Although acute lung injury (ALI) and acute respiratory distress syndrome (ARDS) are caused by different injuries and conditions, their similar clinical picture makes a compelling case for them to be studied as a single entity. An array of potential specific targets for pharmacologic intervention can be applied to ALI/ARDS as one disease. Although a working definition of ALI/ARDS that includes pulmonary and extrapulmonary causes can have benefit in standardizing supportive care, it can also complicate assessments of the efficacy of therapeutic interventions. In this article, definitions that have been recently used for ALI/ARDS in various clinical studies are discussed individually.

Acute respiratory distress syndrome (ARDS) and acute lung injury (ALI) are distinctly modern clinical entities. Recent epidemiologic research has taken advantage of large cohorts in efforts to better describe these highly lethal syndromes with a focus on differentiation of clinically meaningful subtypes and early prediction in an effort to improve treatment and prevention. This article identifies the most significant studies and systematic reviews of recent years, defining the incidence, mortality, risk and prognostic factors, and etiologic classes of ARDS/ALI.

To hasten the development of effective therapy for acute respiratory distress syndrome (ARDS), in 1994, the National Heart, Lung, and Blood Institute initiated a clinical network to carry out multicenter clinical trials of ARDS treatments. The ARDS Network is a clinical research network of approximately 42 hospitals, organized into 12 clinical sites. The goal of the Network is to efficiently test promising agents, devices, or management strategies to improve the care of patients with ARDS. Comprehensive information regarding all completed and ongoing ARDSNet clinical trials is available at www.ardsnet.org, but a brief summary is provided in this article.

Essentially all patients with acute lung injury or acute respiratory distress syndrome require mechanical ventilatory assistance to support gas exchange and reduce the work of breathing associated with the lung impairment. Unfortunately, this life-sustaining support may actually cause further...
lung damage and possibly lead to increased mortality. This article reviews strategies that may help minimize ventilator-induced lung injury.

High-Frequency Oscillatory Ventilation in ALI/ARDS 487
Sammy Ali and Niall D. Ferguson

In the last 2 decades, our goals for mechanical ventilatory support in patients with acute respiratory distress syndrome (ARDS) or acute lung injury (ALI) have changed dramatically. Several randomized controlled trials have built on a substantial body of preclinical work to demonstrate that the way in which we employ mechanical ventilation has an impact on important patient outcomes. Avoiding ventilator-induced lung injury (VILI) is now a major focus when clinicians are considering which ventilatory strategy to employ in patients with ALI/ARDS. Physicians are searching for methods that may further limit VILI, while still achieving adequate gas exchange.

Airway Pressure Release Ventilation in Acute Respiratory Distress Syndrome 501
Adrian A. Maung and Lewis J. Kaplan

Airway pressure release ventilation (APRV) is an alternative mode of ventilation that is increasingly used in patients with acute respiratory failure, acute lung injury (ALI), and acute respiratory distress syndrome (ARDS). Animal and clinical studies have demonstrated that, compared with conventional ventilation, APRV has beneficial effects on lung recruitment, oxygenation, end-organ blood flow, pulmonary vasoconstriction, and sedation requirements. Further studies, however, are required to directly compare APRV to ARDSnet protocol ventilation, specifically in patients with ALI/ARDS, and to determine whether managing ALI/ARDS with APRV will also achieve mortality reduction.

Prone-Positioning Therapy in ARDS 511
Sharon Dickinson, Pauline K. Park, and Lena M. Napolitano

The prone position has been used to improve oxygenation in patients with severe hypoxemia and acute respiratory failure since 1974. All studies with the prone position document an improvement in systemic oxygenation in 70% to 80% of patients with acute respiratory distress syndrome (ARDS), with maximal improvement seen in the most hypoxemic patients. This article reviews data regarding efficacy for use of the prone position in patients with ARDS. Also described is a simple, safe, quick, and inexpensive procedure used to prone patients with severe ARDS on a standard bed in the intensive care unit at the University of Michigan.

Surfactant Therapy for Acute Lung Injury and Acute Respiratory Distress Syndrome 525
Krishnan Raghavendran, D. Willson, and R.H. Notter

This article examines exogenous lung surfactant replacement therapy and its usefulness in mitigating clinical acute lung injury (ALI) and the acute respiratory distress syndrome (ARDS). Surfactant therapy is beneficial in term infants with pneumonia and meconium aspiration lung injury, and in children up to age 21 years with direct pulmonary forms of ALI/ARDS. However, extension of exogenous surfactant therapy to adults with respiratory failure and clinical ALI/ARDS remains a challenge. This article
reviews clinical studies of surfactant therapy in pediatric and adult patients with ALI/ARDS, focusing on its potential advantages in patients with direct pulmonary forms of these syndromes.

