EXPLORING THE BERLIN DEFINITION OF ARDS

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Acute Respiratory Distress Syndrome: The Berlin Definition

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The ARDS Definition Task Force

A novel approach to defining acute respiratory distress syndrome (ARDS) was developed in 1994 by the American-European Consensus Conference (AECC). The AECC defined ARDS as the acute onset of hypoxemia (arterial partial pressure of oxygen to fraction of inspired oxygen [PaO₂/FIO₂] ≤ 200 mm Hg) with bilateral opacities on chest radiograph, with no evidence of left atrial hypertension. A new extracapillary entity—acute lung injury (ALI)—was also described, using similar criteria but with less severe hypoxemia (PaO₂/FIO₂ ≤ 300 mm Hg).

The ARDS definition was widely adopted by clinical researchers and clinicians and has advanced the knowledge of ARDS by allowing the acquisition of clinical and epidemiological data. However, after 18 years of applied research, a number of issues regarding various criteria of the AECC definition have emerged, including a lack of explicit criteria for defining acute respiratory distress syndrome (ARDS) to different ventilator settings, poor reliability of the chest radiograph, and difficulties distinguishing hydrostatic edema (Table 1).
The Berlin definition of ARDS: an expanded rationale, justification, and supplementary material
Why Do We Need an ARDS Definition AT ALL?
Reliable and Valid Definitions are ESSENTIAL to Conduct and Interpret Clinical Research
Importance to Researchers

- Enable epidemiological studies
- Facilitate enrolment into clinical trials
- Allow comparison between studies
- Enhance linkages between clinical and basic science
  - Phenotype – Genotype relationship
Importance to Clinicians

- Ability to implement results of positive RCTs in clinical practice
  - Lower Vt for ALI
- May also be useful in prognostic discussions with patients/families
Importance to Administrators

- Epidemiological studies need definitions
  - These in turn may be useful in planning resource allocation
The American-European Consensus Conference on ARDS

- American-European Consensus (AECC)
  - $\text{PaO}_2/\text{F}_1\text{O}_2 \leq 200$ *
  - Acute onset &
  - CXR with bilateral infiltrates &
  - PAWP $\leq 18$ †

*Regardless of PEEP level
†or no clinical evidence of left atrial hypertension
Sensibility Concerns - AECC

- No definition of ‘acute’
- Risk factors not included
- Inconsistency of PaO₂/F₁O₂ ratio
  - Effect of PEEP
  - Effect of F₁O₂
- ↑ PCWP & ARDS can coexist
- Interpretation of the CXR has poor reliability

Acute respiratory distress syndrome 40 years later:
Time to revisit its definition*  

Crit Care Med 2008; 36:2912-2921

Jason Phua, MRCP; Thomas E. Stewart, MD, FRCPC; Niall D. Ferguson, MD, MSc, FRCPC
Effects of Airway Pressure

$P_{AW} = 22 \quad \frac{PaO_2}{F_1O_2} = 80$

$P_{AW} = 30 \quad \frac{PaO_2}{F_1O_2} = 281$
AECC Sensibility Concerns

- No definition of “acute”
- Appropriate clinical setting not formally included
- Inconsistency of PaO$_2$/F$_1$O$_2$ ratio
  - effect of PEEP
  - effect of F$_1$O$_2$
- ↑ PCWP and ARDS can coexist
- CXR interpretation has poor reliability
High values of the pulmonary artery wedge pressure in patients with acute lung injury and acute respiratory distress syndrome

% of patients with PA catheters

Median PAWP (mm Hg)

Data from Stewart et al. *NEJM* 1998 338:335-61
29% had PAOP > 18
- 97% of these had N or elevated CI
Interobserver variability in applying a radiographic definition of ARDS

Rubenfeld et al.
Chest 1999 116:1347-53
Interobserver variability in applying a radiographic definition of ARDS

- 21 clinical researchers and opinion leaders
- 28 CXRs from hypoxemic ICU patients
  - $\kappa = 0.55 \pm 0.02$ for inter-observer agreement
  - 13/28 CXRs showed near perfect agreement

