Anticoagulation for COVID-19

WEBINAR
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Chief, Division of Hospital Medicine
Chair, MSHS Anticoagulation Committee
Mount Sinai health System, NY
Thrombosis in COVID

- Elevated markers and anecdote
- Autopsy data
- Hospital-acquired VTE
- Management challenging
  - Poor evidence
  - Testing often not done due to infectious risk
  - Role of microthrombi
Autopsy Data

Hamburg, N=12
DVT 7/12 (58%)
PE cause of death 4/12 (33%)

Diffuse alveolar damage, inflammatory infiltrates hyaline membranes, capillary congestion, interstitial edema, microvascular thromboemboli

Austria, N=11
Pulm thrombi small/med 11/11 (100%)

Diffuse alveolar damage (DAD), edema, hyaline membranes, pneumocytes and fibroblasts, thrombosis of small and mid-sized pulmonary arteries bronchopneumonia

High risk of thrombosis in patients with severe SARS-CoV-2 infection: a multicenter prospective cohort study

Julie Helms¹,², Charles Tacquard³, François Severac⁴, Ian Leonard-Lorant⁵, Mickaël Ohana⁵, Xavier Delabranche³, Hamid Merdji¹,⁶, Raphaël Clere-Jehl¹,², Malika Schenck⁷, Florence Fagot Gandet⁷, Samira Fafi-Kremer²,⁸, Vincent Castelain⁷, Francis Schneider⁷, Lélia Grunebaum⁹, Eduardo Anglès-Cano¹⁰, Laurent Sattler⁹, Paul-Michel Mertes³, Ferhat Meziani¹,⁶* and CRICS TRIGGERSEP Group (Clinical Research in Intensive Care and Sepsis Trial Group for Global Evaluation and Research in Sepsis)

- ICU at 2 hospitals in France
- N=150, UFH/LMWH prophylaxis (80%) or treatment-dose (20%)
- Low threshold for testing

<table>
<thead>
<tr>
<th></th>
<th>Population before matching (n = 383)</th>
<th></th>
<th>Population after matching (n = 222)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Non-COVID-19-ARDS (n = 233)</td>
<td>COVID-19-ARDS (n = 150)</td>
<td>OR [95% IC]</td>
<td>p-value</td>
</tr>
<tr>
<td>Thrombo-embolic complications—n (%)</td>
<td>14 (6)</td>
<td>27 (18)</td>
<td>3.4 [1.7–7.3]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Pulmonary embolisms—n (%)</td>
<td>3 (1.3)</td>
<td>25 (16.7)</td>
<td>15.2 [4.5–80.4]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Deep vein thrombosis—n (%)</td>
<td>3 (1.3)</td>
<td>3 (2)</td>
<td>1 [0.1–9.2]</td>
<td>1</td>
</tr>
<tr>
<td>Myocardial infarction—n (%)</td>
<td>6 (2.6)</td>
<td>0 (0)</td>
<td>0 [0–1.3]</td>
<td>0.09</td>
</tr>
<tr>
<td>Cerebral ischemic attack—n (%)</td>
<td>1 (0.4)</td>
<td>2 (1.3)</td>
<td>3.1 [0.2–185.5]</td>
<td>0.68</td>
</tr>
<tr>
<td>Limb ischemia—n (%)</td>
<td>0 (0)</td>
<td>1 (0.7)</td>
<td>Inf [0–Inf]</td>
<td>0.78</td>
</tr>
<tr>
<td>Mesenteric ischemia—n (%)</td>
<td>3 (1.3)</td>
<td>1 (0.7)</td>
<td>0.5 [0–0.6]</td>
<td>0.98</td>
</tr>
<tr>
<td>Nb of RRT filter per dialyzed patient—median, IQR</td>
<td>1 [2–1]</td>
<td>3 [2–7]</td>
<td>–</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Nb of RRT filter per day of RRT—median, IQR</td>
<td>0.3 [0.3; 0.5]</td>
<td>0.7 [0.5; 1]</td>
<td>–</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ECMO oxygenator thrombosis—n (%)</td>
<td>1/10 (10)</td>
<td>2/12 (16.7)</td>
<td>–</td>
<td>0.59</td>
</tr>
<tr>
<td>Hemorrhagic complications—n (%)</td>
<td>1 (1.8)</td>
<td>4 (2.7)</td>
<td>2.4 [0.27–28.5]</td>
<td>0.6</td>
</tr>
</tbody>
</table>

