ICU Management of COVID-19

Corey Hardin MD, PhD

April, 2020
<table>
<thead>
<tr>
<th>Date</th>
<th>ICU Total</th>
<th>Blake7</th>
<th>Blake12</th>
<th>Ellison9</th>
<th>Ellison4</th>
<th>Lunder6</th>
<th>Lunder7</th>
<th>Bigelow 6</th>
<th>E14 Burn</th>
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<tbody>
<tr>
<td>4/4/20</td>
<td></td>
<td>MICU</td>
<td>ICU</td>
<td>CCU</td>
<td>SICU</td>
<td>NICU</td>
<td>NICU</td>
<td>PICU</td>
<td>ICU</td>
</tr>
<tr>
<td>COVID+ ICU</td>
<td>78</td>
<td>15</td>
<td>14</td>
<td>13</td>
<td>14</td>
<td>11</td>
<td>1</td>
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<tr>
<td>RISK ICU</td>
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<tr>
<td>COVID+ ICU Intubated</td>
<td>74</td>
<td>14</td>
<td>14</td>
<td>13</td>
<td>14</td>
<td>9</td>
<td>1</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>RISK ICU Intubated</td>
<td>5</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>3</td>
<td>0</td>
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<td>0</td>
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<tr>
<td>Open Neg Pressure Beds</td>
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<td>0</td>
<td>1</td>
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<td>0</td>
<td>1</td>
<td>1</td>
<td>1</td>
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</tr>
</tbody>
</table>

**COVID-19 at MGH**

- Hosp POS
- ICU POS
Respiratory Failure and COVID-19


- Median time from presentation to ICU admission is ~10 days

- Critical illness and ARDS can present with rapid decompensation:
  - Rapid increase in $f_iO_2$
  - Progressive findings on chest imaging
  - Progressive lymphopenia

What brings patients to the ICU?
An Emerging Profile ARDS in the setting of COVID-19

Initial PEEP: $10.1 \pm 1.6 \text{ cmH}_2\text{O}$
Initial $\Delta P$: $10.9 \pm 1.2 \text{ cmH}_2\text{O}$

Initial airways resistance: $4.8 \pm 1.3 \text{ cmH}_2\text{O}/\text{L/s}$
Average airways resistance: $4.5 \pm 1.1 \text{ cmH}_2\text{O}/\text{L/s}$

Initial static compliance: $40.1 \pm 5.7 \text{ mL/cmH}_2\text{O}$
Average static compliance: $42.0 \pm 5.6 \text{ mL/cmH}_2\text{O}$

Moderate compliance deficit
Hypoxemia ranges from mild to severe
Responsive to MODERATE PEEP

Data courtesy of David Ziehr MD
**MGH COVID-19 Experience**

- Moderate compliance deficit ($C_r s\ 40$)
- P:F not terrible on moderate PEEP (150-200 on PEEP 8-12)

**Lung Safe (JAMA 2016)**

- $P_{plat\ 22.6\ -23.7\ on\ PEEP\ 8-10}$
- P/F:
  - Mild ($n=714$) 246
  - Mod ($n=1106$) 149
  - Sev ($n=557$) 75

Severe ARDS has always been the less common presentation.
## Berlin Definition of ARDS

<table>
<thead>
<tr>
<th>Timing</th>
<th>Within 1 week of a known clinical insult or new/worsening respiratory symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chest Imaging a</td>
<td>Bilateral opacities – not fully explained by effusions, lobar/lung collapse, or nodules</td>
</tr>
<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>
</tr>
<tr>
<td>Oxygenation b</td>
<td>200&lt;(\frac{\text{PaO}_2}{\text{FiO}_2})&lt;300 with PEEP or CPAP ≥ 5 cm(\text{H}_2\text{O})</td>
</tr>
</tbody>
</table>

**Acute Respiratory Distress Syndrome**

**eSUPPLEMENT**

1) Radiographs of consensus interpretations of radiographics
2) Consensus case vignettes of “fully explained” by cardiac failure of fluid overload

Ferguson et al ICM 2012
| Lowest Pao$_2$/FiO$_2$ ratio during mechanical ventilation — median (IQR)‡ |
|---------------------------------|------------------|
| Day 1                           | 142 (94–177)     |
| Day 2                           | 139 (112–171)    |
| Day 3                           | 134 (108–171)    |