Interobserver variation in interpreting chest radiographs for the diagnosis of ARDS
Meade et al. AJRCCM 2000 161:85-90

- Intensivists and radiologists reading 778 CXRs from PLVS study
  - $\kappa = 0.38$ to 0.55 for inter-observer agreement
  - $\kappa = 0.72$ to 0.88 for inter-observer agreement after “training”
The importance of recognising ALI

The New England Journal of Medicine

VENTILATION WITH LOWER TIDAL VOLUMES AS COMPARED WITH TRADITIONAL TIDAL VOLUMES FOR ACUTE LUNG INJURY AND THE ACUTE RESPIRATORY DISTRESS SYNDROME SYNDROME

THE ACUTE RESPIRATORY DISTRESS SYNDROME NETWORK*
<table>
<thead>
<tr>
<th>Treatment</th>
<th>Year</th>
<th>Type of Study</th>
<th>No. of Patients</th>
<th>Findings</th>
<th>Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucocorticoids (during the acute phase)</td>
<td>1987</td>
<td>Phase 3</td>
<td>87</td>
<td>No benefit</td>
<td>Bernard et al.¹²⁶</td>
</tr>
<tr>
<td>Glucocorticoids (during the acute phase)</td>
<td>1988</td>
<td>Phase 3</td>
<td>59</td>
<td>No benefit</td>
<td>Luce et al.¹²⁷</td>
</tr>
<tr>
<td>Alprostadil</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intravenous</td>
<td>1989</td>
<td>Phase 3</td>
<td>100</td>
<td>No benefit</td>
<td>Bone et al.¹²⁴</td>
</tr>
<tr>
<td>Liposomal</td>
<td>1999</td>
<td>Phase 3</td>
<td>350</td>
<td>Stopped for lack of efficacy</td>
<td>Abraham et al.¹²³</td>
</tr>
<tr>
<td>Surfactant</td>
<td>1996</td>
<td>Phase 3</td>
<td>725</td>
<td>No benefit; new preparations and methods of delivery now being studied</td>
<td>Anzueto et al.¹¹⁶</td>
</tr>
<tr>
<td>Inhaled nitric oxide</td>
<td>1998</td>
<td>Phase 2</td>
<td>177</td>
<td>No benefit</td>
<td>Dellinger et al.¹¹⁹</td>
</tr>
<tr>
<td>Inhaled nitric oxide</td>
<td>1999</td>
<td>Phase 3</td>
<td>203</td>
<td>No benefit</td>
<td>Payen et al.¹²⁰</td>
</tr>
<tr>
<td>Ketoconazole</td>
<td>2000</td>
<td>Phase 2</td>
<td>234</td>
<td>No benefit</td>
<td>NIH Acute Respiratory Distress Syndrome Network¹³²*</td>
</tr>
<tr>
<td>Procysteine</td>
<td>1998</td>
<td>Phase 3</td>
<td>214</td>
<td>Stopped for lack of efficacy</td>
<td>Bernard G: unpublished data</td>
</tr>
<tr>
<td>Lisofylline</td>
<td>1999</td>
<td>Phase 2–3</td>
<td>235</td>
<td>Stopped for lack of efficacy</td>
<td>Unpublished data</td>
</tr>
</tbody>
</table>

*NIH denotes National Institutes of Health.
Why randomized controlled trials fail but needn’t: 2.

David L. Sackett

Confidence = \frac{\text{Signal}}{\text{Noise}} \times \sqrt{\text{Sample size}}

CMAJ 2001;165(9):1226-37
Importance of Specificity in RCTs

Components of Risk for Death
- ALI/ARDS

Mortality risk

Control | Treatment | Control | Treatment
Process

- Appointment of Chairs
  - Selection of Panelists
- Presentations & consensus discussions
  - Sept 30 – Oct 1 2011, Berlin, Germany
- Empiric evaluation of draft definition
  - Focus on feasibility, reliability, validity
- Consensus revisions
- Society endorsements
- Evaluation of Berlin Definition
Panelists agreed that ARDS is:

