The Berlin Definition: Does it fix anything?
Outline

• Everything we know about the ARDS clinical phenotype we learned in 1967
• Clinical syndromes are common in medicine
• How do you test a syndrome definition if you don't have a gold standard?
• What is the Berlin Definition?
• How has it fared?
• How do we move forward?
ACUTE RESPIRATORY DISTRESS IN ADULTS

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respiratory-distress syndrome, includes severe dyspnœa, tachypnœa, cyanosis that is refractory to oxygen therapy, loss of lung compliance, and diffuse alveolar infiltration seen on chest X-ray.

Acute onset, hypoxemia, low compliance, chest radiographic appearance
### Everything we know about the ARDS clinical phenotype we learned in 1967

<table>
<thead>
<tr>
<th>#</th>
<th>Age</th>
<th>Gender</th>
<th>Diagnosis</th>
<th>Score</th>
<th>Breath Rate</th>
<th>Oxygen</th>
<th>Initial IV Fluids</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>29</td>
<td>M</td>
<td>Multiple trauma; lung contusion</td>
<td>8</td>
<td>++</td>
<td>++</td>
<td>++++ 7500 ml.</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>19</td>
<td>F</td>
<td>Multiple trauma; lung laceration and contusion</td>
<td>1</td>
<td>+++</td>
<td>++</td>
<td>++++ 3000 ml.</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>19</td>
<td>F</td>
<td>Multiple trauma and fractures; fat-embolism</td>
<td>72</td>
<td>+</td>
<td>..</td>
<td>..</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>25</td>
<td>M</td>
<td>Shotgun wound to abdomen</td>
<td>96</td>
<td>+++</td>
<td>+</td>
<td>++++ 9000 ml.</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>11</td>
<td>M</td>
<td>Blunt chest injury; lung contusion</td>
<td>1</td>
<td>..</td>
<td>++</td>
<td>..</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>43</td>
<td>F</td>
<td>Acute pancreatitis</td>
<td>48</td>
<td>+++</td>
<td>++++</td>
<td>++++ 5000 ml.</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>23</td>
<td>F</td>
<td>? viral pneumonia</td>
<td>48</td>
<td>..</td>
<td>..</td>
<td>..</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>39</td>
<td>F</td>
<td>Drug ingestion; ? viral pneumonia</td>
<td>24</td>
<td>..</td>
<td>..</td>
<td>++</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>19</td>
<td>F</td>
<td>Guillain-Barre; ? viral pneumonitis</td>
<td>96</td>
<td>..</td>
<td>..</td>
<td>++</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>18</td>
<td>M</td>
<td>Multiple trauma; crushed chest; severe concussion</td>
<td>1</td>
<td>..</td>
<td>..</td>
<td>..</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>48</td>
<td>F</td>
<td>Drug ingestion; ? aspiration; ? viral pneumonia</td>
<td>48</td>
<td>..</td>
<td>..</td>
<td>++++ 10328 ml.</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>34</td>
<td>M</td>
<td>Gunshot wound left chest</td>
<td>96</td>
<td>..</td>
<td>..</td>
<td>..</td>
<td></td>
</tr>
</tbody>
</table>

### Risk factors
- Trauma
- Pancreatitis
- Pneumonia including viral
- Aspiration
- Cardiopulmonary bypass
- Fat embolism
- Shock
- Fluid resuscitation
Syndromes are common in medicine and critical care

- Sepsis
- Frailty
- Shock
- Asthma
- COPD
- Depression

- Heterogeneous populations
- Multiple mechanisms leading to same clinical presentation
- No gold standard
- Some fields do a better job evaluating their definitions
AECC definition
Reliability and confusion

- CXR unreliable
- Poor inter-observer agreement on PAOP
- P/F ratio is treatment dependent (TV, PEEP, FiO2)
- Left atrial hypertension often co-exists with ALI
- “ALI/ARDS” used but meaningless
- “ALI” used to refer to PaO2/FiO2 < 300 and 200 ≤ PaO2/FiO2 ≤ 300

Other definition attempts
More formal expert consensus – is it better?