<table>
<thead>
<tr>
<th>Infection analyses — no. positive/total no.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood cultures</td>
</tr>
<tr>
<td>Sputum cultures</td>
</tr>
<tr>
<td>Influenza A</td>
</tr>
<tr>
<td>Influenza B</td>
</tr>
<tr>
<td>Respiratory syncytial virus</td>
</tr>
<tr>
<td>Extended-spectrum respiratory viruses</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Chest radiography findings — no./total no. (%)§</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clear</td>
</tr>
</tbody>
</table>

| Bilateral infiltrates                         | 23/23 (100)      |
| Pleural effusion                              | 0/23             |

<table>
<thead>
<tr>
<th>Computed tomography findings — no./total no. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bilateral ground-glass opacification</td>
</tr>
<tr>
<td>Nodules</td>
</tr>
<tr>
<td>Pleural effusions</td>
</tr>
</tbody>
</table>
Available Pathology from COVID-19 is Consistent with Diffuse Alveolar Damage

Xu et. al, Lancet Respir. Med, 8:420-422

- Loss of pneumocytes
- Hyaline membranes
- Consistent with Diffuse Alveolar Damage (DAD)

Unpublished autopsy series from Seattle:

9/12 pts with DAD
3 years after ARMA (ARDSnet 1)

Editorial
July 16, 2003

Is SARS Just ARDS?
Gordon D. Rubenfeld, MD, MSc

Toronto series 38 pts with critical illness 2/2 SARS (SARS-CoV-1)

- Risks similar to SARS-CoV-2:
  - Age > 50
  - CAD, DM
  - CRP, LDH, DK

- Vt > 8cc/kg, 6 pts 1 survivor
- Vt < 6cc/kg, 23 pts, 15 survivors

- No difference in survival with steroid treatment

SARS-CoV-1 and SARS-CoV-2 ~80% sequence homology
- Same mechanism – S protein binds ACE2 receptor
- Same clinical presentation

Non-standard ARDS care can result in excess mortality
COVID-19 is ARDS

- Acute onset hypoxemia with P:F < 300
- Bilateral infiltrates
- Not caused by heart failure
- DAD

Respiratory Failure in COVID-19 is ARDS
Pathophysiology of ARDS

- Increased permeability of alveolar-capillary interface
- Surfactant dysfunction -> alveolar instability. Cellular apoptosis
- Alveolar instability = increase in opening pressure of some units
- Other units may have preserved mechanics
- Collapse of unstable units -> shunt (perfusion without ventilation) -> hypoxemia
- Remaining ‘Baby Lung’ may be over-distended by usual $V_t$
Management of ARDS
Drug Trials for Sepsis/ARDS: No Specific Rx

- nitric oxide
- surfactant/perfluorocarbon
- corticosteroids
- prostaglandin E1
- lysophylline
- ibuprofen
- procysteine
- anticytokine/antiendotoxin
- ketoconazole
- streptokinase
- neutrophil elastase inhibitor
- sPLA2 Inhibitor
- rhAPC
- Albuterol/salmeterol
- furosemide
- Cisatracurium
- Heparin
- IL-1 receptor antagonism

In general – no specific therapy for ARDS.

No proven therapy for ARDS in the setting of COVID-19
Novel Agents for COVID-19

- **Hydroxychloroquine**: Dramatic results reported in small study with questionable methodology (Gautret et. al).
  
  (Molina et. al (https://doi.org/10.1016/j.medmal.2020.03.006)) same dosing, 11 patients, no effect on viral replication.
Novel Agents for COVID-19

• There are no evidenced-based therapies for SARS-CoV-2 infection or COVID-19.

• Anti-infectives usually improve outcome in ARDS/Sepsis – trials ongoing

• Speculative approaches:
  • Anti-cytokine therapies – failed already in sepsis/ARDS
  • Anticoagulation – failed already in ARDS
  • Steroids – failed in late ARDS, harm in flu, SARS, MERS

Care for COVID-19 will be largely supportive
Cornerstones of ARDS Management

- Low $V_t$ Vent
- Conservative Fluid Management
- Optimize Mechanics

Increasing Strength of Evidence
Cornerstones of ARDS Management

- Optimize Mechanics
- Conservative Fluid Management
- Low $V_t$ Vent

Increasing Strength of Evidence
“Lung Protective” Ventilation

Add PEEP

Limit Distending Pressure

Volume

Pressure
Probability of Survival and of Being Discharged Home and Breathing without Assistance during the First 180 Days after Randomization in Patients with Acute Lung Injury and the Acute Respiratory Distress Syndrome.