ARDS, acute respiratory distress syndrome; ECMO, extracorporeal membrane oxygenation; RRT, renal replacement therapy
VTE Incidence

- ICU patients at 2 hospitals in Wuhan, China
- N=48, LMWH prophylaxis
- Screening LE US

- 41/48 DVT (85%)
- Most distal: 36/48 (75%); 5/48 (10%) proximal

VTE Incidence

Pulmonary Embolism or Pulmonary Thrombosis in COVID-19? Is the Recommendation to Use High-Dose Heparin for Thromboprophylaxis Justified?

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- Medical wards, N=388
- Received proph-dose LMWH
- No sx DVT
- Screening done on subset: 0/64 DVT

VTE Incidence

N=198 patients; 123 wards, 75 ICU
- VTE 20%
- Symptomatic VTE 13%

- VTE associated with death (HR, 2.4)
- Incidence higher in ICU than wards at 7 days (26% vs 6%)

Anticoagulant treatment is associated with decreased mortality in severe coronavirus disease 2019 patients with coagulopathy

Ning Tang | Huan Bai | Xing Chen | Jiale Gong | Dengju Li | Ziyong Sun

1786 consecutive patients with COVID-19 entering Tongji hospital

- 1261 classified as mild and moderate COVID-19
- 76 met the exclusion criteria

449 classified as severe COVID-19

- 99 with heparin treatment for 7 d or longer
- 350 without heparin treatment or treating less than 7 d

30 died within 28 d

104 died within 28 d
# Heparin and Mortality

<table>
<thead>
<tr>
<th>Patients with</th>
<th>28-day mortality</th>
<th>Univariate analysis</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Treating with heparin, %</td>
<td>Nontreating with heparin, %</td>
</tr>
<tr>
<td>SIC score ≥ 4 (n = 97)</td>
<td>40.0</td>
<td>64.2</td>
</tr>
<tr>
<td>SIC score ≤ 4 (n = 352)</td>
<td>29.0</td>
<td>22.6</td>
</tr>
<tr>
<td>D-dimer ≤ 1 ULN (n = 34)</td>
<td>33.3</td>
<td>9.7</td>
</tr>
<tr>
<td>D-dimer &gt; 1 ULN (n = 415)</td>
<td>30.2</td>
<td>32.7</td>
</tr>
<tr>
<td>D-dimer &gt; 2 ULN (n = 317)</td>
<td>32.1</td>
<td>36.9</td>
</tr>
<tr>
<td>D-dimer &gt; 3 ULN (n = 253)</td>
<td>31.1</td>
<td>42.5</td>
</tr>
<tr>
<td>D-dimer &gt; 4 ULN (n = 224)</td>
<td>33.3</td>
<td>44.5</td>
</tr>
<tr>
<td>D-dimer &gt; 5 ULN (n = 190)</td>
<td>34.9</td>
<td>48.8</td>
</tr>
<tr>
<td>D-dimer &gt; 6 ULN (n = 161)</td>
<td>32.8</td>
<td>52.4</td>
</tr>
<tr>
<td>D-dimer &gt; 8 ULN (n = 150)</td>
<td>33.3</td>
<td>54.8</td>
</tr>
</tbody>
</table>

Observational Study - JACC

### Academic Medical Centers – A Spectrum

- **Academic med centers – Developed internal guidelines**
- **Spectrum - Based on severity: D-dimer, subjective assessment, ward/ICU**

