

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

A Thesis

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Contents

	Page
List of abbreviations	II
List of tables	IV
List of figures	V
Introduction and aim of the work	۱
Review of Literature	۳
• <i>Definition of ARDS</i>	۳
• <i>Incidence of ARDS</i>	۴
• <i>Precipitating and risk factors for ARDS</i>	۵
• <i>Pathology and pathogenesis of ARDS</i>	۸
• <i>Diagnosis of ARDS</i>	۲۳
• <i>Differential diagnosis of ALI and ARDS.</i>	۲۵
• <i>Radiological findings of ARDS</i>	۲۷
• <i>Therapeutic strategies for ARDS</i>	۳۲
° <i>Treatment of the inciting clinical disorders in patients with ARDS.</i>	۳۳
° <i>Ventilatory Strategies in ARDS</i>	۳۵
° <i>Fluid and Hemodynamic management</i>	۴۳
° <i>Surfactant therapy</i>	۴۳
° <i>Glucocorticoids and other anti inflammatory agents</i>	۴۴
° <i>Inhaled nitric oxide and other vasodilators</i>	۴۵
° <i>Outcome</i>	۴۶
• <i>Chemokine structure</i>	۵۰
• <i>Chemokine receptors</i>	۵۴
• <i>Role in leuckocyte movement</i>	۵۵
• <i>Role of chemokines in inflammatory disease</i>	۵۶
• <i>ARDS and CXC Chemokine</i>	۵۷
Patients and Methods	۶۴
Results	۷۵
Discussion	۹۷
Recommendations	۱۰۹
Summary & Conclusion	۱۱۰
References	۱۱۳
Arabic summary	۱۳۶

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- _{VA}	Epithelial neutrophil-activating protein _{VA}
FIO _y	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- γ	Interferon induced protein - γ
JVP	Jugular venous pressure
Leu	Leucine (L)
IgA	Immunoglobulin A
LPS	Lipopolysaccharide
MCP- γ	Monocyte chemo-attractant protein -1
MIF	Macrophage inhibitory factor
MIG	Monokine induced by gamma interferon
MOF	Multiple organ failure
MV	Mechanical ventilation
PaO $_r$	Partial pressure of oxygen
PCWP	Pulmonary capillary wedge pressure
PEEP	Positive end expiratory pressure
PMN	Polymorphonuclear lymphocytes
RV	Right ventricle
SaO $_r$	Saturation of oxygen
TLC	Total lung capacity
TNF	Tumor necrosis factor

List of Tables

Table		Page
Table ١	American European Consensus Conference Criteria for Acute Lung Injury (ALI) and the Acute Respiratory Distress Syndrome (ARDS).	٤
Table ٢	Examples of direct and indirect precipitating factors of acute lung injury (ALI) and the acute respiratory distress syndrome (ARDS).	٦
Table ٣	Differential Diagnosis of Acute Lung Injury (ALI) and Acute Respiratory Distress Syndrome (ARDS).	٢٥
Table ٤	Inciting Clinical Disorders Associated With ALI and ARDS.	٣٥
Table ٥	Protective lung ventilation protocol from the ARDS Network study.	٣٧
Table ٦	The CXC chemokines.	٥٢
Table ٧	The CC chemokines.	٥٣
Table ٨	The C and CX γ C chemokines.	٥٤
Table ٩	ELR ⁺ and ELR ⁻ CXC chemokines are angiogenic and angiostatic factors, respectively.	٥٩
Table ١٠	Gender distribution of the studied subjects.	٧٦
Table ١١	Age distribution of the studied subjects.	٧٦
Table ١٢	Diagnosis of the studied patients.	٧٧
Table ١٣	Diagnoses of the studied controls.	٧٨
Table ١٤	Clinical data among patients.	٧٨
Table ١٥	Clinical data among controls.	٧٨
Table ١٦	Comparison between patients and controls as regards the clinical data.	٧٩
Table ١٧	Comparison between patients and controls as regards the mean PRISM score.	٨٠
Table ١٨	Comparison between patients and controls as regards mortality rate.	٨١
Table ١٩	Comparison between patients and controls as	٨١

	regards the routine laboratory investigation.	
Table ٢٠	Comparison between patients and controls as regards the ventilatory settings.	٨٢
Table ٢١	Comparison between patients and controls as regards blood gases.	٨٣
Table ٢٢	Comparison between patients and controls as regards the mean ENA-٧٨ level in BAL.	٨٤
Table ٢٣	Comparison between survivors and non-survivors as regards the primary diagnosis.	٨٥
Table ٢٤	Comparison between non survivors and survivor patients as regards the clinical data.	٨٦
Table ٢٥	Comparison between non survivor and survivor patients as regards the mean PRISM score.	٨٦
Table ٢٦	Comparison between non survivor and survivor patients as regards the ALI score.	٨٧
Table ٢٧	Comparison between non survivors and survivors as regards hypoxic score.	٨٨
Table ٢٨	Comparison between non survivors and survivors as regards the routine laboratory data.	٨٩
Table ٢٩	Comparison between non survivors and survivors as regards the ventilatory settings.	٩٠
Table ٣٠	Comparison between non survivors and survivors as regards blood gases.	٩١
Table ٣١	Comparison between non survivors and survivor patients as regards the mean ENA-٧٨ level in BAL.	٩٢
Table ٣٢	ROC curve (Receiver-operator characteristic curve) for detection of the best cut off point of ENA-٧٨ for prediction of fate in ARDS patients.	٩٤
Table ٣٣	Stepwise regression analysis for the most important predictors of fate.	٩٦