- A type of acute, diffuse, inflammatory lung injury
- Leading to increased pulmonary vascular permeability, increased lung weight, loss of aerated lung tissue
- Clinical hallmarks are hypoxemia, bilateral opacities, ↑shunt, ↑dead space, decreased compliance
- Morphologically – DAD

Evolutionary not Revolutionary change
- Maintain links to AECC definiton
### Berlin Draft Definition

<table>
<thead>
<tr>
<th>Timing</th>
<th>Acute Respiratory Distress Syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Within 1 week of a known clinical insult or new/worsening respiratory symptoms</td>
</tr>
</tbody>
</table>

| Origin of Edema          | Respiratory failure not fully explained by cardiac failure or fluid overload; Need objective assessment (e.g., echocardiography) to exclude hydrostatic edema if no risk factor present |

<table>
<thead>
<tr>
<th>Oxygenation (^b)</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>200&lt;(\text{PaO}_2/\text{FiO}_2)&lt; 300 with PEEP or CPAP (\geq 5) cmH(_2)O</td>
<td>100&lt;(\text{PaO}_2/\text{FiO}_2)&lt;200 with PEEP (\geq 5) cmH(_2)O</td>
<td>(\text{PaO}_2/\text{FiO}_2)&lt;100 with PEEP (\geq 10) cmH(_2)O</td>
</tr>
</tbody>
</table>

| Chest Imaging \(^a\)     | Bilateral opacities - not fully explained by effusions, lobar collapse, masses | Bilateral opacities - not fully explained by effusions, lobar collapse, masses | Opacities involving \(\geq 3\) quadrants |

| Ancillary Physiology     | N/A                                                                 | N/A                                                                 | \(\text{VE}_{\text{CORR}} \geq 10\) L/min \(d, f\) or \(\text{CRS} \leq 40\) mL/cmH\(_2\)O \(e, f\) |
AECC Limitations
Berlin Modifications

- No definition of ‘acute’
- ALI/ARDS confusion
- Inconsistency of PaO$_2$/F$_1$O$_2$ ratio
  - Effect of PEEP
  - Effect of F$_1$O$_2$
- CXR has poor reliability
- ↑ PAWP & ARDS can coexist
- Risk factors not included
The Berlin definition of ARDS: an expanded rationale, justification, and supplementary material

Table 4  Criteria considered but not included in the Berlin definition (with permission from [21])

<table>
<thead>
<tr>
<th>Category</th>
<th>Specific criterion</th>
<th>Rationale for inclusion</th>
<th>Reason not included</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxygenation</td>
<td>Minimal FiO₂ requirement</td>
<td>More consistency to PaO₂/FiO₂ ratio [11]</td>
<td>Less feasible to mandate ventilator settings</td>
</tr>
<tr>
<td></td>
<td>SpO₂/FiO₂ ratio</td>
<td>Improved feasibility [27]</td>
<td>Less relevant for PaO₂/FiO₂ &lt;100</td>
</tr>
<tr>
<td></td>
<td>Higher PEEP requirement</td>
<td>More consistency to PaO₂/FiO₂ ratio [12, 13]</td>
<td>Potential for misclassification of Mild as Severe ARDS [27]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Improved face validity for severe group</td>
<td></td>
</tr>
<tr>
<td>Imaging</td>
<td>Thoracic computed tomography (CT)</td>
<td>Improved characterization of pulmonary opacities and lung volume [45]</td>
<td>Infeasible to mandate based on scanner availability and/or patient safety</td>
</tr>
<tr>
<td></td>
<td>Opacities in 3–4 quadrants on frontal CXR</td>
<td>Improved face validity for severe group</td>
<td>Poor reliability of 2 vs. 3–4 quadrants [46]</td>
</tr>
<tr>
<td></td>
<td>Electrical impedance tomography</td>
<td>Associated with DAD [7]</td>
<td>Does not improve predictive validity</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Improved characterization of pulmonary opacities and lung volume [47]</td>
<td>Infeasible to mandate based on availability</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Operating characteristics not well defined</td>
</tr>
<tr>
<td>Origin of edema</td>
<td>Extravascular lung water</td>
<td>Improved face validity</td>
<td>Infeasible to mandate based on availability</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Higher values associated with mortality [36]</td>
<td>Does not distinguish hydrostatic vs. inflammatory pulmonary edema</td>
</tr>
<tr>
<td></td>
<td>Inflammatory markers (IL-6 etc.)</td>
<td>Improved face validity [38]</td>
<td>Infeasible to mandate based on availability</td>
</tr>
<tr>
<td></td>
<td>Genetic markers</td>
<td>Improved face validity [39]</td>
<td>Operating characteristics poor [38, 40]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Infeasible to mandate based on availability</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Operating characteristics poor and lack of agreement on criterion standard [39]</td>
</tr>
<tr>
<td>Pulmonary mechanics</td>
<td>Plateau pressure</td>
<td>Improved face validity</td>
<td>Less feasible to mandate ventilator settings</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Higher values associated with mortality [31]</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Dead space</td>
<td>Improved face validity</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Higher values associated with mortality [34]</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Respiratory system compliance</td>
<td>Improved face validity</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Does not improve predictive validity</td>
</tr>
<tr>
<td></td>
<td>Minute ventilation</td>
<td>Improved face validity</td>
<td></td>
</tr>
<tr>
<td></td>
<td>DAD on lung biopsy</td>
<td>Confirmed pathological diagnosis [6, 42]</td>
<td></td>
</tr>
</tbody>
</table>
Novel patient-level meta-analysis of 7 cohorts: 4 Clinical and 3 Physiological

