Neil R. MacIntyre, MD is a Professor of Medicine and Medical Director of Respiratory Care Services at Duke University. He received his MD degree from Cornell University, did an internal medicine residency at Cornell-NY Hospital and a pulmonary fellowship at UCSF. In his 31 year career, he has been principal investigator or co-principal investigator on over 37 clinical trials that have enrolled hundreds of patients. Among the most important of these have been the NIH funded ARDS Network evaluating many aspects of respiratory failure, the National Emphysema Treatment Trial (NETT) evaluating lung volume reduction surgery for emphysema and the Long Term Oxygen Treatment Trial (LOTT) evaluating oxygen therapy in COPD patients. He has held a number of national and international leadership positions, including the chair of the large ACCP/SCCM/AARC Evidence Based Guidelines Committee for Ventilator Weaning, the chair of the joint ATS/ERS Committee to Standardize DLCO, the chair of the ACCP Mechanical Ventilation Simulation Program, and on the steering/writing committees of ATS and AACVPR addressing pulmonary rehabilitation and exercise assessment.
Management of Acute Hypoxemic Respiratory Failure

Neil MacIntyre MD
Duke University
Durham NC USA

Acute Hypoxemic Respiratory Failure

- Progressive ILD (“flare”)
- Vascular disease – vasculitis, PE
- Cardiogenic edema
- Coupled with hypercarbic failure (COPD, asthma)
- Extra-pulmonary (eg. pneumothorax)
- Acute lung injury – ARDS
Acute Hypoxemic Respiratory Failure

- Progressive ILD (“flare”)
- Vascular disease – vasculitis, PE
- Cardiogenic edema
- Coupled with hypercarbic failure (COPD, asthma)
- Extra-pulmonary (eg. pneumothorax)
  - *Acute lung injury – ARDS*
### Definition of ARDS

**“S” = syndrome – not a specific disease**

<table>
<thead>
<tr>
<th>AECC Definition</th>
<th>Berlin Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Timing</strong></td>
<td>Acute onset</td>
</tr>
<tr>
<td><strong>Chest imaging</strong></td>
<td>Bilateral infiltrates</td>
</tr>
<tr>
<td><strong>Origin of edema</strong></td>
<td>PAWP ≤ 18 mm Hg or no clinical evidence of left atrial hypertension</td>
</tr>
</tbody>
</table>

#### Category: PaO2/FIO2 Ratio

- **ALI**: ≤ 300 mm Hg regardless of PEEP
- **ARDS**: ≤ 200 mm Hg regardless of PEEP

- **Mild**: 201-300 mm Hg with PEEP or CPAP 5 cm H2O
- **Moderate**: 101-200 mm Hg with PEEP 5 cm H2O
- **Severe**: ≤100 mm Hg with PEEP 5 cm H2O

---

### ALI - ARDS

- Problems with the definitions:
  - Ventilator pressure not specified
  - CXR criteria vague
  - The syndrome is heterogeneous with multiple phenotypes
ARDS – Pathogenetic Overview

Classical ARDS Stages
The Heterogeneity of ARDS

*Can Have Profound Impact on Drug Targeting/Outcomes*

- Primary vs Secondary Triggers
- Physiologic Severity
- Clinical Trajectory
- Pathologic Features
- Distribution on Imaging
- Biomarker Profile

---

**Table 1. Incidence of Acute Lung Injury and ARDS and Mortality from These Conditions.**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Acute Lung Injury</th>
<th>ARDS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cases — no.</td>
<td>1,113</td>
<td>828</td>
</tr>
<tr>
<td>Crude incidence — no. per 100,000 person-yr</td>
<td>78.9</td>
<td>58.7</td>
</tr>
<tr>
<td>Age-adjusted incidence — no. per 100,000 person-yr†</td>
<td>86.2</td>
<td>64.0</td>
</tr>
<tr>
<td>Mortality (95% CI) — %</td>
<td>38.5 (34.9–42.2)</td>
<td>41.1 (36.7–45.4)</td>
</tr>
<tr>
<td>Estimated annual cases — no.†</td>
<td>190,600</td>
<td>141,500</td>
</tr>
<tr>
<td>Estimated annual deaths — no.†</td>
<td>74,500</td>
<td>39,000</td>
</tr>
<tr>
<td>Estimated annual hospital days — no.†</td>
<td>3,622,000</td>
<td>2,746,000</td>
</tr>
<tr>
<td>Estimated annual days in ICU — no.†</td>
<td>2,134,000</td>
<td>1,642,000</td>
</tr>
</tbody>
</table>

