COVID19 and Pulmonary Embolism

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COVID19

- Pathological features
- Macro vs Micro
- Serological markers
- Epidemiology
- Case presentations
COVID19

- Pathological features
  - Macro vs Micro
  - Serological markers
  - Epidemiology
  - Case presentations
Alveolar fibrin in COVID19-ARDS (like most ARDS)

Small *in situ* thrombosis in COVID19-ARDS

Big RV dilatation in COVID19-ARDS

In situ arteriolar thrombosis in COVID19-ARDS

Angiitis in COVID-19-ARDS

Angiitis/angiogenesis in COVID19

COVID19

- Pathological features
- Macro vs Micro
- Serological markers
- Epidemiology
- Case presentations
Macro vs Micro Thrombosis

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Inflammation and Hypoxia lead to Thrombosis

• The Coagulation system evolved as an effector pathway of the immune response
  – Neutrophils release NETs to trap bacteria but also lead to platelet aggregation
  – Fibrin is laid down to entrap infected cells/bacteria

Inflammation and Hypoxia lead to Thrombosis

• The Coagulation system evolved as an effector pathway of the immune response
  – Neutrophils release NETs to trap bacteria but also lead to platelet aggregation
  – Fibrin is laid down to entrap infected cells/bacteria
• Hypoxia, via hypoxia-inducible transcriptions factors, lead to prothrombotic state

Evans CE. Hypoxia and HIF activation as a possible link between sepsis and thrombosis. Thrombosis Journal. 2019;17.
Inflammation and Hypoxia lead to Thrombosis

- Endothelial dysfunction can further impair vascular tone and drive more thrombosis
  - Endothelial injury releases tissue factor resulting in thrombin activation

Microthrombosis vs. Macrothrombosis in COVID-19
High Compliance, High Dead Space Phenotype of COVID-19 ARDS

Is C-ARDS really that different from ARDS?

Viewpoint

COVID-19-associated acute respiratory distress syndrome: is a different approach to management warranted?

Eddy Fan, Jeremy R Beitler, Laurent Brochard, Carolyn S Calfee, Neill D Ferguson, Arthur S Slutsky, Daniel Brodie

The COVID-19 pandemic has seen a surge of patients with acute respiratory distress syndrome (ARDS) in intensive care units across the globe. As experience of managing patients with COVID-19-associated ARDS has grown, so too have efforts to classify patients according to respiratory system mechanics, with a view to optimising ventilatory management. Personalised lung-protective mechanical ventilation reduces mortality and has become the mainstay of treatment in ARDS. In this Viewpoint, we address ventilatory strategies in the context of recent discussions on phenotypic heterogeneity in patients with COVID-19-associated ARDS. Although early reports suggested that COVID-19-associated ARDS has distinctive features that set it apart from historical ARDS, emerging evidence indicates that the respiratory system mechanics of patients with ARDS, with or without COVID-19, are broadly similar. In the absence of evidence to support a shift away from the current paradigm of ventilatory management, we strongly suggest that the lung-protective approach to mechanical ventilation in COVID-19 remains the most rational approach to management.

“Reports of phenotypic heterogeneity in patients with COVID-19-associated ARDS, although interesting, could easily be over-interpreted or inappropriately applied in the intensive care unit, potentially leading to detrimental ventilatory management strategies in these patients.”

Bleeding and Clotting in COVID-19

400 hospital-admitted patients with COVID-19 (144 critically ill)

Confirmed VTE

Overall bleeding events

Predictors of Thrombosis

Predictors of Bleeding

Overall thrombotic complications

9.5%
18.1% critically ill

Major Bleeding

5.6%
2.3% critically ill

There are over 30 currently enrolling clinical trials for anticoagulation paradigms in COVID-19

<table>
<thead>
<tr>
<th>Study acronym of PI</th>
<th>Trial ID</th>
<th>Source registry</th>
<th>Countries</th>
<th>Date of registration</th>
<th>Estimated study completion date</th>
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<td>COVID-HEP</td>
<td>NCT04345848</td>
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<td>Berger et al.</td>
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<td>REMAP-CAP</td>
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<td>Abaghdadi et al.</td>
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<td>COVID-19 HD</td>
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<td>June 2021</td>
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<td>COVI-DOSE</td>
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<td>November 2020</td>
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<td>Heparin-SARS-CoV2</td>
<td>EUCTR2020- 001891-14-E5</td>
<td>EU Clinical Trials Register</td>
<td>Spain</td>
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<td>Not provided</td>
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<tr>
<td>Perep et al.</td>
<td>NCT04320824</td>
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<td>Austria</td>
<td>10 April 2020</td>
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</table>

Operation Warp Speed: ACTIV-4 Anti-thrombotics

• ACTIV-4 Inpatient Protocol
  – Therapeutic vs. Prophylactic anticoagulation
  – 2000 Hospitalized patients
  – Primary Endpoint: 21 Day Organ Support (respiratory or vasopressor) Free Days
  – Secondary Endpoint: Composite endpoint of death, pulmonary embolism, systemic arterial thromboembolism, myocardial infarction, or ischemic stroke at hospital discharge or 28 days
  – Anticipated study completion by March 2021