Inhaled Nitric Oxide and Inhaled Prostacyclin in Acute Respiratory Distress Syndrome: What is the Evidence? 561

Nitin Puri and Richard Phillip Dellinger

The mortality for acute respiratory distress syndrome remains unacceptably high. Two vasodilators, inhaled prostacyclin and inhaled nitric oxide, are reviewed in this article. Knowledge of inhaled prostacyclin has grown substantially in the past 30 years, but less research exists about its utility in acute respiratory distress syndrome. Inhaled prostacyclin and other prostaglandin derivatives are used in acute respiratory distress syndrome with increasing frequency. Currently, only randomized controlled trials exist for inhaled nitric oxide in acute respiratory distress syndrome patients. Randomized controlled trials with consistent dosing methods are needed for both vasodilators to better define their role in the treatment of acute respiratory distress syndrome.

Glucocorticoid Treatment in Acute Lung Injury and Acute Respiratory Distress Syndrome 589

Paul E. Marik, G. Umberto Meduri, Patricia R.M. Rocco, and Djillali Annane

Experimental and clinical evidence show a strong association between dysregulated systemic inflammation and progression of acute respiratory distress syndrome (ARDS). This article reviews eight controlled studies evaluating corticosteroid treatment initiated before day 14 of ARDS. Available data provide a consistent strong level of evidence for improving outcomes. Treatment was also associated with a markedly reduced risk of death. This low-cost highly effective therapy is well-known, and has a low-risk profile when secondary prevention measures are implemented. The authors recommend prolonged methylprednisolone at 1 mg/kg/d initially in early ARDS, increasing to 2 mg/kg/d after 7 to 9 days of no improvement.

Extracorporeal CO₂ Removal in ARDS 609

James E. Lynch, Don Hayes Jr, and Joseph B. Zwischenberger

Acute respiratory distress syndrome remains one of the most clinically vexing problems in critical care. As technology continues to evolve, it is likely that extracorporeal CO₂ removal devices will become smaller, more efficient, and safer. As the risk of extracorporeal support decreases, devices’ role in acute respiratory distress syndrome patients remains to be defined. This article discusses the functional properties and management techniques of CO₂ removal and intracorporeal membrane oxygenation and provides a glimpse into the future of long-term gas-exchange devices.

Extracorporeal Membrane Oxygenation in Adult Acute Respiratory Distress Syndrome 627

Pauline K. Park, Lena M. Napolitano, and Robert H. Bartlett

The role of extracorporeal membrane oxygenation (ECMO) in supporting adult refractory respiratory failure continues to evolve. Technical advances and the clinical challenges of H1N1 associated severe ARDS have spurred
a resurgence of interest in ECMO. Published systematic review and pooled analyses point out the limitations of available studies, however, a growing body of evidence suggest potential for benefit. Referral to a specialized center with ECMO experience should be considered early after the initiation of high-level ventilator support in adult patients with severe ARDS.

**Nutrition Therapy for ALI and ARDS**

Anna Krzak, Melissa Pleva, and Lena M. Napolitano

The importance of nutrition support in critically ill patients with acute lung injury (ALI) and acute respiratory distress syndrome (ARDS) cannot be overstated. ALI and ARDS are characterized by a proinflammatory response associated with hypercatabolism that could lead to significant nutrition deficits. Nutrition support is necessary to prevent cumulative caloric deficits, malnutrition, loss of lean body mass, and deterioration of respiratory muscle strength. Furthermore, early delivery of enteral nutrition has been associated with the modulation of stress and the systemic immune response as well as the attenuation of disease severity.

**Biomarkers in Acute Lung Injury Marking Forward Progress**

Nicolas Barnett and Lorraine B. Ware

This article reviews the state of the art regarding biomarkers for prediction, diagnosis, and prognosis in acute lung injury. Biomarkers and the goals of biomarker research are defined. Progress along 4 general routes is examined. First, the results of wide-ranging existing protein biomarkers are reported. Second, newer biomarkers awaiting or with strong potential for validation are described. Third, progress in the fields of genomics and proteomics is reported. Finally, given the complexity and number of potential biomarkers, the results of combining clinical predictors with protein and other biomarkers to produce better prognostic and diagnostic indices are examined.

**Recovery and Long-Term Outcome in Acute Respiratory Distress Syndrome**

Margaret S. Herridge

Interest in longer-term outcomes after acute respiratory distress syndrome (ARDS) and the understanding of patterns of recovery have increased enormously over the past 10 years. This article highlights important advances in outcomes after ARDS and describes pulmonary outcomes, the most recent data on functional and neuropsychological disability in patients, health care cost, family caregivers, and early models of rehabilitation and intervention.