*ARDS denotes acute respiratory distress syndrome, and CI confidence interval.† U.S. estimates, age-adjusted to the 2000 Census, are shown.*
HETEROGENEITY: ARDS Triggers

• Primary - Direct lung injury (e.g., aspiration, pneumonia, contusion, inhalation)
  – If it doesn’t evolve into SIRS/MODS, outcome better than secondary

• Secondary - Lung is one of many organs involved in SIRS/MODS (sepsis, pancreatitis, hypotension)
  – Outcome worse than primary

HETEROGENEITY: Physiologic severity

JAMA 2016;315:788
HETEROGENEITY: Trajectory

Log-rank test
\[ P < 0.0001 \]

Survival Probability

Days Since Enrollment

Rapidly improving ARDS
ARDS > 1 d

Chest 2019;133:475H

HETEROGENEITY: Pathology

Autopsy findings in 356 pts with clinical ARDS

No pulmonary lesion
Other diagnostic
Pneumonia
Diffuse alveolar damage

Mild ARDS
Moderate ARDS
Severe ARDS

AJRCCM 2013; 187:761
HETEROGENEITY: Distribution of Disease

Important implications for positive pressure ventilation – majority of patients do NOT have diffuse disease

HETEROGENEITY: Biomarker Profiles
Hypo-inflammatory (Type 1) and Hyper-inflammatory (Type 2) ARDS

Lancet Resp Med 2014:611

Blue = Hypo
Pink = Hyper

Lancet Resp Med 2014:611
Outcomes and Inflammatory State

Table 3. Clinical Outcomes by ARDS Subphenotype

<table>
<thead>
<tr>
<th>Subphenotype 1 (n = 727)</th>
<th>Subphenotype 2 (n = 273)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>60-d mortality, %</td>
<td>21</td>
<td>44</td>
</tr>
<tr>
<td>90-d mortality, %</td>
<td>22</td>
<td>45</td>
</tr>
<tr>
<td>Ventilator-free days, median</td>
<td>19</td>
<td>3</td>
</tr>
</tbody>
</table>

Definition of abbreviation: ARDS=acute respiratory distress syndrome.
P value represents chi-square analysis for mortality and Wilcoxon rank sum for ventilator-free days.

AJRCCM 2017;195:331

The Heterogeneity of ARDS

*Can Have Profound Impact on Drug Targeting/Outcomes*

- Primary vs Secondary Triggers
- Physiologic Severity
- Clinical Trajectory
- Pathologic Features
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The Heterogeneity of ARDS
Can Have Profound Impact on Drug Targeting/Outcomes

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*All must be considered in setting of host factors*

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**ALI/ARDS - Management**
ALI/ARDS - Management

• Treat the trigger:
  – Infections need correct antibiotics quickly
  – Steroids/anti-inflammatory therapies for specific steroid sensitive triggers (eg auto-immune, hypersensitivity reaction, ?AIP)
Anti-inflammatory strategies for ALI?ARDS
Some of the more spectacular failed clinical trials I have been involved with ($billions in costs)

- Anti-endotoxin antibodies
- IL1-ra
- anti-TNF
- ketoconazole
- lysophylline
- statins

ALI/ARDS -failed anti-inflammatory trials

- Failures due to:
  - Bad drugs/concept?
    - In vivo activity may be different than in vitro
  - Inappropriate dosing?
    - Timing issues, tissue penetration
  - Effects of co-morbidities NOT present in animals?
  - Bad study design?
    - Sample size, realistic endpoints, biologic activity
  - Wrong patients/heterogeneous “dilution”?
    - Importance of mechanistic diagnoses
What about steroids in ALI/ARDS?