• ACTIV-4 Inpatient Protocol (ASA/Apixiban/Placebo; 7000 patients)

• ACTIV-4 Convalescent Protocol
COVID19

• Pathological features
• Macro vs Micro
• Serological markers
• Epidemiology
• Case presentations
# APL antibodies with COVID19

<table>
<thead>
<tr>
<th>aPL antibody</th>
<th>Number positive (manufacturer’s cut-off)</th>
<th>%</th>
<th>Number positive (titer ≥40 units)</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>aCL IgG</td>
<td>8</td>
<td>4.7%</td>
<td>2</td>
<td>1.2%</td>
</tr>
<tr>
<td>aCL IgM</td>
<td>39</td>
<td>23%</td>
<td>13</td>
<td>7.6%</td>
</tr>
<tr>
<td>aCL IgA</td>
<td>6</td>
<td>3.5%</td>
<td>1</td>
<td>0.58%</td>
</tr>
<tr>
<td>αβ2GPI IgG</td>
<td>5</td>
<td>2.9%</td>
<td>3</td>
<td>1.7%</td>
</tr>
<tr>
<td>αβ2GPI IgM</td>
<td>9</td>
<td>5.2%</td>
<td>7</td>
<td>4.1%</td>
</tr>
<tr>
<td>αβ2GPI IgA</td>
<td>7</td>
<td>4.1%</td>
<td>3</td>
<td>1.7%</td>
</tr>
<tr>
<td>aPS/PT IgG</td>
<td>42</td>
<td>24%</td>
<td>21</td>
<td>12%</td>
</tr>
<tr>
<td>aPS/PT IgM</td>
<td>31</td>
<td>18%</td>
<td>21</td>
<td>12%</td>
</tr>
<tr>
<td>any positive aPL</td>
<td>89</td>
<td>52%</td>
<td>52</td>
<td>30%</td>
</tr>
</tbody>
</table>

But lots of viral infections have APL Ab

<table>
<thead>
<tr>
<th>Infection type</th>
<th>No. of positive patients/total (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Anticardiolipin antibodies</strong></td>
<td></td>
</tr>
<tr>
<td>HIV + no OI ($n=19$)</td>
<td>840/1499a (56)</td>
</tr>
<tr>
<td>HIV + all combined OI ($n=6$)</td>
<td>193/306 (63)</td>
</tr>
<tr>
<td>Hepatitis C virus ($n=20$)</td>
<td>368/1785 (21)</td>
</tr>
<tr>
<td>Hepatitis B virus ($n=9$)</td>
<td>93/483 (19)</td>
</tr>
<tr>
<td>Epstein-Barr virus ($n=4$)</td>
<td>68/137 (50)</td>
</tr>
<tr>
<td>Human T-lymphotropic virus type 1 ($n=3$)</td>
<td>31/191 (16)</td>
</tr>
<tr>
<td>Hepatitis A virus ($n=1$)</td>
<td>2/2 (100)</td>
</tr>
<tr>
<td>Human herpesvirus type 6 ($n=1$)</td>
<td>19/32 (59)</td>
</tr>
<tr>
<td>Lymphotropic viruses ($n=1$)</td>
<td>8/20 (40)</td>
</tr>
<tr>
<td>Parvovirus B19 ($n=1$)</td>
<td>8/60 (13)</td>
</tr>
<tr>
<td>Varicella zoster virus ($n=1$)</td>
<td>8/12 (67)</td>
</tr>
</tbody>
</table>

Viral-associated APL Ab aren’t necessarily associated with VTE

APL antibodies in COVID19 are mostly in the first week or two.

Persistent ACL and A-PT Ab are associated with VTE

<table>
<thead>
<tr>
<th>APLA subtype</th>
<th>Persistent</th>
<th>Persistent or transient</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR (95% CI)</td>
<td>P</td>
</tr>
<tr>
<td>ACLA IgG</td>
<td>10.0 (1.8-56)</td>
<td>.013</td>
</tr>
<tr>
<td>ACLA IgM</td>
<td>32.7 (4.2-256)</td>
<td>.001</td>
</tr>
<tr>
<td>Anti-β2-GPI IgG</td>
<td>17.3 (2.0-116)</td>
<td>.005</td>
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<tr>
<td>Anti-β2-GPI IgM</td>
<td>6.7 (1.2-37)</td>
<td>.036</td>
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<tr>
<td>Anti-PT IgG</td>
<td>3.5 (0.7-19)</td>
<td>.155</td>
</tr>
<tr>
<td>Anti-PT IgM</td>
<td>3.6 (0.3-46)</td>
<td>.358</td>
</tr>
</tbody>
</table>

Laboratory criteria for antiphospholipid syndrome

1. Lupus anticoagulant (LA) present in plasma, on two or more occasions at least 12 weeks apart.

2. Anticardiolipin (aCL) antibody of IgG and/or IgM isotype on two or more occasions, at least 12 weeks apart.

3. Anti-b2 glycoprotein-I antibody of IgG and/or IgM isotype on two or more occasions at least 12 weeks apart.

COVID19

- Pathological features
- Macro vs Micro
- Serological markers
- Epidemiology
- Case presentations
High incidence of PE among COVID19 who get scanned

How many COVID19 patients didn’t get CT scans?