<table>
<thead>
<tr>
<th>Defining characteristic</th>
<th>Operational definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Hypoxemia</td>
<td>PaO₂/FiO₂ &lt; 200 mm Hg with PEEP ≥ 10</td>
</tr>
<tr>
<td>2 Acute onset</td>
<td>Rapid onset in &lt; 72 h</td>
</tr>
<tr>
<td>3 Radiographic abnormalities</td>
<td>Bilateral airspace disease&lt;sup&gt;b&lt;/sup&gt; involving ≥ 2 quadrants on frontal chest x-ray</td>
</tr>
<tr>
<td>4 Noncardiogenic in origin</td>
<td>No clinical evidence of congestive heart failure (including use of PA catheter and/or echo if clinically indicated)</td>
</tr>
<tr>
<td>5 Decreased lung compliance</td>
<td>Static respiratory system compliance &lt; 50 mL/cm H₂O (with patient sedated, Vt of 8 mL/kg, IBW, PEEP ≥ 10)</td>
</tr>
<tr>
<td>6 Predisposition</td>
<td>Direct and/or indirect factor associated with lung injury&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup> Modified clinical definition of ARDS

<sup>b</sup> Bilateral airspace disease

<sup>c</sup> Direct and/or indirect factor associated with lung injury

*Journal of Critical Care (2005) 20, 147–154*
Everyone agrees we need a **better** ARDS definition but, what does **better** mean?

- Reliability, Validity, Feasibility
- How do you study validity without a gold standard?

<table>
<thead>
<tr>
<th>Validity Measure</th>
<th>Explanation</th>
<th>ALI Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>Face validity</td>
<td>Definition appears “on its face” to represent the disease</td>
<td>Patients identified by the proposed ALI definition “feel right” to clinicians and other users</td>
</tr>
<tr>
<td>Content validity</td>
<td>Definition contains all of the elements relevant to the disease</td>
<td>Proposed diagnostic criteria contain all of the elements deemed essential to the diagnosis of ALI, usually as assessed by a group of experts. Example: AECC criteria for ARDS</td>
</tr>
<tr>
<td>Criterion validity</td>
<td>Definition corresponds to a gold standard</td>
<td>Proposed diagnostic criteria for ALI correspond to a gold standard</td>
</tr>
<tr>
<td>Predictive validity</td>
<td>Definition is able to predict something it theoretically should be able to predict</td>
<td>Proposed diagnostic criteria predict some outcome that is unique to ALI (e.g., mortality, duration of mechanical ventilation, or response to therapy)</td>
</tr>
<tr>
<td>Concurrent validity</td>
<td>Definition is able to distinguish between groups that it theoretically should be able to distinguish between</td>
<td>Proposed diagnostic criteria are able to distinguish ALI from other forms of acute hypoxemic respiratory failure</td>
</tr>
</tbody>
</table>

ALI, acute lung injury; AECC, American-European Consensus Conference; ARDS, acute respiratory distress syndrome.
Are direct (pulmonary) and indirect (extra-pulmonary) ARDS different?

No difference in mortality
Potential impact of recent changes in the definition of ARDS for clinical research

• The Berlin ARDS definition is evolutionary not revolutionary

• Main changes:
  – Introduces a framework
  – Eliminates ALI term as it was being misused (ALI/ARDS)
  – 3 simple categories (mild, moderate, severe)
  – Requires minimal PEEP level for assessing gas exchange
  – Allows for diagnosis in non-intubated patients (mild)
  – Allows for CT diagnosis
  – Empiric evaluation (rejection) of a more complex severe definition
  – Provides educational materials to enhance reliability
# Berlin Draft Definition

## Acute Respiratory Distress Syndrome

<table>
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<tr>
<th>Timing</th>
<th>Within 1 week of a known clinical insult or new/worsening respiratory symptoms</th>
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<tr>
<td>Origin of Edema</td>
<td>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</td>
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<table>
<thead>
<tr>
<th></th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
</tr>
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<tbody>
<tr>
<td>Oxygenation&lt;sup&gt;b&lt;/sup&gt;</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>
<tr>
<td>Chest Imaging&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Bilateral opacities - not fully explained by effusions, lobar collapse, masses</td>
<td>Bilateral opacities - not fully explained by effusions, lobar collapse, masses</td>
<td>Opacities involving $\geq 3$ quadrants</td>
</tr>
<tr>
<td>Ancillary Physiology</td>
<td>N/A</td>
<td>N/A</td>
<td>$\text{VE}<em>{\text{CORR}} \geq 10$ L/min&lt;sup&gt;d,f&lt;/sup&gt; or $\text{C}</em>{\text{RS}} \leq 40$ mL/cmH$_2$O&lt;sup&gt;e,f&lt;/sup&gt;</td>
</tr>
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<sup>a</sup> Bilateral opacities - not fully explained by effusions, lobar collapse, masses.  
<sup>b</sup> Oxygenation criteria.  
<sup>c</sup> Additional criteria include bilateral opacities on chest imaging and increased pulmonary vascular resistance.  
<sup>d</sup> VE: conductive equivalent, C: complement.  
<sup>e</sup> CRS: respiratory system compliance.  
<sup>f</sup> These criteria are used in the absence of other criteria or if criteria are not met.
Novel patient-level meta-analysis of 7 cohorts: 4 Clinical and 3 Physiological

