Coagulopathy of COVID-19

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COVID-19: A global crisis
Objectives

• To describe the hypercoagulable state in COVID-19

• To discuss the pathophysiology of the prothrombotic milieu

• To provide guidance on use of D-dimer and anticoagulation prophylaxis and treatment
Risk of thrombosis in pneumonia/ARDS

• Venous thromboembolism (VTE) risk is increased in pneumonias
• Associations noted with SARS-CoV-1 and MERS-CoV
• Risk factors: immobility, mechanical ventilation, central venous access devices, inflammation and infection
Evidence for a hypercoagulable state in COVID-19

• D-dimer as a poor prognostic marker was first brought to notice by Zhou et al (Lancet, March 9th, 2020)
• DIC in COVID-19 patients more frequent in non-survivors (71%) than survivors (0.6%)
• Initially considered a prognostic parameter, warranting enhanced vigilance
• Hypothesis that DIC may not be a concomitant finding but more a pathophysiological process contributing to circulatory and organ failure, especially pulmonary damage
Coagulation parameters in COVID-19

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Normal range</th>
<th>Total (n=183)</th>
<th>Survivors (n=162)</th>
<th>Non-survivors (n=21)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PT (sec)</td>
<td>11.5-14.5</td>
<td>13.7 (13.1-14.6)</td>
<td>13.6 (13.0-14.3)</td>
<td>15.5 (14.4-16.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>aPTT (sec)</td>
<td>29.0-42.0</td>
<td>41.6 (36.9-44.5)</td>
<td>41.2 (36.9-44.0)</td>
<td>44.8 (40.2-51.0)</td>
<td>0.096</td>
</tr>
<tr>
<td>Fibrinogen (g/L)</td>
<td>2.0-4.0</td>
<td>4.55 (3.66-5.17)</td>
<td>4.51 (3.65-5.09)</td>
<td>5.16 (3.74-5.69)</td>
<td>0.149</td>
</tr>
<tr>
<td>D-dimer (μg/mL)</td>
<td>&lt;0.5</td>
<td>0.66 (0.38-1.50)</td>
<td>0.61 (0.35-1.29)</td>
<td>2.12 (0.77-5.27)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>FDP (μg/mL)</td>
<td>&lt;5.0</td>
<td>4.0 (4.0-4.9)</td>
<td>4.0 (4.0-4.3)</td>
<td>7.6 (4.0-23.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>AT (%)</td>
<td>80-120</td>
<td>91 (83-97)</td>
<td>91 (84-97)</td>
<td>84 (78-90)</td>
<td>0.096</td>
</tr>
</tbody>
</table>
What is a D-dimer?
<table>
<thead>
<tr>
<th>Location (first author)</th>
<th>Sample size</th>
<th>D-dimer cut-off for risk assessment</th>
<th>Outcome of interest</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wuhan, China (Zhou et al)</td>
<td>191</td>
<td>&gt;1mcg/ml</td>
<td>Mortality</td>
</tr>
<tr>
<td>Wuhan, China (Yao et al)</td>
<td>248</td>
<td>&gt;2.14 mg/L</td>
<td>Mortality</td>
</tr>
<tr>
<td>Wuhan, China (Zhang et al)</td>
<td>343</td>
<td>&gt;2 mcg/ml</td>
<td>Mortality</td>
</tr>
<tr>
<td>Wuhan, China (Tang et al)</td>
<td>183</td>
<td>N/A (continuous variable)</td>
<td>Mortality</td>
</tr>
<tr>
<td>Mainland China (Guan et al)</td>
<td>1099</td>
<td>N/A (continuous variable)</td>
<td>Severe disease; Primary composite endpoint was admission to ICU/mechanical ventilation or death</td>
</tr>
<tr>
<td>Wuhan, China (Huang et al)</td>
<td>41</td>
<td>N/A (continuous variable)</td>
<td>ICU admission</td>
</tr>
<tr>
<td>Wuhan, China (Wang et al)</td>
<td>138</td>
<td>N/A (continuous variable)</td>
<td>ICU admission</td>
</tr>
<tr>
<td>Wuhan, China (Wu et al)</td>
<td>201</td>
<td>N/A (continuous variable)</td>
<td>ARDS; mortality</td>
</tr>
<tr>
<td>Milan, Italy (Lodigiani et al)</td>
<td>388</td>
<td>N/A (continuous variable)</td>
<td>ICU; mortality</td>
</tr>
<tr>
<td>Beijing, China (Cui et al)</td>
<td>81</td>
<td>&gt;1.5 mcg/ml</td>
<td>VTE</td>
</tr>
<tr>
<td>Strasbourg, France (Leonard-Lorant et al)</td>
<td>106</td>
<td>&gt;2660 mcg/L</td>
<td>Pulmonary embolism</td>
</tr>
</tbody>
</table>
High Risk of Thrombosis in Patients with Severe SARS-CoV-2 Infection