1500 Consecutive CTPA scans performed from 3/16/2020 – 4/18/2020 Across multiple hospitals

73 (22%) COVID19 with Acute PE

256 (78%) COVID19 without Acute PE

1171 Excluded

Incidence of PE among COVID-19 patients

- RCTs
- Retrospective review of scans

Wang (n = 233) 0.9%
Beigel (n = 1063) 0.6%
Bavaro (n = 20) 40.0%
Bompard (n = 125) 24.0%
Leonard-Lorant (n = 106) 30.0%
Poyiadji (n = 328) 22.0%
Grillet (n = 100) 23.0%
Mazzaccaro (n = 32) 65.6%
COVID19

- Pathological features
- Macro vs Micro
- Serological markers
- Epidemiology

- Case presentations
Case presentations

Daniel Bond, MD
Fellow,
Division of Pulmonary and Critical Care Medicine
University of California, San Diego
Case #1
Case presentation #1

- 53 yo M with history of HTN and HLD who presented to the ED with progressive SOB following recent COVID-19 diagnosis 6 days prior to admission.
Admission vital signs

- T 100.9F
- HR 69
- BP 125/73
- RR 30
- SpO2 94% on RA
- BMI 31.6
Physical exam

- Gen: No acute distress, speaking complete sentences
- CV: Regular rate and rhythm, no murmur, rubs or gallops
- Lungs: Clear bilaterally
- GI: Abdomen soft and non-tender
- Ext: No swelling or erythema
- Skin: No rashes, wounds
Initial labs

- CBC
  - 6.1 > 15.1/45.6 < 158
    - 71% segs, 21% lymph, 8% mono, 0% eos/basophils
- BMP – 136 / 4 / 96 / 26 / 13 / 1.0 < 113
- Liver enzymes – Normal except AST 49, ALT 52
- Pro-BNP – 67 pg/ml (normal 0-899)
- Troponin 5th Gen – 6ng/L (normal <22 ng/L)
- D-Dimer – 221 ng/mL (normal <241ng/mL)
- Rapid Covid-19 Assay - Positive
Hospital course

- Admitted to Medicine and started on Remdesivir
  - initially saturating well on RA, overnight requiring 2-3L via NC to maintain sat >88%
- HD 4 – Increasing oxygen requirement overnight, now requiring NRB
  - Transferred to ICU and started on Dexamethasone 6mg daily
  - Over the next several days remains on NRB with intermittent self proning and occasional desaturations
- HD 9 – Increased WOB and significantly elevated D-dimer

D-Dimer (normal <241 ng/mL)
Next step?

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Case 1, CT slide 1
Case 1, CT slide 2
Case 1, CT slide 3
Hospital course

- Rx Heparin IV
- LE US: No evidence of DVT
- Oxygen gradually weaned down to NC
- HD 11 Transferred out of the ICU
- Transitioned from Heparin to Apixiban
- HD 15 Discharged home on RA
Comments

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Case #2
Case presentation #2

- 34 yo man
  - Poorly controlled non-insulin dependent T2DM
  - HTN
- Transferred from OSH with COVID-19 ARDS for consideration of VV-ECMO
Hospital course

- Admitted to OSH after 1 week of dyspnea

- Received Remdesivir, Dexamethasone and convalescent plasma

- HD 12 Intubated

- HD 15 Transferred to UCSD
Continued

- HD 16 Cannulated for VV-ECMO (P/F = 55)
  - Started on Heparin gtt (goal Xa 0.11-0.3)

- HD 26 Percutaneous tracheostomy
  - HD 26-29 Heparin held due to oozing from trach site

- HD 30-60 Required ECMO flows of ~6L/min and Sweep 6-8 lpm,
  - pulmonary compliance ~10-20 ml/cmH20
HD 57 acute episode of hypotension

- Previously on no vasopressors now requiring norepinephrine 26mcg/min, epinephrine 0.06mcg/kg/min, and phenylephrine 200mcg/min despite IVF boluses

- Unstable for transport
Next step?

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• Concern for possible PE
  • Empiric treatment with therapeutic heparin (Xa 0.2-0.45)
Case 2, CT slide 2
Case 2, CT slide 3
Echocardiogram
Hospital course

- Serial TTE with continued concern for RV thrombus

- Platelets drop from ~250 -> 120 over 4 days
  - PF4 0.446 (normal <0.400 OD) -> transitioned to bivalirudin gtt (Goal PTT 60 to 90 seconds)
Next step?

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Hospital course

- HD 66 - Patient’s left pupil is fixed and dilated
Hospital course

- HD 71 – Transitioned to Comfort Care
Comments

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