- As noted, useful in steroid responsive triggers
- High dose not effective in sepsis/SIRS.
  - How about moderate doses – CAP? All comers?
- Several studies suggest benefit with “stress doses” in septic shock
- Controversial benefit in reducing fibrosis in the repair process (late stage)
  - One trial suggested a shorter need for ventilatory support. However, effect short lived (rapid steroid withdrawal?)

Int Care Med 2016; 42:829
Int Care Med 2016; 42:918
Int Care Med 2016; 42:921
Immunonutrition?

• Additions of various combinations of arginine, glutamine, nucleotides, antioxidants and omega 3 fatty acids to feeding formulas have anti-inflammatory properties ("immunonutrition")
• Evidence based review in JAMA 2001;286:944:
  – 22 clinical trials, 2419 patients
  – Infection RR 0.66 (0.54-0.8)
  – Mortality RR 1.1 (0.93-1.31)
• Three positive RCTs since 1998 (Gadek, Singer, Pontes-Arruda)

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• Three positive RCTs since 1998 (Gadek, Singer, Pontes-Arruda)
• ARDS Network OMEGA trial comparing omega 3 enriched diet with standard diet stopped after 500 patients for futility
ALI/ARDS - Management

**Recent Developments**

- Hi flow nasal cannula for impending respiratory failure
- Evolving concepts in lung protective mechanical ventilation strategies
- Evolving role of VV-ECMO in the MICU

![Diagram of ALI/ARDS management](image)
ALI/ARDS Management

*Recent Developments*

- Hi flow nasal cannula for impending respiratory failure
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---

**High Flow O2 Systems**

- Flows 40-60 L/min, FiO2 0.21-1.0, Humidity >40mg/L
  - Closely meets Inspiratory Flow Demands
  - Provides small levels of CPAP (3-7cmH20)
  - Washes out anatomic deadspace
  - Decreases upper airway resistance
- Comfortable, facilitates communication
- Cough uninhibited
# Intubations

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Efficacy</th>
<th>Control</th>
<th>Odds Ratio</th>
<th>95% CI</th>
<th>M-H Statistics</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>2,1 HMNC vs. COF</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Efficacy 2016</td>
<td>0</td>
<td>49</td>
<td>1.07</td>
<td>0.83</td>
<td>1.37</td>
<td></td>
</tr>
<tr>
<td>Efficacy 2014</td>
<td>1</td>
<td>34</td>
<td>1.14</td>
<td>0.89</td>
<td>1.45</td>
<td></td>
</tr>
<tr>
<td>Efficacy 2016</td>
<td>4</td>
<td>92</td>
<td>1.11</td>
<td>0.87</td>
<td>1.42</td>
<td></td>
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<tr>
<td>Efficacy 2011</td>
<td>13</td>
<td>205</td>
<td>0.64</td>
<td>0.49</td>
<td>0.84</td>
<td></td>
</tr>
<tr>
<td>Efficacy 2014</td>
<td>8</td>
<td>137</td>
<td>0.67</td>
<td>0.49</td>
<td>0.91</td>
<td></td>
</tr>
<tr>
<td>Efficacy 2016</td>
<td>2</td>
<td>52</td>
<td>1.12</td>
<td>0.86</td>
<td>1.47</td>
<td></td>
</tr>
<tr>
<td>Efficacy 2011</td>
<td>3</td>
<td>13</td>
<td>1.04</td>
<td>0.70</td>
<td>1.55</td>
<td></td>
</tr>
<tr>
<td>Efficacy 2014</td>
<td>6</td>
<td>18</td>
<td>0.44</td>
<td>0.28</td>
<td>0.68</td>
<td></td>
</tr>
<tr>
<td>Efficacy 2011</td>
<td>0</td>
<td>9</td>
<td>0.37</td>
<td>0.23</td>
<td>0.59</td>
<td></td>
</tr>
<tr>
<td>Total events</td>
<td>79</td>
<td>119</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity</td>
<td>Tau² = 0.00</td>
<td>1.98</td>
<td>1.0</td>
<td>1.0</td>
<td>99%</td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 1.02 (P = 0.31)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