- 4 ICUs at 2 centers in France
- 150 patients (122 males, median age 63), all received anticoagulation (70% prophylactic, 30% therapeutic)
- 64 clinically relevant thrombotic complications
  - 16.7% Pulmonary Embolism
  - 28/29 (96.6%) clotting CRRT circuits
  - 3 thrombotic occlusions of ECMO circuits in 2/12 patients
  - 15% stroke on CT/MRI; 1 acute limb ischemia, 1 mesenteric ischemia

COVID ARDS (n=77) vs. non-COVID ARDS (n=145)
  - PE: 11.7% vs 2.1% OR 6.2 (1.6-23.4) p<0.008
  - VTE: 11.7% vs 4.6% OR 2.6 (1.1-6.1) p=0.035

Despite anticoagulation, a high number of patients with ARDS secondary to COVID-19 developed life-threatening thrombotic complications. Higher anticoagulation targets than usual should probably be suggested.
High incidence of VTE despite thromboprophylaxis

- 198 hospitalized patients, 38% direct ICU admissions
- ALL patients received VTE prophylaxis, weight adjusted (100kg)
- Cumulative incidence of symptomatic VTE:
  
  Day 7: 10% (85% CI 5.8-16)  
  Day 14: 21% (95% CI 14-30)  
  Day 21: 25% (95% CI 16-36)

(Middledorp et al. JTH 2020)
Anticoagulation = Improved outcomes

• 2,773 hospitalized patients in NY
• In hospital mortality 29% on anticoagulation vs 62% without anticoagulation in the mechanically ventilated patients
• Major bleeding 3% versus 1.9%

Paranjpe et al. JACC May 6th, 2020
Anticoagulation = Improved outcomes

Paranjpe et al. JACC. May 6. Mt Sinai, NY
<table>
<thead>
<tr>
<th>Location (first author)</th>
<th>Type of study</th>
<th>Sample size</th>
<th>Use of thromboprophylaxis</th>
<th>VTE incidence</th>
<th>Arterial thrombosis incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wuhan, China (Cui et al)</td>
<td>Retrospective; hospitalized patients</td>
<td>81</td>
<td>No</td>
<td>VTE 25%; all lower extremity thrombi</td>
<td>None</td>
</tr>
<tr>
<td>Netherlands (Klok et al)</td>
<td>Retrospective; multicenter; hospitalized patients</td>
<td>184</td>
<td>Yes (nadroparin at different doses)</td>
<td>VTE (n=28) 27%; of those PE (n=25) was most common finding in 81%</td>
<td>Ischemic strokes (n=3) 3.7%</td>
</tr>
<tr>
<td>Netherlands (Middeldorp et al)</td>
<td>Retrospective; single center; hospitalized patients</td>
<td>198</td>
<td>Yes (nadroparin 2850 units daily for &lt;100 kg and 5700 units daily for &gt;100 kg)</td>
<td>7-day incidence of VTE (15%) and 14-day incidence of VTE (34%)</td>
<td>None</td>
</tr>
<tr>
<td>Italy (Lodigiani et al)</td>
<td>Retrospective; single center; hospitalized patients</td>
<td>388</td>
<td>Yes (LMWH) Ward: 75% used (41% prophylactic dose, 21% intermediate dose; 23% therapeutic dose) ICU: 100% used</td>
<td>VTE 21% (cumulative rate)</td>
<td>Ischemic stroke 2.5% and ACS/MI 1.1%</td>
</tr>
<tr>
<td>France (Llitjos et al)</td>
<td>Retrospective study; 2 ICUs</td>
<td>26</td>
<td>Yes (31% with prophylactic dose and 69% with therapeutic dose)</td>
<td>VTE 69%</td>
<td>None</td>
</tr>
<tr>
<td>France (Helms et al)</td>
<td>Prospective study; COVID-19 ARDS patients at 4 ICUs in 2 centers</td>
<td>150</td>
<td>Yes (LMWH)</td>
<td>PE 16.7%; DVT 2%</td>
<td>Ischemic stroke 1.3%; limb ischemia 0.7%; mesenteric ischemia 0.7%</td>
</tr>
<tr>
<td>France (Poissy et al)</td>
<td>Retrospective case series; ICU</td>
<td>107</td>
<td>Yes</td>
<td>PE (20.6%)</td>
<td>None</td>
</tr>
<tr>
<td>Netherlands (Beun et al)</td>
<td>Retrospective; ICU</td>
<td>75</td>
<td>Unknown</td>
<td>PE (26.6%; 21.3% subsegmental and 5.3% central); DVT 4%</td>
<td>Ischemic stroke 2.7%</td>
</tr>
</tbody>
</table>
Post-mortem evidence of thrombosis in COVID-19

