


WHAT'S NEW IN INTENSIVE CARE



What's new about circulating biomarkers in pediatric acute lung disease

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Introduction

Acute lung disease is a frequent cause of admission in pediatric intensive care units with at least 30 % requiring invasive mechanical ventilation (MV) [1]. Disruption of the alveolar-capillary barrier and subsequent increased permeability results from the acute lung disease itself and/or MV. This leads to protein leakage and spillover of inflammatory mediators from and to the pulmonary and systemic circulations. Circulating biomarkers among adult patients with acute respiratory distress syndrome (ARDS) have been extensively studied, but the number of pediatric studies is limited. Pediatric intensivists frequently extrapolate adult data to pediatrics but there are significant differences in incidence, etiology, and outcome of acute lung disease in children, primarily related to developmental changes in the lungs and immune system [2–4]. Nevertheless, circulating biomarkers in children, as in adults, have the potential to identify patients at risk of poor outcomes, to improve our understanding of the pathobiology, and eventually to help to develop more targeted therapies. We present a concise review of “what's new” in plasma or serum biomarkers of acute lung disease in children, with a focus on clinical utility and need for future work in this area. These biomarkers can be classified in a pathophysiological approach.

Epithelial markers

Circulating biomarkers of lung epithelial injury seem specific for direct insults. In respiratory syncytial virus (RSV) bronchiolitis and bronchopneumonia, there is an association between blood levels of surfactant protein SP-D, Krebs von den Lungen (KL)-6, and severity of pulmonary injury [4, 5]. Combining measurements of

plasma Clara cell protein (CC)-16 and SP-D with soluble receptor for advanced glycation (sRAGE), a marker of epithelial injury, is useful for monitoring severity of lung damage in MV patients [4, 6]. Plasma levels of sRAGE are elevated in postoperative lung injury after cardiopulmonary bypass, in both children and adults [7], suggesting that it is also a good marker of non-infectious pulmonary injury and need for prolonged MV. Given the interaction between sRAGE levels and use of high tidal volume MV on mortality in adults with ARDS [8], it is likely that sRAGE may be useful in identifying groups of patients with acute lung disease that warrant particular attention to ventilation with low tidal volumes.

Endothelial markers

Various plasma endothelial markers have been associated with prolonged mechanical ventilation, severity of multiorgan dysfunction, and/or mortality in pediatric and adult ARDS, especially in indirect forms. These biomarkers include soluble intercellular adhesion molecule (sICAM), which activates lung macrophages; von Willebrand factor (vWF), which is a platelet aggregation promoter; angiotensin (Ang)-2, which is involved in vascular permeability regulation; and more recently the soluble thrombomodulin (sTM), which is an activator of protein C [9–13]. Angiotensin-2 (Ang-2) inhibits Tie-2 signaling by blocking the Tie-2 receptor leading to increased endothelial permeability [14]. We have recently reported that elevated plasma Ang-2 levels are associated with mortality in pediatric ARDS and that an increase in Ang-2 level from day 1 to day 3, among children with a history of bone marrow transplant, is associated with a 16-fold increase in the odds of death [11]. Further evidence for the involvement of the endothelium is indicated by the association of increased levels of sTM with mortality and organ dysfunction (PELOD scores), in children with indirect ARDS [12]. This association is observed in adults as well [13], emphasizing the

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significance of endothelial injury in pediatric and adult ARDS, and suggests that therapies directed at stabilizing and minimizing endothelial injury may lead to improved clinical outcomes.

Coagulation and fibrinolysis markers

Disruption or imbalance in the coagulation system is an integral part of inflammation, sepsis, and acute lung damage. Therefore, regardless of lung protective ventilation, abnormalities in plasma levels of plasminogen activator inhibitor-1 (PAI-1), activated protein C, and soluble urokinase plasminogen activator receptor (sUPAR) have been recognized to be independent risk factors for mortality and adverse clinical outcomes in both adults and children with ARDS [15, 16]. In fact, an early evidence of fibrinolysis attenuation (like PAI-1 increase) signals endothelial injury, and might be suitable as a novel therapeutic target.

Inflammation markers

One of the central aspects of lung inflammation is the marked influx of neutrophils into the alveoli, which is attained by a network of cytokines whose global biological activity depends on an equilibrium between pro- and anti-inflammatory elements. Similar to adults,

a few small pediatric studies could show an association between altered blood levels of cytokines, namely interleukin (IL)-6, IL-8, IL-10, and IL-13, and morbidity and mortality [17, 18]. Thus, by recognizing the cytokines profile of the child perhaps we could develop individualized treatments rebalancing the inflammatory response.