**Gene Therapy for ALI/ARDS**

Xin Lin and David A. Dean

Acute lung injury (ALI) and acute respiratory distress syndrome (ARDS) are characterized by acute respiratory failure and are associated with diverse disorders. Gene therapy is a potentially powerful approach to treat diseases related to ALI/ARDS, and numerous viral and nonviral methods for gene delivery to the lung have been developed. Discussed are recent advances in the development of more efficient viral and nonviral gene transfer...
systems, and the current status of gene therapy applied to ALI/ARDS-associated pulmonary diseases is reviewed. With the development of more efficient gene therapy vectors, gene therapy is a promising strategy for clinical application.

Mesenchymal Stem Cells and Acute Lung Injury
Jeffrey E. Gotts and Michael A. Matthay
Acute respiratory distress syndrome (ARDS) is a clinical syndrome of acute respiratory failure presenting with hypoxemia and bilateral pulmonary infiltrates, most often in the setting of pneumonia, sepsis, or major trauma. The pathogenesis of ARDS involves lung endothelial injury, alveolar epithelial injury, and the accumulation of protein-rich fluid and cellular debris in the alveolar space. No pharmacologic therapy has so far proved effective. A potential strategy involves cell-based therapies, including mesenchymal stem cells (MSCs). Herein we review basic properties of MSCs, their use in preclinical models of lung injury and ARDS, and potential therapeutic mechanisms.

Experimental Models and Emerging Hypotheses for Acute Lung Injury
Thomas R. Martin and Gustavo Matute-Bello
Acute lung injury (ALI) involves the activation of multiple pathways leading to lung injury, resolution, and repair. Exploration of the roles of individual pathways in humans and animal models has led to a greater understanding of the complexity of ALI and the links between ALI and systemic multiorgan failure. However, there is still no integrated understanding of the initiation, the progression, and the repair of ALI. A better understanding is needed of how pathways interact in the human ALI syndrome and how complementary treatments can be used to modify the onset, severity, and outcome of ALI in humans.

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Preface

ALI and ARDS: Challenges and Advances

Krishnan Raghavendran, MD
Lena M. Napolitano, MD

Guest Editors

Acute lung injury (ALI) and acute respiratory distress syndrome (ARDS) are life-threatening diseases, and patients with ALI/ARDS require extensive critical care support for treatment of acute respiratory failure with hypoxemia and hypercarbia, and support of other failing organs. This issue of Critical Care Clinics is aimed at providing an overview of the significant advances that have been made in the last decade in the understanding and treatment of this disease, and the persistent challenges that still remain.

Since the initial description of ARDS more than 40 years ago by Ashbaugh and colleagues in 1967, much has changed. Epidemiologic data confirm that there has been a significant decline in the incidence of ALI/ARDS over the past decade, related to both direct pulmonary and indirect extrapulmonary causes. Despite this reduced incidence, mortality rates in ARDS are high, at approximately 40%. Severe ARDS due to the 2009 Influenza A (H1N1) virus occurred in young adults and was associated with severe hypoxemia and high mortality rates, and epidemiologic data from this pandemic are still emerging. Our enhanced knowledge of ARDS has uncovered important limitations to the current ARDS definitions that are being used in clinical trials, and we critically evaluate the current ARDS criteria and discuss whether a new ARDS definition should be considered.

The development of the ARDS Network was a groundbreaking advance with the completion of many multicenter clinical trials of ARDS treatments that have now refined our standard therapy for ARDS. The present therapeutic approaches for ALI/ARDS include: (1) identification and treatment of the underlying cause; (2) optimal fluid management–fluid conservative approach; (3) lung protective mechanical ventilation [lower tidal volume, optimal positive end-expiratory pressure (PEEP)]; (4) avoidance of secondary lung injury and infection; and (5) supportive critical care. Despite provision of these standard treatments, some ALI/ARDS patients progress to develop severe hypoxemia, requiring additional “rescue” therapies.
Key topics reviewed in this issue include innovative treatment strategies for ARDS including high-frequency oscillatory ventilation (HFOV), airway pressure release ventilation (APRV), extracorporeal membrane oxygenation (ECMO), and extracorporeal carbon dioxide removal (ECCO₂R). Potential pharmacologic treatment strategies for ARDS include surfactant therapy, inhaled nitric oxide, prostacyclin, and corticosteroid therapy, and comprehensive reviews of the evidence supporting these treatments are provided. Prone positioning therapy and specialized nutrition support are also discussed fully as adjunct treatments in ALI/ARDS.

