GRAND ROUNDS

Acute Respiratory Distress Syndrome, Interleukin-6, and Cytokine Storm Induced by COVID-19

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APRIL 8, 2020 from 12-1:30pm
Remember when ... (Pulmonary Edition)?

- EVALI – Vape Lung
- Oz Bushfires
- Worst influenza season in a decade
COVID-19 Pneumonia → ARDS → MOF → Death
## ARDS Berlin Criteria vs. Endophenotypes for Prognostic/Predictive Enrichment

<table>
<thead>
<tr>
<th>Clinical Feature</th>
<th>ARDS Definition</th>
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<tbody>
<tr>
<td><strong>Timing</strong></td>
<td>Within 1 week of inciting event or symptom onset</td>
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<td><strong>Imaging</strong></td>
<td>Bilateral opacities not fully explained by effusions, atelectasis, or nodules</td>
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<td><strong>Origin of edema</strong></td>
<td>Respiratory failure not fully explained by cardiac failure or fluid overload</td>
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<td><strong>Oxygenation</strong></td>
<td><strong>MILD</strong>: 201-300 mmHg <strong>MODERATE</strong>: 101-200 mmHg <strong>SEVERE</strong>: ≤ 100 mmHg</td>
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### Inflammatory Endophenotypes

- **Phenotype-1:** Hypoinflammatory 90d MR ~20%
  - ↓IL-6, IL-8
  - INF-g, Ang1/Ang2, PAI-1
  - sTNFr-1
  - HCO$_3^\text{-}$
  - Vasopressors

- **Phenotype-2:** Hyperinflammatory 90d MR ~40%

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VM Ranieri ARDS Definition Task Force, JAMA 2012  
CS Calfee Lancet Respir Med 2014  
KR Famous AJRCCM 2017  
CS Calfee Lancet Respir Med 2018
Clinical Spectrum of COVID-19 Infection

**Stage I** (Early Infection)
- Viral response phase
- Clinical Symptoms: Mild constitutional symptoms (Fever >99.6°F, Dry Cough, diarrhea, headache)
- Clinical Signs: Lymphopenia, increased prothrombin time, increased D-Dimer and LDH (mild)
- Potential Therapies: Remdesivir, chloroquine, hydroxychloroquine, convalescent plasma transfusions, Reduce immunosuppression

**Stage II** (Pulmonary Phase)
- IIA
- IIB
- Host inflammatory response phase
- Shortness of Breath Hypoxia (PaO2/FIO2≤300mmHg)
- Abnormal chest imaging Transaminitis Low-normal procalcitonin
- Elevated inflammatory markers (CRP, LDH, IL-6, D-dimer, ferritin) Troponin, NT-proBNP elevation

**Stage III** (Hyperinflammation Phase)
- ARDS SIRS/Shock Cardiac Failure

Time course

Severity of Illness
Admit 2/20-3/18/2020  N=1581 ICU Pt  72 hospitals

Died in ICU 405 (26%)
Discharge from ICU 256 (16%)
In ICU 3/25/2020 920 (58%)
ICU LOS (median/IQR) 9 (6-13)
Invasive/NIV ventilation (data from 1300 pt) IV: 1150 (88%) NIV: 137 (11%)

- 16 ARDS pt: Severe hypoxemia, unusually compliant lungs.
  - Cst $50.2 \pm 14.3$ ml/cmH2O
  - Qs/Qt $0.50 \pm 0.11$.
  - loss of lung perfusion regulation and hypoxic vasoconstriction.