<table>
<thead>
<tr>
<th>Standard VTE prophylaxis: All patients</th>
<th>Aggressive VTE prophylaxis: Enox 30mg q 12 hr</th>
<th>High-risk: Intermediate-dose anticoagulation</th>
<th>High-risk: Treatment-dose anticoagulation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conservative</td>
<td>Intermediate</td>
<td>Aggressive</td>
<td></td>
</tr>
<tr>
<td>NYH</td>
<td>Cleveland Clinic</td>
<td>UNC</td>
<td>Sinai</td>
</tr>
<tr>
<td>Mass Gen</td>
<td>Northwestern (Wells score)</td>
<td>U Col</td>
<td>Tulane</td>
</tr>
<tr>
<td>Ohio State</td>
<td>Wisconsin (consult Heme)</td>
<td>Michigan (Wells score)</td>
<td>Emery</td>
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<td></td>
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<td></td>
<td>U Penn</td>
</tr>
</tbody>
</table>
Mount Sinai Protocol

All admitted patients with COVID

- Assess VTE risk factors, signs/symptoms of DVT/PE, severity, bleeding risk
- Severity - based on clinician judgment
  - symptoms (worsening dyspnea)
  - signs (e.g., RR >24)
  - oxygen requirement (e.g., ≥6L O2 NC)
  - biomarkers (e.g., D-dimers >1.5 or increasing)
- Increased risk for bleeding - active bleeding, PLT <50K, or INR >1.8
Mount Sinai Protocol - Medicine wards

Without evidence of severe respiratory compromise - Aggressive VTE prophylaxis

- **BMI <40**
  - CrCl >30: Enoxaparin 30 mg SQ Q12H
  - CrCl ≤30: Enoxaparin 30 mg SQ daily; Alternative - heparin 5,000 units SQ Q8hrs

- **BMI ≥40**
  - CrCl >30: Enoxaparin 40 mg SQ Q12H
  - CrCl ≤30: Enoxaparin 40 mg SQ daily; Alternative - heparin 7,500 units SQ Q8hrs
Severe respiratory compromise or worsening respiratory status - Intermediate-dose AC

- Intermediate-dose AC: Enoxaparin 1mg/kg SC q 24hr
- CKD
  - CrCl <30, not on RRT – No dose change
  - RRT – Consider substituting apixaban 2.5mg PO BID
Mount Sinai Protocol - ICU

ICU - Treatment dose anticoagulation

- Enoxaparin 1mg/kg SC q 12hr
- CrCl <30 - IV heparin
- Duration – Treatment-dose anticoagulation for 2 weeks after transfer from ICU
Confirmed VTE - positive diagnostic test

- Treatment dose anticoagulation
  - Treatment-dose apixaban/rivaroxaban - no need to transition from LMWH to oral agent
    - Apixaban dose: 10mg PO BID for 7 days then 5mg PO BID
    - Rivaroxaban dose: 15mg PO BID for 21 days then 20mg daily
  - CrCl <30, including RRT: No adjustment to apixaban needed. Alternative - IVH/warfarin

- Duration – Minimum of 3 months. Total duration based on risk of recurrent VTE and bleeding.
VTE not documented

- If treated empirically with intermediate or treatment-dose anticoagulation - Treatment dose apixaban (5mg PO BID) or rivaroxaban (20mg PO once daily) for 2 weeks
- CKD – If CrCl <30 or RRT, consider apixaban 2.5mg PO BID
Take Home Points

- There is an increased incidence of VTE and likely a role of microthrombi in COVID
- Aggressive VTE prophylaxis is warranted
- Consider intermediate-dose or treatment-dose AC for highest risk patients (decompensating, ICU)
- First, minimize the harm
  - Identify patients at increased risk for bleeding
  - Select based on greatest possible benefit
- Better data is coming!
THANK YOU!