Recent data regarding long-term follow-up of ARDS survivors revealed sustained lung recovery with near-normal lung function, but persistent physical functional limitations, advocating for early mobility in ALI/ARDS patients during their intensive care unit stay. Significant progress has been made in the field of biomarkers for prediction, diagnosis, and prognosis in ALI/ARDS. The development and refinement of experimental models for ALI/ARDS will continue to move research forward in this important area. The current state of research in two exciting areas—the potential for gene therapy as an effective treatment for ALI/ARDS and possible cell-based therapy with mesenchymal stem cells—are both reviewed.

We would like to thank the authors for their generous contributions of both their time and their expertise in the preparation of this issue. We would also like to acknowledge Dr Richard Carlson and the Elsevier editorial staff for their tireless support and assistance in bringing this issue to completion.

We hope that this issue of Critical Care Clinics provides an up-to-date resource for critical care practitioners regarding the optimal management of patients with ALI/ARDS and also reviews the current areas of active investigation in this life-threatening disease.

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Definition of ALI/ARDS

Krishnan Raghavendran, MD*, Lena M. Napolitano, MD

The description of acute respiratory distress syndrome (ARDS) as a distinct entity was first reported by Ashbaugh and colleagues\(^1\) in 1967, defined as a clinical pattern including “severe dyspnea, tachypnea, cyanosis that is refractory to oxygen therapy, loss of lung compliance, and diffuse alveolar infiltration seen on chest x-ray.” In their initial report of 12 patients, 7 patients died, and the autopsy finding confirmed striking findings on lung microscopy including the presence of hyaline membranes, diffuse interstitial inflammation, and interstitial and intra-alveolar edema and hemorrhage. Since the initial description of ARDS more than 40 years ago, the optimal definition of acute lung injury (ALI)/ARDS remains a controversial subject.

ALI and ARDS are characterized by rapid-onset respiratory failure following a variety of direct and indirect insults to the parenchyma or vasculature of the lungs. The pulmonary pathology of ALI/ARDS can be divided conceptually into acute and fibroproliferative phases that have distinctive features but vary in detail depending on the cause of injury. Mortality from ALI/ARDS is substantial, and current therapy primarily emphasizes lung-protective mechanical ventilation and a restrictive fluid management strategy plus standard treatment of the initiating insult or underlying disease.

Although ALI/ARDS are “syndromes” caused by different injuries and conditions, the pathobiology of the lung injury and similar clinical picture makes a compelling case for us to study them as a single entity rather than characterize the individual risk factors as separate clinical entities. More importantly, an array of potential specific targets for pharmacologic intervention can be applied to ALI/ARDS as one disease entity.

Clinical presentations consistent with ALI and ARDS can arise in patients of all ages from direct (pulmonary) or indirect (extrapulmonary) insults that induce pulmonary inflammation, damage the cells of the alveolar-capillary membrane, and lead to severe acute respiratory failure. Uniform diagnostic criteria are essential for meaningful clinical studies and therapeutic development for ALI/ARDS. The clinical entities of ALI and

KEYWORDS

- Acute respiratory distress syndrome
- Acute lung injury
- Respiratory failure
- Terminology

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ARDS are syndromes defined by a relatively limited set of descriptive pathophysiological clinical findings, and patients are included regardless of the specific etiology of acute pulmonary dysfunction.

Although a working definition of ALI/ARDS that includes both pulmonary and extrapulmonary causes can have benefit in standardizing supportive intensive care, it can also complicate assessments of the efficacy of therapeutic interventions. For example, the lack of stratification of patients with ALI/ARDS by etiology has the potential to confound data interpretation in therapeutic trials, because interventions that might benefit one cause of ALI/ARDS may have no benefit or may even be harmful in treating another cause.

In this article, the definitions that have been recently used for ALI/ARDS in various clinical studies are discussed individually.

**IMPORTANCE OF DEFINING ALI/ARDS**

A precise definition of ARDS is necessary to facilitate research into the pathogenesis and standardize treatment modalities. There is broad recognition that ALI/ARDS has many predisposing risk factors, and the definition merely represents a functional indicator of the severity of the lung injury. Should we be studying individual risk factors/disease that led to this syndrome, such as aspiration-induced lung injury, lung contusion, transfusion-related acute lung injury (TRALI), or lung injury secondary to sepsis? There exist major differences in the pathogenesis of these individual insults, especially when studied in animal model systems. However, there are major advantages of defining a syndrome like ALI/ARDS.

