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Invited critical review

Biologic markers of mortality in acute lung injury

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Abstract

Acute lung injury (ALI) is a clinical syndrome in which patients develop severe and progressive pulmonary gas exchange defects and pulmonary mechanical dysfunction. The high morbidity and mortality (40%) associated with ALI provide a compelling need to identify clinical and/or biochemical parameters that robustly risk stratify patients for both accurate prognostication and clinical trial purposes. In this review, we will examine and critically evaluate studies pertaining to biochemical markers of mortality in ALI. These markers may not only serve as prognostic measures of disease, but in some cases, add to our overall understanding of the pathophysiology of ALI.

Keywords: Acute lung injury; Biomarkers

Contents

1. Introduction

The acute lung injury (ALI)/acute respiratory distress syndrome (ARDS) is a clinical syndrome defined by the acute development of progressive bilateral airspace infiltrates in the

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Table 1
Studies of edema fluid characteristics, cell-specific and inflammatory markers

Biologic marker	Description	Biologic fluid	ALI detection	Predictive value for mortality	References
A. Edema fluid					
Pulmonary edema protein	Total and high molecular weight	Pulmonary edema	ALI=EF/plasma ratio >0.65	BAL protein concentration elevated in non-survivors	[13]
Rate of protein clearance	>14% clearance in 1st 4 h	Pulmonary edema	ND	RR=4 for clearance <14%/h	[12]
B. Endothelium					
ET-1	Vasoconstrictor released from endothelium	Plasma	ALI>normal	ND	[18,19]
vWF	Synthesized vascular endothelium	Plasma	vWF >4.5×NL=80% PPV for ARDS development	OR=1.9 for vWF >4.5×NL values	[11,20]
C. Epithelium					
Surfactant protein A	Nonspecific marker of epithelial injury	BAL	SP-A >1200 pg/ml=100% sens., 60% spec. for ALI development	ND	[21]
Surfactant protein D	Nonspecific marker of epithelial injury	Plasma	ND	OR of 1.21 per 100 ng/ml increment	[22,23]
KL-6	Epithelial-derived mucin	Plasma, EF	Elevated in ALI vs. NL, vent. pts.	Elevated in non-survivors	[24,25]
D. Inflammatory cell-derived					
Total neutrophil (PMN) count	Total PMN count in first 2 weeks	BAL	Conflicting results	Elevated in non-survivors with sepsis etiology	[16]
Neutrophil elastase	Serine protease from PMN	BAL	No association	No association	[26]
Matrix metalloproteases (MMPs)	Family of Zn-containing endopeptidases	EF	MMP-9 elevated in ALI vs. hydro	ND	[26,27]
Nitrate and nitrite	Reactive nitrogen species	EF, plasma	Elevated in ALI vs. HYDRO	ND	[28,29]
Macrophage percentage	Percent macrophages at day 14	BAL	No association	Elevated in survivors at day 14	[16]
TGF-α	Potent epithelial and fibroblast mitogen	BAL	Elevated in ALI vs. NL	Level >1.08 pg/ml (1–2 weeks)=OR of 1.6	[30]
E. Fibroblast					
PCP III	Fibroblast derived	BAL, serum	Elevated in ALI vs. HYDRO/NL	Level >1.75 U/ml=OR of 2.7	[15,35]

ALI—acute lung injury; NL—normal; HYDRO—hydrostatic pulmonary edema; EF—edema fluid; BAL—bronchoalveolar lavage; RR—relative risk; OR—odds ratio; ND—not determined; ET-1—endothelin-1; vWF—von Willebrand's factor; PCP III—procollagen peptide type III.

absence of clinical signs of heart failure. ALI and ARDS are distinguished by the severity of hypoxemia. ALI is defined by the ratio of the partial pressure of arterial oxygen to the fraction of inspired oxygen (P/F ratio; PaO_2 in mm Hg/FIO_2) of ≤300 while ARDS is classified as having a ratio of ≤200 [1,2]. As many of the studies that form the basis for this review were performed prior to the establishment of these P/F ratio stratification criteria, we will group them together under the rubric of ALI for clarity.

The incidence of ALI is not precisely known, but most recent estimates based on extrapolation of ICU beds utilization range from 22 to 64 cases per 100,000 population/year in the United States [3]. However, a more direct measure of all mechanically ventilated patients in Kings County, Washington demonstrates an age-adjusted incidence of for ALI of 86.2/100,000 persons [3]. Major underlying etiologies for the condition include sepsis, pneumonia, direct inhalation injury, aspiration of gastric contents, and trauma [1]. Among those at risk for the development of ALI, the presence of underlying sepsis, the simultaneous presence of multiple predisposing disorders, and/or chronic lung disease, chronic alcohol abuse, and low serum pH are associated with a higher propensity to develop ALI [1]. Therapy consists predominately of supportive care. Despite the significant progress in the understanding of the disease made over the past 10 years, the only clinical intervention found to have a significant impact on mortality in ALI is the use of low tidal volume ventilation (6 ml/kg ideal body weight) [4]. Interestingly, this strategy was associated with a reduction in neutrophil number and concentration of pro-inflammatory cytokines in the BAL as well [5]. However, along with mechanical ventilation improvements, enhanced supportive care has improved the outcome of ALI from 40% the survival noted fifteen years ago to the current 60% survival rate [6]. An important consideration here is that epidemiological studies provide a more accurate estimate of actual disease-related mortality, as patients with significant confounding co-morbidities are excluded from most therapeutic trials.

ALI is divided into two temporally overlapping clinicopathologic phases. The initial exudative phase (days 1–7) is manifested by the appearance of bilateral infiltrates on the chest radiograph, severely impaired oxygen uptake and hypoxemia, and reduced pulmonary compliance. An analysis of the bronchoalveolar lavage fluid (BAL) indicates this phase is characterized by a large influx of neutrophils and protein into the alveolar space, with diffuse alveolar