NNT = 10
Airway pressure and Volume Limited Strategy

Vt 6 ml/kg Predicted Body Weight was reduced to a min of 4 ml/kg if Pplat > 30

Initial Vt 4-6 ml/kg PBW
Initial PEEP 8-10
Reduce Vt, PEEP as needed to reach Pplat<30
Low tidal volume ventilation is not free

• High respiratory drive and low minute ventilation = dysynchrony

• Trade off is vent compliance vs sedation
• Low $V_t$ will require sedation/paralytic
• Low $V_t$ is the single most established therapy in all of critical care
• Okay to increase sedation:
  • Propofol
  • Dilaudid (fent,morphine)
  • Midaz (Ketamine)
  • Paralytics prn
Driving Pressure

\[ \Delta P = P_{\text{plat}} - \text{PEEP}. \]

Since \( C_{rs} = \frac{V_t}{\Delta P} \), \( \Delta P \) is tidal volume scaled by compliance.
PEEP Titration Methods

• Multiple methods published
• None superior
• Likely harm associated with aggressive recruitment in unselected patients (ART). Avoid repeated recruitment maneuvers
• COVID-19 Pts so far with relatively preserved mechanics
• Can optimize PEEP via ARDSnet table:

<table>
<thead>
<tr>
<th>FiO₂</th>
<th>0.3</th>
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<th>0.4</th>
<th>0.5</th>
<th>0.5</th>
<th>0.6</th>
<th>0.7</th>
<th>0.7</th>
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<td>5</td>
<td>8</td>
<td>8</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>12</td>
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<table>
<thead>
<tr>
<th>FiO₂</th>
<th>0.7</th>
<th>0.8</th>
<th>0.9</th>
<th>0.9</th>
<th>0.9</th>
<th>1.0</th>
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<tbody>
<tr>
<td>PEEP</td>
<td>14</td>
<td>14</td>
<td>14</td>
<td>16</td>
<td>18</td>
<td>18-24</td>
</tr>
</tbody>
</table>
What about Prone?
~17 hrs/day of Prone for ~4 days versus low Vt and low PEEP

P<0.001

Guerin NEJM 2013
Prone positioning improves survival in severe ARDS: a pathophysiologic review and individual patient meta-analysis

L. GATTINONI 1, 2, E. CARLESSO 2, P. TACCONE 1, F. POLLI 2, C. GUÉRIN 3, J. MANCEBO 4

| Table II. — Mortality rate of patients with severe hypoxemia (i.e., PaO₂/FIO₂ < 100 mmHg) in the different trials (prone vs. supine group). |
|---------------------------------|---------------------------------|---------------------------------|---------------------------------|
|                                | Prone vs. Supine               | Prone vs. Supine               | Prone vs. Supine               | Prone vs. Supine               |
| N. of patients                 | 74 vs. 76                       | 43 vs. 29                       | 90 vs. 75                       | 53 vs. 46                       |
| 28-day mortality               | 37.8% vs. 46.0%                 | 41.9% vs. 58.6%                 | 47.8% vs. 53.3%                 | 60.4% vs. 65.2%                 |
| ICU Mortality                  | +8% vs. 55.3%                   | +17% vs. 65.5%                  | +6% vs. 61.3%                   | +5% vs. 65.2%                   |
| Last follow-up mortality       | +8% vs. 63.2%                   | +17% vs. 72.4%                  | +6% vs. 65.3%                   | +5% vs. 76.1%                   |

Minerva Anestesiologica 2010
Prone positioning reduces mortality from acute respiratory distress syndrome in the low tidal volume era: a meta-analysis
Prone Position