A standardized universal definition for ALI/ARDS has many benefits. Most importantly, it would allow comparison of the findings of various clinical trials in ALI/ARDS with a greater degree of certainty. For the clinician, a functional definition of ALI/ARDS allows early institution of standardized clinical care, that is, certain therapeutic modalities that have been tested and proved to have benefits. For instance, early identification of patients with ALI/ARDS allows the early application of protective lung ventilation with lower tidal volumes based on predicted body weights.

In addition, a standardized definition including ALI and ARDS can assist with outcome prognostication, and is of help especially while discussing the care of the patient with families. For the researcher, it helps to capture a larger patient population for potential recruitment into large clinical studies, as proved by multiple clinical trials conducted under the auspices of the ARDS Network. Moreover, it offers a common language of communication between the basic and clinical researcher whereby therapeutic modalities can be constantly tested in the laboratory and brought to the clinical arena.

Moreover, for the public and health care administrators, the many epidemiologic studies reporting on the incidence and outcomes of ALI/ARDS in specific countries and populations helps determine the amount of ever shrinking health care dollars that can be ascribed to this disease and its societal impact. Finally, it has to be understood that while combining both ALI and ARDS as one entity offers advantages, the results of the clinical studies with testing of therapeutic modalities have to be carefully interpreted, as many specific discrete disease entities have been examined as one.

**DEFINITIONS OF ALI/ARDS**

*The American-European Consensus Conference Definition*

The American-European Consensus Conference (AECC) on ARDS in 1994 defined ALI as respiratory failure of acute onset with a PaO$_2$/FiO$_2$ ratio of less than 300 mm Hg (regardless of the level of positive end-expiratory pressure, PEEP), bilateral infiltrates
on frontal chest radiograph, and a pulmonary capillary wedge pressure of 18 mm Hg or less (if measured) or no evidence of left atrial hypertension. ARDS was defined identically except for a lower limiting value of less than 200 mm Hg for PaO$_2$/FiO$_2$ (Box 1). The AECC definition of ALI/ARDS is in common use and is simple to apply, but also has serious deficiencies in discrimination. There is often not a good correlation between these broad clinical definitions and diffuse alveolar damage (DAD), which is widely considered to be a major characteristic histologic feature of ALI/ARDS. The AECC definitions also do not take into consideration variables such as the mode of ventilation and the level of PEEP, which can significantly influence oxygenation. In addition, with the publication of studies that have shown that routine use of Swan-Ganz catheters can be associated with higher complications, the pulmonary capillary occlusive pressure (PCOP) component of the definition is not commonly measured, thus placing significant emphasis on chest radiograph interpretation whereby there is a significant lack of interobserver reliability. However, the AECC definition, particularly with the ARDS component, has proven predictability. For instance, patients with ARDS as per this definition have higher mortality than patients without.

The AECC definition of ALI/ARDS has been used in all of the ARDS Network clinical trials (www.ardsnet.org). The important question to consider is: does the ARMA ARDS Network trial (lower [6 mL/kg] vs traditional [12 mL/kg] tidal volumes) with its finding of improved survival (31% vs 39% mortality) for lower tidal volumes using this ALI/ARDS definition lend increased credibility to this definition?

Murray Lung Injury Score

In 1988, Murray and colleagues proposed an expanded definition of ARDS, taking into account various pathophysiological features of the clinical syndrome. The Murray scoring system includes 4 criteria for the development of ALI/ARDS: a “scoring” of hypoxemia, a “scoring” of respiratory system compliance, chest radiographic findings, and level of PEEP. Each criterion receives a score from 0 to 4 according to the severity of the condition. The final score is obtained by dividing the collective score by the number of components used. A score of zero indicates no lung injury, a score of 1 to 2.5 indicates mild to moderate lung injury, and a final score of more than 2.5 indicates the presence of ARDS (Table 1).

The AECC definition of ALI/ARDS is frequently supplemented by lung injury or critical care scores such as the Murray score. The major advantage of this scoring system is that it takes into consideration the amount of PEEP and pulmonary

