Pathogenesis and Management of ARDS

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Conflicts of Interest:

bioMerieux/Biofire

Curetis
Pathogenesis and Management of COVID-19 ARDS

- The most common and most lethal complication of SARS-CoV-2 infection is acute hypoxemic respiratory failure
  - Acute cardiomyopathy much less than early reports
  - AKI common but not as lethal
  - Multiple effects on long term morbidity

- Management of COVID-19 pneumonia/ARDS has a major impact on outcomes independent of pharmacologic manipulations
  - Data collection for interventions in hospitalized patients with COVID-19 should include non-pharmacologic management
    - Precedent set with ARDS studies – mandate or record whether following LTVV strategy
Dexamethasone in Hospitalized Patients with Covid-19 — Preliminary Report

The RECOVERY Collaborative Group

- Controlled, open-label trial
- Dexamethasone 6mg PO/IV daily x10
- Randomized to other active treatments as well
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Pathogenesis and Management of COVID-19 ARDS

• While ordinal, the COVID-19 scale is not proportional
  • Correctly get the important transition for inpatients at the need for more than low flow nasal cannula
    – Previously required ICU transfer
    – Subjective decisions
    – HFNC not available everywhere; shortages
    – Benefit-risk of noninvasive ventilation unknown, especially early in pandemic

• Critical issue is threshold for intubation
  – Early – concern for rapid deterioration
  – Late – concern for high mortality with ventilation
    • Limited ventilator availability
    • Excessive mortality in overwhelmed healthcare systems thought to be baseline – promulgated by social media

Late breached standard critical care teaching – is COVID-19 really different or not?

<table>
<thead>
<tr>
<th>Patient State</th>
<th>Descriptor</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uninfected</td>
<td>No clinical or virological evidence of infection</td>
<td>0</td>
</tr>
<tr>
<td>Ambulatory</td>
<td>No limitation of activities</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Limitation of activities</td>
<td>2</td>
</tr>
<tr>
<td>Hospitalized</td>
<td>Hospitalized, no oxygen therapy</td>
<td>3</td>
</tr>
<tr>
<td>Mild disease</td>
<td>Oxygen by mask or nasal prongs</td>
<td>4</td>
</tr>
<tr>
<td>Hospitalized</td>
<td>Non-invasive ventilation or high-flow oxygen</td>
<td>5</td>
</tr>
<tr>
<td>Severe Disease</td>
<td>Intubation and mechanical ventilation</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>Ventilation + additional organ support – pressors, RRT, ECMO</td>
<td>7</td>
</tr>
<tr>
<td>Dead</td>
<td>Death</td>
<td>8</td>
</tr>
</tbody>
</table>
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Is COVID-19 ARDS or not?

- Obvious answer is **yes**: meets all components or most recent syndrome definition (Berlin criteria)
  - Earliest versions included a compliance measurement = “stiff” lungs
- Early noted many patients with COVID-19 pneumonia had normally compliant lungs despite severe hypoxemia
- **Recruitability** – very beneficial effect of proning which is often not practiced outside of academic centers in US

Camporota et al, Lancet Respir Med, 2020
Prevention of Self-Induced Lung Injury (S-ILI) in COVID-19 Pneumonia/ARDS

- Early intubation – many have significant role in preventing low compliance phenotype
- Avoiding noninvasive ventilation
- Optimizing ventilator settings
- Neuromuscular blockade
- High levels of sedation

- Not clear what stimulates excessive respiratory drive and what limits protective reflexes
- Appears unique to some types of viral pneumonia

Seem to correlate with pro-inflammatory biomarkers

Brochard et al, AJRCCM, 2017
• Steroids benefited ARDS for high tidal volume-induced lung injury
• Maybe benefit of steroids has nothing to do with anti-inflammatory, anti-cytokine strategy
  – Worse outcomes in NMH cohort but baseline mortality in 15-20% range
  – Failure of anti-IL6r strategies would be explained
Bacterial Co-infection in Initial BALs of COVID-19 Pneumonia/ARDS Patients

• Roughly 20% of COVID-19 patients have bacterial pneumonia at the time of intubation

• Usual Cap pathogens are the most common etiologies of bacterial superinfection in COVID-19
Proportion of Cell Types in Early COVID-19 BALs
Within 48 hours of Intubation

- SARS-CoV-2 has a disproportionate enrichment of lymphocytes in BAL
BAL cell types by flow cytometry

https://www.biorxiv.org/content/10.1101/2020.08.05.238188v1
SARS-CoV-2 CAN infect macrophages and monocytes

SARS-CoV-2 antisense RNA as well as sense

https://www.biorxiv.org/content/10.1101/2020.08.05.238188v1
Pathogenesis and Management of COVID-19 ARDS

- Mortality and changes in the ordinal scale are dependent on non-pharmacologic management of severe COVID-19 pneumonia

- Interventional trials that seek to specifically impact the severe end of the COVID-19 pneumonia spectrum face significant challenges to dissect signal from noise
  - Effect of these non-randomized issues are more likely in smaller studies and in those from very heterogeneous centers
  - If unable to be standardized, data on management should at least be recorded

- Examples of strategies:
  - Time from need for more than simple nasal cannula to intubation
  - Tidal volume/PEEP/FiO₂
“An expert is a person who has made all the mistakes that can be made in a very narrow field”

Niels Bohr