List of Figures

Figure		Page
Figure ١	Lung autopsy specimen showing the exudative stage of acute respiratory distress syndrome.	١٠
Figure ٢	The Normal Alveolus and the Injured Alveolus in the Acute Phase of Acute Lung Injury and Acute Respiratory Distress Syndrome.	١١
Figure ٣	Lung biopsy specimen revealing overlapping of the fibroproliferative stage and the exudative stage.	١٣
Figure ٤	DAD, fibrotic stage. Microcystic honeycomb pattern follows ARDS of ٥٥ days duration.	١٤
Figure ٥	Mechanisms Important in the Resolution of Acute Lung Injury and the Acute Respiratory Distress Syndrome.	٢١
Figure ٦	Radiographic and Computed Tomographic (CT) Findings in the Acute, or Exudative Phase and the Fibrosing-Alveolitis Phase of Acute Lung Injury and Acute Respiratory Distress Syndrome.	٢٩
Figure ٧	Diagnoses of the studied patients.	٧٧
Figure ٨	Comparison between cases and controls as regards the mean PRISM score.	٨٠
Figure ٩	Comparison between cases and controls as regards the mean ENA-٧٨ in BALF.	٨٤
Figure ١٠	Comparison between survivors and non-survivors as regards the mean ALI score.	٨٧
Figure ١١	Comparison between survivors and non-survivors as regards the mean ENA-٧٨.	٩١
Figure ١٢	Correlation coefficient between ENA-٧٨ in BAL of ARDS patients and PRISM score.	٩٣
Figure ١٣	Correlation coefficient between ENA-٧٨ in BAL of ARDS patients and ALI score.	٩٣
Figure ١٤	Correlation coefficient between ENA-٧٨ in BAL of ARDS patients and hypoxic score.	٩٤
Figure ١٥	ROC curve of ENA-٧٨ in ARDS patients.	٩٥

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, 2000*).

The cellular and molecular basis for ARDS remains uncertain for 30 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, 1999*).

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., 1998*).

This suggests that the pathogenesis of DAD that ultimately leads to the chronic fibrosis of ARDS has features of dysregulated repair with intra-alveolar deposition of extracellular matrix and vascular remodeling, leading to progressive alveolar fibrosis and impaired lung function (*Strieter et al., 1990*).

Keane et al. (2002) 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 1 (ENA-1/ CXCL6) and down-regulation of angiostatic CXC chemokines like interferon-induced protein 10 (IP-10/ CXCL10) and Monokine induced by interferon gamma (MIG/ CXCL9).

The extensive pharmacological and physiological evidence that ENA-1 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., 1994*)

The most recent definition of ARDS is that proposed by the 1994 American–European Consensus Conference Committee (AECC) (*Bernard et al., 1994*): a syndrome of acute onset, with bilateral infiltrates on chest radiography consistent with pulmonary edema, pulmonary-artery wedge pressure less than 18 mmHg or clinical absence of left atrial hypertension, and hypoxemia with a ratio of partial pressure of arterial oxygen to fraction of inspired oxygen ($\text{PaO}_2/\text{FIO}_2$) ≤ 300 . Patients meeting the above criteria but with $\text{PaO}_2/\text{FIO}_2$ ratio ≤ 300 are diagnosed with acute lung injury (ALI).

Table (1): American European Consensus Conference Criteria for Acute Lung Injury (ALI) and the Acute Respiratory Distress Syndrome (ARDS) (*Bernard et al., 1994*)

Clinical Variable	Criteria for ALI	Criteria for ARDS
Onset	Acute	Acute
Hypoxemia	$P_{aO_2}/F_{IO_2} \leq 300$ mm Hg	$P_{aO_2}/F_{IO_2} \leq 200$ 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 ≤ 18 mm Hg	No clinical evidence of left atrial hypertension or , if measured, pulmonary artery occlusion pressure ≤ 18 mm Hg

Incidence:

A recent study was done by *Goss et al* ;(2007) applied the AECC definition and found that the annual incidence of ALI in the United States is 22-64 per 10⁵ persons (*Angus et al., 2001* & *Rubenfeld., 2007*). It is estimated that the incidence of ARDS from severe sepsis alone approximates 0.4 (range 0.1-1.3) per 10⁵ per year in the United States. The recent European ALIVE study (Acute Lung Injury Verification of Epidemiology) found that 4% of all intensive care unit (ICU) admissions and 16% of patients receiving mechanical ventilation for more than 48 hours have ALI/ARDS (*Brun-Buisson et al., 2004*); while almost 3% of patients initially presented with ‘mild ALI’ (P_{aO_2}/F_{IO_2} ratio between 200 and 300),

almost two-thirds of these evolved to ARDS within 7 days. These data are consistent with an Australian survey (*Bersten et al., 2002*) showing that 40% of ICU admissions meet criteria for ALI/ARDS, with a similar rate of progression from mild ALI to ARDS. A 28-day international survey by Esteban and colleagues found that 40% of ICU patients requiring mechanical ventilation for more than 12 h and 60% of patients requiring mechanical ventilation for acute respiratory failure have ARDS (*Esteban et al., 2002*).

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., 1994*)