A Study of Epithelial Cell Neutrophil Activating Factor-٧٨ in Bronchoalveolar Lavage of Critically Ill Pediatric Patients with Acute Lung Injury

A Thesis

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٢٠٠٧

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٢٠٠٧

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Contents

List of abbreviations

ALI	Acute lung injury
ALIS	Acute lung injury score
AP	Antero posterior
ARDS	Acute respiratory distress syndrome
Arg	Arginine (R)
BAL	Bronchoalveolar lavage
CHF	Congestive heart failure
CPK	Creatine phosphokinase
CT	Computerized tomography
CVP	Central venous pressure
DAD	Diffuse alveolar damage
DLco	Carbon monoxide diffusion
ECG	Electrocardiogram
ELR motif	Glutamic acid leucine arginine
ENA-٧٨	Epithelial neutrophil-activating protein ٧٨
FIO_2	Fraction of inspired oxygen
FOB	Fiberoptic bronchoscope
FVC	Forced vital capacity
G-CSF	Granulocyte colony stimulating factor
Glu	Glutamic acid (E)
GSH	Glutathione
ICU	Intensive care unit

Il	Interleukin
IP-١٠	Interferon induced protein -١٠
JVP	Jugular venous pressure
Leu	Leucine (L)
lgA	Immunoglobulin A
LPS	Lipopolysaccharide
MCP-١	Monocyte chemo-attractant protein -l
MIF	Macrophage inhibitory factor
MIG	Monokine induced by gamma interferon
MOF	Multiple organ failure
MV	Mechanical ventilation
PaO_2	Partial pressure of oxygen
PCWP	Pulmonary capillary wedge pressure
PEEP	Positive end expiratory pressure
PMN	Polymorphonuclear lymphocytes
RV	Right ventricle
SaO_2	Saturation of oxygen
TLC	Total lung capacity
TNF	Tumor necrosis factor

List of Tables

List of Figures

Introduction and aim of the work

Acute lung injury (ALI) refers to a syndrome of acute respiratory failure characterized by respiratory distress, severe impairment of oxygenation and non cardiogenic pulmonary edema. As ALI, like any other clinical syndrome, can vary in severity, acute respiratory distress syndrome (ARDS) is a term applied to patients with more severe manifestations of ALI. Both terms are used to reflect a relatively specific form of pathologic injury to the lung occurring from a wide range of causes or associated conditions ***(Steinberg & Hudson, ٢٠٠٠)***.

The cellular and molecular basis for ARDS remains uncertain for ٣٠ years after the original description of the syndrome. With the explosion of information about the involvement of cells and cytokines in inflammation, there has been an intense interest in understanding the involvement of cytokines in the pathogenesis of ARDS ***(Mitchell & Martin, ١٩٩٩).***

Diffuse alveolar damage (DAD) is the histopathological hallmark of (ARDS) and a significant portion of ARDS survivors have residual pulmonary fibrosis and compromised pulmonary function ***(Medruri et al., ١٩٩٨).***

This suggests that the pathogenesis of DAD that ultimately leads to the chronic fibrosis of ARDS has features of dysgulated repair with intra-alveolar deposition of extracellular matrix and vascular remodeling, leading to progressive alveolar fibrosis and impaired lung function ***(Strieter et al., ١٩٩٥).***

Keane et al. (٢٠٠٢) hypothesized that the pathogenesis of DAD with pulmonary microvascular remodeling and alveolar fibrosis is due to dysregulated angiogenesis, mediated by the unique CXC chemokines family which is known for their abilities to behave in a disparate manner in the regulation of angiogenesis. Where angiogenesis is determined, by an imbalance in favor of the overexpression of angiogenic (ELR+), like Epithelial neutrophil-activating protein ٧٨ (ENA-٧٨/ CXCL٥) and down-regulation of angiostatic CXC chemokines like interferon-induced protein ١٠ (IP-١٠/ CXCL١٠) and Monokine induced by interferon gamma (MIG/ CXCL٩).