Clinical Cohort
- 4188 Patients

Physiological Cohort
- 269 Patients
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%

Final ARDS
PaO2/FiO2 < 100 mmHg
PEEP ≥ 5 cm H2O
Bilateral opacities on CXR

Mild 22%
Moderate 50%
The Berlin definition of ARDS: an expanded rationale, justification, and supplementary material

Vignette 3
A 43 year old otherwise healthy woman is taken to the operating room for a routine laparoscopic cholecystectomy. The trocar perforates the inferior vena cava. The injury is identified immediately and a laparotomy is performed. As vascular control is obtained the patient goes into shock and has a brief episode of pulseless electrical activity. She is resuscitated with 1 mg of epinephrine, 10 liters of crystalloid and 6 units of packed red cells. At the end of the case she is brought to the post-anesthesia care area intubated with a blood pressure of 160/90 mmHg. The serum lactate is 7 mmol/L, a CXR shows bilateral opacities and the arterial PaO₂/FiO₂ ratio of 180. The central venous pressure is 20 mmHg.

CXR #1 – CONSISTENT WITH ARDS
# Berlin Definition of ARDS

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<td>(\text{PaO}_2/\text{FiO}_2&lt;100) with PEEP (\geq 5) cm(\text{H}_2\text{O})</td>
<td></td>
</tr>
</tbody>
</table>
Does or does not add to predictive validity for mortality
Does not correlate with DAD
Does correlate with EVLW
Generally critical of the exercise
Generally missed the point
Concerns with Berlin Definition

- Association with mortality poor and not reproducible
- The Berlin Definition is not a prognostic model
- Predictive validity was used to evaluate a more complex "severe" definition which was rejected based on this criteria
Concerns with Berlin Definition

- Association with mortality poor and not reproducible
- Does not identify patients with DAD – but does identify patients with pneumonia, edema, hemorrhage
- Not all animal models of ARDS create DAD
- DAD is time dependent phenomenon
- DAD is not a known drug target – if it is, then we need a biomarker or restrict the study to severe ARDS and power accordingly

Concerns with Berlin Definition

Standardized ventilator settings and PEEP responsiveness stratify patients well

- Association with mortality poor
- Does not identify patients with DAD – but does identify patients with pneumonia, edema, hemorrhage
- Did not standardize mechanical ventilation at time of oxygenation assessment

- Oxygenation after 24h standardized mechanical ventilation clearly associated with mortality better than baseline oxygenation

![Graph showing oxygenation improvement](image)
PEEP responsiveness associated with lower mortality

- Functional recruitment as measured by change in oxygenation but not change in pCO2 or static compliance predicts mortality
- PEEP responsiveness is a good prognostic test and risk stratifier

Golligher EW Am J Respir Crit Care Med. 2014 Jul 1;190(1):70-6
Concerns with Berlin Definition

Standardized ventilator settings and PEEP responsiveness stratify patients well

- Association with mortality poor
- Does not identify patients with DAD – but does identify patients with pneumonia, edema, hemorrhage
- Did not standardize mechanical ventilation at time of oxygenation assessment

- Oxygenation after 24h standardized mechanical ventilation clearly associated with mortality better than baseline oxygenation
- However requiring
- Would eliminate all observational research and enrolment in trials requiring early intervention
Concerns with Berlin Definition

• Association with mortality poor
• Did not standardize mechanical ventilation at time of oxygenation assessment
• Did not include:
  – CT, EVLW, PET, biomarkers ...
• Test performance of these measures not evaluated in broad populations of patients with respiratory failure
• Literature review on reliability and validity not persuasive
• Not feasible for all centers
• Berlin does not preclude using any for a specific trial
A way forward – smarter biology
latent class modeling for subphenotypes


Septic – nonpneumonia
Higher mortality
A way forward: the right cohort, better imaging

Accuracy of the chest radiograph to identify bilateral pulmonary infiltrates consistent with the diagnosis of acute respiratory distress syndrome using computed tomography as reference standard


Juan B. Figueroa-Casas MD, Noemi Brunner MD, Alok K. Dwivedi PhD, Anoop P. Ayyappan MD

- 90 patients with hypoxemia and risk factor: CXR + CT
- 12% CXR false positive (bilateral effusions, atx, emphysema)
- 52% CXR false negative (focal)
- Gender but not BMI worsened accuracy
A Way Forward
Reliability Testing

• The “advances” of Berlin were methodological
  – Use of reliability, feasibility, and validity framework
  – A priori empiric evaluation methods
  – Beyond consensus

• Actual value in reliability should be tested
Put the data you have uncovered to beneficial use.

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