geiser T, Atabai K, Jarreau PH, Ware LB, Pugin J, Matthay MA. Pulmonary edema fluid from patients with acute lung injury augments in vitro alveolar epithelial repair by an IL-1beta-dependent mechanism. Am J Respir Crit Care Med 2001;163:1384–1388. [PubMed: 11371405]

4. Tremblay LN, Miatto D, Hamid Q, Govindarajan A, Slutsky AS. Injurious ventilation induces widespread pulmonary epithelial expression of tumor necrosis factor-alpha and interleukin-6 messenger RNA. Crit Care Med 2002;30:1693–1700. [PubMed: 12163778]

5. McClintock D, Zhuo H, Wickersham N, Matthay MA, Ware LB. Biomarkers of inflammation, coagulation and fibrinolysis predict mortality in acute lung injury. Crit Care 2008;12:R41. [PubMed: 18358078]

6. Ware LB, Matthay MA, Parsons PE, Thompson BT, Januzzi JL, Eisner MD. Pathogenetic and prognostic significance of altered coagulation and fibrinolysis in acute lung injury/acute respiratory distress syndrome. Crit Care Med 2007;35:1821–1828. [PubMed: 17667242]

7. Moss M, Ackerson L, Gillespie MK, Moore FA, Moore EE, Parsons PE. von Willebrand factor antigen levels are not predictive for the adult respiratory distress syndrome. Am J Respir Crit Care Med 1995;151:15–20. [PubMed: 7812545]

8. Ware LB, Conner ER, Matthay MA. von Willebrand factor antigen is an independent marker of poor outcome in patients with early acute lung injury. Crit Care Med 2001;29:2325–2331. [PubMed: 11801836]

9. Uchida T, Shirasawa M, Ware LB, et al. Receptor for advanced glycation end-products is a marker of type I cell injury in acute lung injury. Am J Respir Crit Care Med 2006;173:1008–1015. [PubMed: 16456142]

10. Greene KE, Wright JR, Steinberg KP, et al. Serial changes in surfactant-associated proteins in lung and serum before and after onset of ARDS. Am J Respir Crit Care Med 1999;160:1843–1850. [PubMed: 10588595]

11. Burnham EL, Taylor WR, Quyyumi AA, Rojas M, Brigham KL, Moss M. Increased circulating endothelial progenitor cells are associated with survival in acute lung injury. Am J Respir Crit Care Med 2005;172:854–860. [PubMed: 15976374]

12. Nuckton TJ, Alonso JA, Kallet RH, et al. Pulmonary dead-space fraction as a risk factor for death in the acute respiratory distress syndrome. N Engl J Med 2002;346:1281–1286. [PubMed: 11973365]

13. Phillips CR, Chesnutt MS, Smith SM. Extravascular lung water in sepsis-associated acute respiratory distress syndrome: indexing with predicted body weight improves correlation with severity of illness and survival. Crit Care Med 2008;36:69–73. [PubMed: 18090369]

14. Martin GS, Eaton S, Mealer M, Moss M. Extravascular lung water in patients with severe sepsis: a prospective cohort study. Crit Care 2005;9:R74–R82. [PubMed: 15774053]

15. Mauri T, Coppadoro A, Bellani G. Pentraxin 3 (PTX3) in acute respiratory distress syndrome; an early marker of severity. Crit Care Med. (in press)

16. Biomarkers Definitions Working Group. Biomarkers and surrogate endpoints: preferred definitions and conceptual framework. Clin Pharmacol Ther 2001;69:89–95. [PubMed: 11240971]

17. He X, Han B, Liu M. Long pentraxin 3 in pulmonary infection and acute lung injury. Am J Physiol Lung Cell Mol Physiol 2007;292:L1039–L1049. [PubMed: 17277044]

18. Muller B, Peri G, Doni A, et al. Circulating levels of the long pentraxin PTX3 correlate with severity of infection in critically ill patients. Crit Care Med 2001;29:1404–1407. [PubMed: 11445697]

19. Okutani D, Han B, Mura M, Waddell TK, Keshavjee S, Liu M. High-volume ventilation induces pentraxin 3 expression in multiple acute lung injury models in rats. Am J Physiol Lung Cell Mol Physiol 2007;292:L144–L153. [PubMed: 16936248]

20. Souza DG, Soares AC, Pinho V, et al. Increased mortality and inflammation in tumor necrosis factor-stimulated gene-14 transgenic mice after ischemia and reperfusion injury. Am J Pathol 2002;160:1755–1765. [PubMed: 12000727]

21. How to read clinical journals III. To learn the clinical course and prognosis of disease. Can Med Assoc J 1981;124:869–872. [PubMed: 7214286]