# ICU Mortality

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Efficacy</th>
<th>Control</th>
<th>Odds Ratio</th>
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<tr>
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<td>12</td>
<td>105</td>
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<td>1.70</td>
<td></td>
</tr>
<tr>
<td>Efficacy 2016</td>
<td>3</td>
<td>63</td>
<td>1.00</td>
<td>0.76</td>
<td>1.32</td>
<td></td>
</tr>
<tr>
<td>Efficacy 2011</td>
<td>7</td>
<td>77</td>
<td>0.93</td>
<td>0.67</td>
<td>1.28</td>
<td></td>
</tr>
<tr>
<td>Efficacy 2014</td>
<td>6</td>
<td>51</td>
<td>1.14</td>
<td>0.83</td>
<td>1.55</td>
<td></td>
</tr>
<tr>
<td>Efficacy 2011</td>
<td>3</td>
<td>34</td>
<td>1.00</td>
<td>0.72</td>
<td>1.41</td>
<td></td>
</tr>
<tr>
<td>Efficacy 2014</td>
<td>10</td>
<td>22</td>
<td>0.45</td>
<td>0.28</td>
<td>0.70</td>
<td></td>
</tr>
<tr>
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<td>0</td>
<td>9</td>
<td>0.37</td>
<td>0.23</td>
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Chest. Published online January 19, 2017. 10.1016/chest.2017.01.004
ALI/ARDS Management

Recent Developments

• Hi flow nasal cannula for impending respiratory failure
• Evolving concepts in lung protective mechanical ventilation strategies
• Evolving role of VV-ECMO in the MICU

Mechanical Ventilation in 2019 is a Cornerstone of Respiratory Life Support

• Positive pressure ventilation provides alveolar ventilation, muscle unloading, and maintains alveolar recruitment through PEEP
• However, excessive stress and strain on the lungs have been known for centuries to cause harm
  – John Fothergill 1744: mouth-mouth recussitation better than bellows because lung volumes limited to the rescuers volumes
  – Leroy of Paris 1829: “Bellows in the hand of an ignorant person might become a lethal weapon”
VILI Mechanisms

Transpulmonary Pressure

“Strain”

“Stress”

Overdistention
Excessive static strain

Collapse/re-open

Excessive tidal strain

Mechanical Ventilation 2019

• Support life:
  • Global PO2 55-80 mm Hg
  • Global pH >7.15 (higher if CV issues)
• Protect the lungs
  • Maximal transpulmonary stretching pressure <30 cm H2O
  • Tidal volume in normal range (4-8 ml/kg IBW) – maybe smaller in lungs with markedly reduced functional lung
  • Expiratory pressure (PEEP) to prevent de-recruitment of lung regions
  • FiO2 <0.60 (or lower)
Lung protective ventilation reduces mortality in patients with ARDS

9% absolute reduction in mortality

Trade-offs are involved

Crs also better in the HIGH Vt group
PEEP: A two edged sword

Trans-Alveolar Pressure

GOOD

BAD

exp

insp

exp

insp

exp


Little to recruit, high risk of overdistention, favor FiO2 support over PEEP

Much to recruit, favor PEEP over FiO2

Gattinoni NEJM 2006
Mechanical Ventilation 2019

- **Support life:**
  - Global PO2 55-80 mm Hg
  - Global pH >7.15 (higher if CV issues)
- **Protect the lungs**
  - Maximal transpulmonary stretching pressure <30 cm H2O
  - Tidal volume in normal range (4-8 ml/kg IBW) – maybe smaller in lungs with markedly reduced functional lung
  - Expiratory pressure (PEEP) to prevent de-recruitment of lung regions
  - FiO2 <0.60 (or lower)
MV Adjuncts for ALI/ARDS - 2019

• Prone positioning
  – Distributes gas delivery more evenly
  – Heart moved to dependent position
  – Downside: nursing issues, skin injuries

• Neuromuscular blockade
  – Reduces oxygen consumption
  – Improves resp system compliance
  – Eliminates patient-ventilator dys-synchrony
  – Downside: May delay weaning, increase weakness

• Fluid management
  – “Dry lungs are happy lungs but dry kidneys are very sad”

Supine Positioning

Prone Positioning


Prone positioning in severe ARDS

17.4% absolute reduction in mortality

P<0.001

<table>
<thead>
<tr>
<th>No. at Risk</th>
<th>Prone group</th>
<th>Prone group</th>
<th>Prone group</th>
<th>Prone group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Supine group</td>
<td>229</td>
<td>202</td>
<td>191</td>
<td>186</td>
</tr>
</tbody>
</table>

Neuromuscular blockers in early ARDS

So how often are these other strategies used?