<table>
<thead>
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<th>Box 1</th>
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<tbody>
<tr>
<td><strong>The AECC definition of ALI and ARDS developed in 1994</strong></td>
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<tr>
<td><strong>ALI Criteria</strong></td>
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<tr>
<td>Timing: Acute onset</td>
</tr>
<tr>
<td>Oxygenation: PaO$_2$/FiO$_2$ ≤300 mm Hg (regardless of PEEP level)</td>
</tr>
<tr>
<td>Chest radiograph: Bilateral infiltrates seen on frontal chest radiograph</td>
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<tr>
<td>Pulmonary artery wedge: ≤18 mm Hg when measured or no clinical evidence of left atrial hypertension</td>
</tr>
<tr>
<td><strong>ARDS Criteria</strong></td>
</tr>
<tr>
<td>Same as ALI except:</td>
</tr>
<tr>
<td>Oxygenation: PaO$_2$/FiO$_2$ ≤200 mm Hg (regardless of PEEP level)</td>
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</table>
compliance, a sensitive indicator of lung injury. Recent studies such as the CESAR trial\textsuperscript{15} (conventional ventilator support vs extracorporeal membrane oxygenation for severe ARDS) incorporated this scoring system as entry criteria for the study, and only patients with a lung injury score greater than 3 were considered for the trial. The main disadvantage of the Murray score, especially in the conducting of large clinical studies, is that pulmonary compliance is not routinely measured. A significant deficiency of the Murray score is that cardiogenic pulmonary edema is not excluded.

### Delphi Consensus Panel Definition

An alternative definition of ARDS by a consensus panel of senior investigators using the Delphi method includes PEEP restrictions (\( \geq 10 \)) in defining hypoxemia (partial pressure of arterial oxygen/fraction of inspired oxygen, ie, \( \text{PaO}_2/\text{FiO}_2 \) [P/F] ratio of \(<200\)) radiographic criteria for air space disease in 2 or more quadrants, and requires either quantitative pulmonary compliance abnormalities (static compliance of \(<50\) cm H\(_2\)O pressure with tidal volume of 8 mL/kg) or the presence of a predisposing condition (direct/indirect cause of lung injury).\textsuperscript{16} In addition, the panel emphasized

### Table 1

<table>
<thead>
<tr>
<th>The Murray Lung Injury Score</th>
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<tbody>
<tr>
<td>1. Chest roentgenogram score</td>
</tr>
<tr>
<td>No alveolar consolidation</td>
</tr>
<tr>
<td>Alveolar consolidation confined to 1 quadrant</td>
</tr>
<tr>
<td>Alveolar consolidation confined to 2 quadrants</td>
</tr>
<tr>
<td>Alveolar consolidation confined to 3 quadrants</td>
</tr>
<tr>
<td>Alveolar consolidation in all 4 quadrants</td>
</tr>
<tr>
<td>2. Hypoxemia score</td>
</tr>
<tr>
<td>( \text{PaO}_2/\text{FiO}_2 ) &gt;300</td>
</tr>
<tr>
<td>( \text{PaO}_2/\text{FiO}_2 ) 225–299</td>
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<tr>
<td>( \text{PaO}_2/\text{FiO}_2 ) 175–224</td>
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<tr>
<td>( \text{PaO}_2/\text{FiO}_2 ) 100–174</td>
</tr>
<tr>
<td>( \text{PaO}_2/\text{FiO}_2 ) &lt;100</td>
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<tr>
<td>3. PEEP score (when ventilated) (cm H(_2)O)</td>
</tr>
<tr>
<td>PEEP (&lt;5)</td>
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<tr>
<td>PEEP 6–8</td>
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<tr>
<td>PEEP 9–11</td>
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<tr>
<td>PEEP 12–14</td>
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<tr>
<td>PEEP &gt;15</td>
</tr>
<tr>
<td>4. Respiratory system compliance score (when available) (mL/cm H(_2)O)</td>
</tr>
<tr>
<td>Compliance (&lt;80)</td>
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<tr>
<td>Compliance 60–79</td>
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<tr>
<td>Compliance 40–59</td>
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<tr>
<td>Compliance 20–39</td>
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<tr>
<td>Compliance &lt;19</td>
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</tbody>
</table>

The final score is calculated by the addition of the component parts.

**Abbreviations:** Score 0, no lung injury; score 1–2.5, mild to moderate lung injury; score \( >2.5 \), severe lung injury.

the noncardiogenic origin of the pulmonary dysfunction by either pulmonary artery catheter or cardiac echocardiography evaluation. The investigators acknowledged that signs of left atrial hypertension can coexist in patients with ARDS. However, the same investigators reported that although the Delphi definition is more specific than the AECC criteria, it is less sensitive when autopsy findings of DAD were chosen as the gold standard for the diagnosis of ARDS.17

**Oxygenation Index and P/F Ratio**

Oxygenation Index\(^{18}\) (OI) is the system most widely used to quantify the degree of lung injury and hypoxemia in pediatric critical care. OI specifically takes into account mean airway pressure (MAP), an important determinant of oxygenation. OI is defined as the product of MAP \(\times \frac{\text{FiO}_2 \times 100}{\text{PaO}_2}\). OI has been associated with outcome in both adults and children with ALI/ARDS. The original study in 2005 reported on the ability of OI to predict the duration of mechanical ventilation but not survival.\(^{18}\) Since then many adult studies have examined the efficacy of OI as a predictor of both duration of mechanical ventilation and mortality.\(^{19–21}\) In comparison, measurement of P/F ratio as a predictor of mortality in ALI/ARDS is uncertain. Although there are few differences in outcome based on P/F ratio early in the course of ARDS, it is likely that persistently lower P/F ratios are associated with higher mortality.\(^{22}\) A summary of the pros and cons of the definitions is listed in Table 2.