Future directions

Currently, there is sufficient rationale to support that in future trials in pediatric acute lung disease, measuring biomarkers of lung damage as a secondary outcome should be strongly encouraged. It would be reasonable to include combinations of primarily structural (epithelial/endothelial) and functional markers (involved in coagulation and/or inflammation cascades) [8]. Moreover, investigators should take into consideration the age of the patient and the type of acute lung disease (resulting from a direct or indirect pulmonary insult).

Besides the fact that circulating biomarker patterns may help to better understand pathogenesis of acute lung disease, interactions with mechanical ventilation, and identify novel therapeutic targets, they may also guide use of targeted therapies in specific groups of patients in a personalized medicine approach (Table 1). For example, markers of lung epithelial damage might help identify

Table 1 Circulating biomarkers with potential for future diagnostic and/or therapeutic use in pediatric acute lung disease patients

Potential clinical use	Biomarkers	Description
Prediction/diagnosis of direct acute lung damage (pulmonary infection, VILI, direct ARDS)	SP, KL-6, CC-16, sRAGE	SP-D: diagnosis of lung injury in bronchiolitis and bronchopneumonia, also useful for predicting VILI as CC-16, KL-6, and sRAGE [4–6] KL-6: higher blood concentrations in severe RSV-bronchiolitis, particularly when ventilated [5] sRAGE: early marker of ARDS development post cardiopulmonary bypass [7]
Prediction of indirect acute lung damage (indirect ARDS) and/or outcome	sICAM-1, Ang-2, sTM, vWF, PAI-1, sUPAR, cytokines	Increased levels of Ang-2 and sTM are associated with mortality and organ dysfunction in indirect ARDS [11–14] sICAM-1 and vWF: increased risk of prolonged mechanical ventilation and death in ARDS [9, 10] PAI-1 and sUPAR are risk factors for mortality and bad outcome in ARDS [15, 16] Pro-inflammatory (like IL-6 and IL-8) and anti-inflammatory (like IL-10 and IL-13) cytokine expression is related to mortality [17, 18]
Therapeutic target for anti-inflammation and reduction of alveolar-capillary permeability	Ang-2	Vasculotide (agonist of Tie-2 receptor) Neutralizes the effect of Ang-2, which blocks Tie-2 receptor impairing endothelial barrier function [14]
Therapeutic target for anti-inflammation and anticoagulation	sTM	Recombinant TM: reinforces the effect of sTM, which accelerates activation of protein C and has anti-inflammatory properties [19]

VILI ventilation-induced lung injury, ARDS acute respiratory distress syndrome, SP surfactant proteins, CC Clara cell, KL Krebs von den Lungen, sRAGE soluble receptor for advanced glycation end products, RSV respiratory syncytial virus, sICAM soluble intercellular adhesion molecule, Ang angiotensin, vWF von Willebrand factor, sTM soluble thrombomodulin, IL interleukin, PAI plasminogen activator inhibitor, sUPAR soluble urokinase plasminogen activator receptor

patients most likely to benefit from potential lung protective ventilation modes and strategies. Likewise, it is plausible that markers of systemic inflammation and deranged coagulation may identify patients likely to profit from additional systemic measures such as appropriate hemodynamic support concomitant in severe systemic infection and/or sepsis, early use of antibiotics, or targeted anti-inflammatory or antithrombotic therapies. Recombinant TM, which suppresses high mobility group box protein (HMGB)-1-induced inflammation, reduced fatal outcome in an ARDS mouse model [19]. Since sTM measured in plasma of patients with sepsis and ARDS is a marker of endothelial damage and depletion of TM from endothelium, it may therefore have potential to identify patients that will respond to therapy with recombinant TM. Similarly, vasculotide, a synthetic agonist of Tie-2 receptor, which neutralizes the effect of excess Ang-2 and has anti-inflammatory properties, could be used as a potential therapeutic agent in patients with elevated Ang-2 [14].

Given that pathophysiology and outcome of acute lung disease in a developing child may differ from adults, we cannot extrapolate all adult experience without particular attention to lung growth and repair mechanisms in children. Consequently we strongly encourage further research in this area and advocate for collection of biological specimens in clinical trials. The need to study biomarkers of lung damage in children is both urgent and necessary as it is likely to lead to discovery of biomarkers that will help identify patients at greatest risk of adverse outcomes, and will provide mechanistic insights required for development of novel, patient-specific, therapeutic strategies.

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Compliance with ethical standards

Conflicts of interest

No conflicts of interest for any of the authors.

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