**Clinical Cohort**
- 4188 Patients

**Physiological Cohort**
- 269 Patients

**Incidence and Outcomes of Acute Lung Injury**

**Incidence and Mortality of Acute Lung Injury and the Acute Respiratory Distress Syndrome in Three Australian States**

**Tidal Hyperinflation during Low Tidal Volume Ventilation in Acute Respiratory Distress Syndrome**

**Lung Regional Metabolic Activity and Gas Volume Changes Induced by Tidal Ventilation in Patients with Acute Lung Injury**

**Lung Recruitment in Patients with the Acute Respiratory Distress Syndrome**
Demographics of ARDS Clinical Cohort

- 2 population based cohorts
- 1 clinical trials’ cohort
- 1 academic hospitals’ cohort

<table>
<thead>
<tr>
<th></th>
<th>N=4188</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sites</strong></td>
<td>56-79</td>
</tr>
<tr>
<td><strong>Years enrolled</strong></td>
<td>1996-2007</td>
</tr>
<tr>
<td><strong>Age (mean)</strong></td>
<td>54.5</td>
</tr>
<tr>
<td><strong>Gender (% male)</strong></td>
<td>57%</td>
</tr>
<tr>
<td><strong>Primary Risk Factor</strong></td>
<td></td>
</tr>
<tr>
<td>Pulmonary Sepsis</td>
<td>35%</td>
</tr>
<tr>
<td>Other Sepsis</td>
<td>34%</td>
</tr>
<tr>
<td>Trauma</td>
<td>7%</td>
</tr>
<tr>
<td>Other/None</td>
<td>24%</td>
</tr>
<tr>
<td><strong>PaO$_2$/FiO$_2$ ratio mean</strong></td>
<td>150</td>
</tr>
<tr>
<td><strong>PaO$_2$/FiO$_2$ &lt; 200</strong></td>
<td>76%</td>
</tr>
<tr>
<td><strong>CXR with &gt; 3 quadrants</strong></td>
<td>73%</td>
</tr>
<tr>
<td><strong>Mortality</strong></td>
<td>34%</td>
</tr>
</tbody>
</table>
Evaluation Process - Analytic Framework

- Evaluate the value of proposed ancillary variables in defining the Severe ARDS subgroup in the draft definition
- Determine the distribution of patient characteristics across definition severity categories
- Determine the predictive validity for mortality of the final Berlin Definition
- Compare the final Berlin definition to the AECC definition
Evaluation of Severe
Ancillary variables identify a smaller group of patients with similar mortality