**ACCURACY OF CURRENT ALI/ARDS DEFINITIONS**

The diagnostic accuracy of the ALI/ARDS definitions currently in use has been critically examined. A comparison of the AECC definition with autopsy findings of DAD in a series of 382 patients found the sensitivity (75%) and specificity (84%) to be only moderate.\(^{12}\)

<table>
<thead>
<tr>
<th>Definition</th>
<th>Pros</th>
<th>Cons</th>
</tr>
</thead>
<tbody>
<tr>
<td>AECC(^8)</td>
<td>Simple and easy to use</td>
<td>Acute onset: not defined</td>
</tr>
<tr>
<td></td>
<td>Differentiates ALI and ARDS</td>
<td>PAOP often not measured</td>
</tr>
<tr>
<td></td>
<td>Prognostic capability based on ARMA study?</td>
<td>PEEP/Compliance/MAP not taken into consideration</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Risk factors not emphasized</td>
</tr>
<tr>
<td>Murray score(^{14})</td>
<td>Takes PEEP/Compliance into consideration</td>
<td>Does not include MAP</td>
</tr>
<tr>
<td></td>
<td>Differentiates mild to moderate from severe lung injury</td>
<td>Does not exclude heart failure</td>
</tr>
<tr>
<td></td>
<td>Radiologic criteria more specific</td>
<td>Does not identify individual risk factors</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Prognostic ability not validated</td>
</tr>
<tr>
<td>Delphi(^{16})</td>
<td>Defines criteria for onset(&lt;72 h)</td>
<td>Excludes P/F &gt;200 and &lt;300</td>
</tr>
<tr>
<td></td>
<td>Risk factor emphasized</td>
<td>Does not include compliance or MAP</td>
</tr>
<tr>
<td></td>
<td>Takes PEEP into consideration</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Objectively rules out heart failure</td>
<td></td>
</tr>
<tr>
<td>Oxygenation Index(^{18})</td>
<td>Takes MAP into consideration</td>
<td>Does not take PEEP and compliance in consideration</td>
</tr>
<tr>
<td></td>
<td>Prognostic ability validated</td>
<td>Does not exclude heart failure</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Does not evaluate radiologic signs</td>
</tr>
</tbody>
</table>

**Abbreviations:** AECC, American European Consensus Conference; MAP, mean airway pressure; PAOP, pulmonary artery occlusion pressure; PEEP, positive end expiratory pressure; P/F, Partial pressure of arterial oxygen/Fraction of inspired oxygen.
Of interest, the AECC definition was more accurate for patients with extrapulmonary risk factors than for patients with pulmonary risk factors. The AECC definition has performed poorly in limited reliability testing. Furthermore, there is only moderate agreement between the AECC and the Murray Lung Injury Score (LIS) definitions.

A study of 183 intensive care unit (ICU) patients who underwent autopsy after being mechanically ventilated compared the diagnostic accuracy of 3 clinical ARDS definitions (AECC, Murray LIS, and Delphi). Sensitivity and specificity were as follows: AECC