• Protocol available on Apollo
• Safe with few contraindications (unstable spine, sternum)
• Consider early, P:F < 150 and not responding to initial attempts to set PEEP
• Longer periods in prone are safe and effective – re-supine qAM, less frequently if labile
• If P:F > 150 mmHg on 10 or less of PEEP after 2hrs supine can leave supine
• Consider PEEP adjustment prior to supine attempt
Prone Position

- Prone position only shown to benefit with low Vt vent
- Large percentage of COVID-19 getting proned in ICU
- But...safe, many centers experimenting in non-intubated
- MGH protocol for non-intubated patients approved this week and available on Apollo:
  - 1 hr prone on admit, RR, SpO2, L/min pre and post
  - Encourage prone “more often than not” thereafter
  - Escalating O2 – 1 hr prone, mandatory 1 hr re-assess
Volume Overload is Harmful in ARDS

• High pulmonary vascular pressures and flow
  • May lead to stress failure of capillaries
• Reduction in PAOP a/w improved survival
• EVLW targeted therapy a/w less fluid administration and improved survival
• Hypoproteinemia a/w ARDS and mortality in sepsis
• Diuresis after shock reversal shortens time on vent

Conservative 25.5%
Liberal 28.4% p=0.3

3.2 fewer days on vent in survivors (p<0.001)
FACTT: Protocol...short form

• When shock-free -> Post-resuscitation fluid management
  • No maintenance fluids
  • Diuretics to *normalize* CVP until off-vent, *as tolerated*
  • Hold diuretic for rising creatinine and/or active urine sediment
  • If patient becomes hypotensive with small increases in PEEP consider hypovolemia.
**Shock in COVID-19**

- Management is not different than usual distributive shock (levo/vaso, assess for fluid responsiveness)
- Comparatively little multiple organ failure:

### Wuhan

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Wuhan</th>
<th>Shanghai</th>
<th>Beijing</th>
</tr>
</thead>
<tbody>
<tr>
<td>High flow nasal cannula</td>
<td>17(85)</td>
<td>16(50)%</td>
<td>33(63)%</td>
</tr>
<tr>
<td>Mechanical ventilation</td>
<td>7(35)</td>
<td>30(94)%</td>
<td>37(71)%</td>
</tr>
<tr>
<td>Non-invasive</td>
<td>6(30)</td>
<td>23(72)%</td>
<td>29(56)%</td>
</tr>
<tr>
<td>Invasive</td>
<td>3(15)</td>
<td>19(59)%</td>
<td>22(42)%</td>
</tr>
<tr>
<td>Prone position ventilation</td>
<td>2(10)</td>
<td>4(13.5)%</td>
<td>6(11.5)%</td>
</tr>
<tr>
<td>Extracorporeal membrane oxygenation</td>
<td>1(5)</td>
<td>5(16)%</td>
<td>6(11.5)%</td>
</tr>
</tbody>
</table>

### Seattle

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Wuhan</th>
<th>Seattle</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vasopressors</td>
<td>17/24(71)</td>
<td>9/24(38)</td>
</tr>
<tr>
<td>Echocardiogram completed</td>
<td></td>
<td>0/9</td>
</tr>
<tr>
<td>Echocardiogram showing new left ventricular dysfunction</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- Variable reports of late myocarditis (7% in one Chinese series)
- Diagnostic criteria not clearly met (“By review of chart”)
- One MGH case now on VA ECMO with isolated cardiogenic shock
- Consider CvO2, EKG, lactate, exam, POCUS is new shock

Lancet Respir Med 2020
Above all, **BE PATIENT**....in the H1N1 outbreak a substantial proportion of patients were still intubated at 14 days. 10 days in Seattle. There is no magic bullet: Intubate, PEEP, prone and wait

Supportive care works – Currently > 70 intubated patients. To date, 8 discharges, only 1 death

Hold the line – as long as we have vents and N95’s we will get patients better

• **Standard lung protective ventilation:** $V_t \ 4\text{-}6\text{ml/kg PBW};$ focus on goals: $P_{\text{plat}} < 30$, $D\Delta P < 15$

• **Low PEEP** ARDSnet okay

• **Prone early, prone long**

• **Most shock** is distributive $>$ standard rx

• **R/O** cardiogenic

• **Conservative fluid management** when out of shock

• **Therapeutics unproven,** best in context of trial
MGH Protocol for management of COVID-19:


MGH Protocol for Prone Ventilation:

Questions?