JAMA 2016;315:788
LUNG SAFE
“Dry”: Conservative fluid strategy
Furosemide
Fluid restrict

- KIDNEY
  - Accept lower BP, UO

- LUNG
  - CVP low
  - PAOP low
  - Favors gas exchange

“Wet”: Liberal fluid strategy

- LUNG
  - Accept higher FiO2 and Vent pressure

- KIDNEY
  - CVP high
  - PAOP high
  - Favors perfused organs
ARDSnet fluid management trial: Cumulative fluid balance

![Graph showing cumulative fluid balance over study days for liberal and conservative strategies, with ALMA 6 ml (1996-1999) and ALVEOLI all (1999-2002).]

Liberal
Conservative
ARMA 6 ml (1996-1999)
ALVEOLI all (1999-2002)

P<0.001
P=ns

Proportion of Patients
0.0 0.1 0.2 0.3 0.4 0.5 0.6 0.7 0.8 0.9 1.0
0 10 20 30 40 50 60
Days
Breathing without assistance, conservative strategy
Breathing without assistance, liberal strategy
Alive, liberal strategy
Alive, conservative strategy

P<0.001
P=ns
Outcomes and Impact of Fluid Management by Inflammatory State

Table 4. Interaction between ARDS Subphenotype and Fluid-Management Strategy for the Outcomes of Mortality and Ventilator-Free Days

<table>
<thead>
<tr>
<th>Subphenotype 1</th>
<th>Fluid-management strategy</th>
<th>Subphenotype 2</th>
<th>Fluid-management strategy</th>
<th>Subphenotype 2</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Conservative (n = 341)</td>
<td>Liberal (n = 367)</td>
<td>Conservative (n = 142)</td>
<td>Liberal (n = 131)</td>
<td></td>
</tr>
<tr>
<td>60-d mortality, %</td>
<td>24</td>
<td>17</td>
<td>39</td>
<td>49</td>
<td>0.0003</td>
</tr>
<tr>
<td>90-d mortality, %</td>
<td>26</td>
<td>18</td>
<td>40</td>
<td>50</td>
<td>0.0039</td>
</tr>
<tr>
<td>Ventilator-free days, median</td>
<td>17</td>
<td>21</td>
<td>5</td>
<td>0</td>
<td>0.35</td>
</tr>
</tbody>
</table>

Definition of abbreviation: ARDS = acute respiratory distress syndrome.
P-value represents the interaction between subphenotype as defined by latent class analysis and randomly assigned fluid-management strategy for the outcome.

AJRCCM 2017;195:331

ALI/ARDS Management

Recent Developments

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Approaches to Venovenous ECMO

The Oxygenator in Venovenous ECMO.

• Oxygenation depends on circuit flow
  – VV ECMO can only handle 75% of CO –
    oxygenation not complete
  – Coagulation system activation increases with flow

• CO2 removal depends on gas flow
  – Substantial CO2 removal even at lower flows
    • How about “dialysis level” flows? (ECCO2R)
**Figure 2.** Kaplan–Meier Survival Estimates in the Intention-to-Treat Population during the First 60 Days of the Trial.

**Table 3.** Adverse Events as Defined by the Trial Protocol in the Intention-to-Treat Population.
ALI/ARDS Management

*Recent Developments*

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The Future

• Better disease bio-marker profiling
  – Include genetic profiling
  – May “resurrect” some of the failed agents of the past
• ECLS – solve the anti-coagulation challenges
• Permissive hypercapnia and hypoxemia
  – Harness innate mechanisms that allow the fetus to thrive with PO2s in the 30s, Sherpas to thrive on Mt Everest
  – Hibernation capabilities
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• *Mechanical ventilators only in museums!*