G. Grasselli, JAMA 2020
Pulmonary Pathology: SARS-CoV-2 COVID19 - ARDS

- 50yo M – Wuhan. Died d14 after refusing intubation (HFNC only)
- Diffuse alveolar damage
  - Cellular fibromyxoid exudates.
  - Desquamation of pneumocytes.
  - Hyaline membrane formation.
- Interstitial mononuclear inflammatory infiltrates, (++lymphocytes).
- Multinucleated syncytial cells
- Atypical enlarged pneumocytes large nuclei, amphophilic granular cytoplasm, prominent nucleoli in the intraalveolar spaces, → viral CPE.
- No intranuclear/intracytoplasmic viral inclusions
- FEATURES VERY SIMILAR TO SARS and MERS

Zhe Xu, Lancet Respir Med 2020
COVID-19 Pneumonia/ARDS - Subtypes

“Type L” 70%: $\text{PaO}_2/\text{FiO}_2 = 95$

- Low elastance;
- Low VA/Q ratio
- Low lung weight;
- Low lung recruitability

“Type H” 30%: $\text{PaO}_2/\text{FiO}_2 = 84$

- High elastance,
- High right-to-left shunt
- High lung weight,
- High lung recruitability

Gattinoni L. et al. (2020) Intensive Care Medicine
Clinical Pathophysiology of Sepsis ARDS

Bacterial Sepsis ARDS
Alveolar Type I and II death

- Endothelial injury, microthrombosis
- Immunothrombosis: Thrombin $\rightarrow$ PAR-1 $\rightarrow$ TREM $\rightarrow$ cytokine storm
- Fibrinolysis Shutdown: PAI-1 $\rightarrow$ tPA

SARS-CoV2 ARDS

MA Matthay, Nat Rev Dis Primers. 2019

EE Moore, J. Trauma Acute Care Surgery, 2020
Microvascular “immunothrombosis” in COVID-19 ARDS

Extensive pulmonary hemorrhagic changes and infarction.
Microthrombi occluding the pulmonary vasculature.
Inflammation in COVID-19 ARDS
Endothelial/microvascular Injury in C-19 ARDS – Clinical Correlations

Potential mechanisms contributing loss of pulmonary microvascular autoregulation

Pulmonary Vasodilation

“L” Phenotype

Worsening Pneumonitis

“H” Phenotype
Form of Macrophage Activation Syndrome?
(2ndry HLH – virus triggered)
- Unremitting fever
- Cytopenias
- ↑ IL-6
- ↑ IL-2, IL-7, GMCSF, INF-γ, IP10, MCP-1, MIP 1-α, and TNF-α.
- ↑ Ferritin (1298 non-survivors vs 614 ng/ml survivors; p<0.001)
- Pulmonary involvement (incl. ARDS)

"Cytokine Storm" in COVID-19

"Henson Hypothesis": Resident vs. Recruited Lung МΦ

SF. Pedersen, YC Ho J Clin Invest. 2020
Time course of BAL IL-6 ARDS, PNA, CHF

- ▲: primary ARDS
- ■: primary pneumonia
- ●: cardiogenic edema

H. Schütte, Eur Respir J. 1996

WY Park, (T. Martin) AJRCCM 2001
## Management Approaches

### “Conventional” Septic ARDS

- HFNC O₂, possibly NIV
- Lung Protective MV
  - Lower VT < 6mL/kg PBW
  - Low PEEP/FiO₂ ARDSnet ladder
- Oxygenation Targets?
- Prone Position ventilation, later. (Early @ DH)
- Recruitment maneuvers
- Corticosteroids controversial
- Inhaled pulmonary vasodilator discouraged
- ECLS – vvECMO ???
- Aggressive Weaning and Liberation on lower PEEP

### COVID-19 ARDS

- Avoid NIV, ?HFNC
- Lung Protective MV
  - Lower VT < 6mL/kg PBW
  - High PEEP/FiO₂ ARDSnet ladder
- Oxygenation Targets?
- Prone Position ventilation, early, (FiO₂>60%, PEEP>10, prolonged)
- Corticosteroids contraindicated
- Consider Inhaled pulmonary vasodilator for L type
- ECLS – vvECMO. Too resource intensive
- Caution Weaning on higher PEEP;
- Pre-liberation PSV 0, PEEP 0 for 30min.
Albert Camus “La Peste”

“I have no idea what's awaiting me, or what will happen when this all ends. For the moment I know this: there are sick people and they need curing.”

“What’s true of all the evils in the world is true of plague as well. It helps (wo)men to rise above themselves.”