The extensive pharmacological and physiological evidence that ENA-٧٨ influences the acute respiratory distress syndrome was a stimulus to study the relation between its level in bronchoalveolar lavage fluid (BALF) and the severity as well as the outcome of acute respiratory distress syndrome (ARDS).

Review of Literature

Acute lung injury and acute respiratory distress syndrome

Definition:

Acute lung injury and its extreme manifestation, acute respiratory distress syndrome, complicate a wide variety of serious medical and surgical conditions, only some of which affect the lung directly. ***(Bernard et al., ١٩٩٤)***

The most recent definition of ARDS is that proposed by the ١٩٩٤ American–European Consensus Conference Committee (AECC) ***(Bernard et al., ١٩٩٤)***: a syndrome of acute onset, with bilateral infiltrates on chest radiography consistent with pulmonary edema, pulmonary-artery wedge pressure less than ١٨ mmHg or clinical absence of left atrial hypertension, and hypoxemia with a ratio of partial pressure of arterial oxygen to fraction of inspired oxygen ($PaO_٢/FIO_٢$) $\leq$ ٢٠٠. Patients meeting the above criteria but with $PaO_٢/FIO_٢$ ratio $\leq$ ٣٠٠ are diagnosed with acute lung injury (ALI).

Table (١): American European Consensus Conference Criteria for Acute Lung Injury (ALI) and the Acute Respiratory Distress Syndrome (ARDS) ***(Bernard et al., ١٩٩٤)***

Clinical Variable	Criteria for ALI	Criteria for ARDS
Onset	Acute	Acute
Hypoxemia	$Pao_{٢}$ /$FIo_{٢}$ ≤٣٠٠ mm Hg	$Pao_{٢}$ /$FIo_{٢}$ ≤٢٠٠ mm Hg
Chest radiograph	Bilateral infiltrates consistent with pulmonary edema	Bilateral infiltrates consistent with pulmonary edema
Non-cardiac cause	No clinical evidence of left atrial hypertension **or**, if measured; pulmonary artery occlusion pressure ≤١٨ mm Hg	No clinical evidence of left atrial hypertension **or**, if measured, pulmonary artery occlusion pressure ≤١٨ mm Hg

Incidence:

A recent study was done by ***Goss et al ;(٢٠٠٣)*** applied the AECC definition and found that the annual incidence of ALI in the United States is ٢٢–٦٤ per $١٠^{٥}$ persons ***(Angus et al., ٢٠٠١&Rubenfeld., ٢٠٠٣)***. It is estimated that the incidence of ARDS from severe sepsis alone approximates ٥٤ (range ٤٥–٦٣) per $١٠^{٥}$ per year in the United States. The recent European ALIVE study (Acute Lung Injury Verification of Epidemiology) found that ٧٪ of all intensive care unit (ICU) admissions and ١٦٪ of patients receiving mechanical ventilation for more than ٢٤ hours have ALI/ARDS ***(Brun-Buisson et al., ٢٠٠٤);*** while almost ٣٠٪ of patients initially presented with 'mild ALI' ($PaO_{٢}/FIO_{٢}$ ratio between ٢٠٠ and ٣٠٠),

almost two-thirds of these evolved to ARDS within ٣ days. These data are consistent with an Australian survey ***(Bersten et al., ٢٠٠٢)*** *showing* that ٨,٥٪ of ICU admissions meet criteria for ALI/ARDS, with a similar rate of progression from mild ALI to ARDS. A ٢٨-day international survey by Esteban and colleagues found that ٤,٥٪ of ICU patients requiring mechanical ventilation for more than ١٢ h and ٦,٥٪ of patients requiring mechanical ventilation for acute respiratory failure have ARDS ***(Esteban et al., ٢٠٠٢)***.

Precipitating factors:

ALI and ARDS can be considered to be a “final common pathway” reaction of the lung to a large variety of precipitating causes. Some authors have classified these causes as direct (pulmonary) or indirect (extra-pulmonary or systemic) injury to the lung. Not all patients with these precipitating conditions develop ALI/ARDS. ***(Gattinoni et al., ١٩٩٨)***