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>PaO₂/FiO₂ ratio (mm Hg)</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meade et al, 2008</td>
<td>983</td>
<td>41 106 106 &gt;106 142 &gt;142 180 &gt;180 250</td>
<td>Lung Open Ventilation Control</td>
</tr>
<tr>
<td></td>
<td></td>
<td>57 (50%) 77 (58%) 46 (39%) 55 (43%) 43 (33%) 40 (33%) 27 (25%) 33 (26%)</td>
<td></td>
</tr>
<tr>
<td>Villar et al, 2011</td>
<td>220</td>
<td>&lt;112 112 142 &gt;142</td>
<td>Hospital Mortality</td>
</tr>
<tr>
<td></td>
<td></td>
<td>47% 30% 23%</td>
<td></td>
</tr>
<tr>
<td>Cooke et al, 2008</td>
<td>1113</td>
<td>≤100 ≤100 + shock ≤100 + oliguric renal failure</td>
<td>Hospital Mortality</td>
</tr>
<tr>
<td></td>
<td></td>
<td>50% 58% 71%</td>
<td></td>
</tr>
<tr>
<td>Villar et al, 2007</td>
<td>170</td>
<td>&lt;112 112 142 &gt;142</td>
<td>ICU Mortality Hospital Mortality</td>
</tr>
<tr>
<td></td>
<td></td>
<td>45 (45.5%) 11 (20%) 1 (6.3%) 45 (45.5%) 11 (20%) 2 (12.6%)</td>
<td></td>
</tr>
<tr>
<td>Rubenfeld et al, 2005</td>
<td>1113</td>
<td>&lt;200 (ARDS) 200 300 (ALI) ALI progressed to ARDS on day 3 or day 7 ALI: no progression to ARDS on day 3 or day 7</td>
<td>ICU Mortality Hospital Mortality</td>
</tr>
<tr>
<td></td>
<td></td>
<td>41.1% 38.5% 41.0% 28.6%</td>
<td></td>
</tr>
<tr>
<td>Brun Buisson et al, 2004</td>
<td>463</td>
<td>&lt;200 (ARDS) 200 300 (ALI)</td>
<td>ICU Mortality Hospital Mortality</td>
</tr>
<tr>
<td>ALIVE study</td>
<td></td>
<td>49.4% 22.6% 57.9% 32.7%</td>
<td></td>
</tr>
<tr>
<td>Esteban et al, 2002</td>
<td>120</td>
<td>&lt;100 100 149 150 199 200 300 &gt;300</td>
<td>ICU Mortality</td>
</tr>
<tr>
<td></td>
<td></td>
<td>83% 47% 31% 25% 24%</td>
<td></td>
</tr>
<tr>
<td>Taccone et al, 2009</td>
<td>342</td>
<td>&lt;100 (severe ARDS) 100 200 (ARDS)</td>
<td>ICU Mortality Hospital Mortality</td>
</tr>
<tr>
<td>Prone Supine II</td>
<td></td>
<td>42.0% 24.0% 50.7% 31.8%</td>
<td></td>
</tr>
</tbody>
</table>
Specificity was significantly higher for both the Murray LIS and the Delphi definition than for the AECC definition, but sensitivity was not significantly different. It should be noted that none of the data for the Murray LIS require subjective interpretation, whereas this is not true for the other ARDS definitions.

**IS THE SEVERITY OF HYPOXEMIA IMPORTANT?**

The traditional thinking with ARDS is that it is the multiorgan dysfunction and not hypoxemia that is responsible for mortality. This assumption was based on several ARDS network trials in which hypoxia was well tolerated (up to saturations of 88%) and improvements in oxygenation did not translate into a survival advantage. A detailed discussion of such studies is provided in the chapter by Thompson and Bernard elsewhere in this issue.

It must be pointed out that some studies after the adoption of lung-protective strategies have suggested a strong correlation between the severity of hypoxemia and ICU or hospital mortality. In light of this, it is recommended that in future clinical trials of ARDS, severity of hypoxemia should be considered on patient enrollment into the study, and that outcomes should be assessed based on severity of hypoxemia.

What could be the reasons for these observations? One can speculate on the following possibilities. In patients with severe hypoxia, there is perhaps increased incidence of hyperoxia-induced lung injury from increased requirements of FiO₂ to maintain saturations of 88%. Hyperoxia has been implicated as a factor responsible for increased lung injury in many animal models by the generation of reactive oxygen species, increased apoptosis, and necrosis.

Second, it is important to consider the pathophysiologic disturbances linking ARDS with multiorgan dysfunction. Is the multiorgan dysfunction as a result of ALI/ARDS or is the ALI/ARDS a result of multiorgan dysfunction? Are these two separate entities? These questions need to be fully explored in additional studies through basic and clinical research.

**IS IT TIME TO CHANGE THE DEFINITION OF ALI/ARDS?**

Over the past few years many different study groups have raised doubts about the validity of the current ALI/ARDS definitions and have recommended a change. The authors believe strongly that it is time to change the definition after 17 years of the predominant use of the AECC definition for ALI/ARDS. Based on available data with various validity studies, it is suggested that the new definition should be standardized as follows. (a) Risk factors: direct (pulmonary) or indirect (extrapulmonary), as most experimental data suggest that these two entities have distinct pathogenic mechanisms. (b) Calculation of P/F ratios with specific and standard ventilator settings (PEEP and MAP). (c) Exclude heart failure objectively (use of echocardiogram). (d) Only include patients with P/F ratio with standard ventilator settings of less than 200.

**REFERENCES**