Draft ARDS
PaO2/FiO2 ≤ 100 mmHg
PEEP ≥ 10 cm H2O
3 or 4 quadrant opacities on CXR
Crs ≤ 40 ml/cm H2O
VeCorr ≥ 10 L/min

Moderate 64%
Mild 22%
Severe 14%

Mortality 45%

Severe 28%
Mild 22%
Moderate 50%

Final ARDS
PaO2/FiO2 ≤ 100 mmHg
PEEP ≥ 5 cm H2O
Bilateral opacities on CXR
# Berlin Definition of ARDS

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| Chest Imaging<sup>a</sup> | Bilateral opacities – not fully explained by effusions, lobar/lung collapse, or nodules |

| Origin of Edema | Respiratory failure not fully explained by cardiac failure or fluid overload; Need objective assessment (e.g., echocardiography) to exclude hydrostatic edema if no risk factor present |

<table>
<thead>
<tr>
<th>Oxygenation&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>200&lt;PaO₂/FiO₂&lt; 300</td>
<td>100&lt;PaO₂/FiO₂&lt;200</td>
<td>PaO₂/FiO₂&lt;100</td>
<td></td>
</tr>
<tr>
<td>with PEEP or CPAP ≥ 5 cmH₂O&lt;sup&gt;c&lt;/sup&gt;</td>
<td>with PEEP ≥ 5 cmH₂O</td>
<td>with PEEP ≥ 5 cmH₂O</td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup> Bilateral opacities – not fully explained by effusions, lobar/lung collapse, or nodules.  
<sup>b</sup> Respiratory failure not fully explained by cardiac failure or fluid overload; Need objective assessment (e.g., echocardiography) to exclude hydrostatic edema if no risk factor present.  
<sup>c</sup> PEEP or CPAP ≥ 5 cmH₂O.
Distribution of patients across categories of ARDS

ARDS
3670

Mild
22%
27% Mortality

Moderate
50%
32% Mortality

Severe
28%
45% Mortality
Predictive validity of Berlin Definition - Clinical

P<0.001 across ARDS categories for all outcomes
P<0.001 comparing mortality prediction Berlin to AECC
ARDS Progression in 7 days from Baseline

- ARDS (3670)
  - Mild (22%)
  - Moderate (29%)
  - Severe (28%)

- Moderate (50%)
  - Severe (13%)

- Severe (4%)
Predictive validity of Berlin Definition - Physiologic
Conclusions

• First study to combine consensus and evaluation of a critical illness syndrome definition in a single iterative process

• Berlin Definition addresses some of the limitations of the AECC Definition for ARDS
  - Provides training set of CXRs and Clinical Vignettes

• Without evaluation a more complex definition that identified a smaller subset of Severe ARDS patients would have been adopted

• Future modifications to critical illness syndrome definitions should be guided by a process that combines empiric evaluation with expert consensus
Berlin Definition – Limitations and Future Directions

- Predictive validity only one criterion for revised definition

- While PEEP, compliance, chest radiograph, and dead space do not add to predictive validity of Severe ARDS definition, they are important variables for clinicians to measure and understand in ARDS

- Many variables and measures of interest (EVLW, Biomarkers, CT) not included in definition primarily due to feasibility concerns and lack of data on validity

- Mechanistic variables may be included for study specific research questions (recruitability, inflammatory markers)

- Other aspects of validity and reliability not empirically measured
  - Anticipate further work to evaluate and improve the Berlin Definition
The ARDS Definition Task Force

Chairs
Marco Ranieri
Gordon Rubenfeld
Taylor Thompson

Members
Massimo Antonelli
Antonio Anzueto
Richard Beale
Laurent Brochard
Roy Brower
Luigi Camporota
Andrés Esteban
Eddy Fan
Niall D Ferguson
Luciano Gattinoni
Andrew Rhodes
Arthur S. Slutsky
Jean-Louis Vincent

Data or statistical support
Ellen Caldwell
Andrew Bersten
Dale Needham
Antonio Pesenti

Additional attendees
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Agostino Gemelli
Anders Larsson
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leading science, leading practice

October 28-31, 2012
Sheraton Centre Hotel, Toronto

www.criticalcarecanada.com