Wichmann De et al. Annal Int Med 2020
Increased incidence of arterial thrombosis

- Arterial events occur as well
- 5 patients (<50 years) presented with sudden large vessel strokes
- Klok FA et al. VTE 27% and 3.7 % arterial events

Oxley TJ et al. NEJM April 28 2020
Klok et al. Thromb Res, 2020
Qian e al. JCVA. doi:10.1053/j.jcva.2020.03.063
## Increased incidence of arterial thrombosis

<table>
<thead>
<tr>
<th>Location (first author)</th>
<th>Type of study</th>
<th>Sample size</th>
<th>Use of thromboprophylaxis (Yes/No/Unknown; drug used, if any)</th>
<th>Arterial thrombosis incidence (w/ type or site)</th>
</tr>
</thead>
<tbody>
<tr>
<td>New York, USA (Oxley et al)</td>
<td>Case series</td>
<td>5</td>
<td>No</td>
<td>Ischemic stroke 5 young patients in 2 week period</td>
</tr>
<tr>
<td>Beijing, China (Zhang et al)</td>
<td>Case series</td>
<td>3</td>
<td>Unknown</td>
<td>Ischemic strokes in 3 patients</td>
</tr>
<tr>
<td>Italy (Bellosta et al)</td>
<td>Observational cohort study</td>
<td>20</td>
<td>25% were on anticoagulation at baseline due to atrial fibrillation</td>
<td>Acute limb ischemia in 20 patients (16.3%)</td>
</tr>
</tbody>
</table>
Microvascular thrombosis

Pulmonary

Renal

Dermal microvasculature

Magro et al. Transl Res. 2020 April 15
Su H et al. Kidney Int. April 9 2020
Ackermann M et al. NEJM 2020
Pathophysiology of hypercoagulable state in COVID-19
SARS-CoV-2 uses ACE2 for cell entry
ACE2 expression is ubiquitous

<table>
<thead>
<tr>
<th>ACE receptor well described</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type II pneumocytes</td>
</tr>
<tr>
<td>Enterocytes of small bowel</td>
</tr>
<tr>
<td>Nasal and oral mucosa</td>
</tr>
<tr>
<td>Kidney</td>
</tr>
<tr>
<td>Myocardium</td>
</tr>
<tr>
<td>Smooth muscle cells and <strong>endothelium</strong> of vessels</td>
</tr>
</tbody>
</table>

Lukassen S, et al. *EMBO* 2020
Physiologic role of endothelium

[Blood (2019) 133 (9): 906–918]
1. Endotheliitis is an early process leading to thrombosis

Varga et al. Lancet 2020 https://doi.org/10.1016/
2. Hyperinflammation in severe COVID-19 leads to immunothrombosis

Siddiqui et al. JHLT May 2020
The lung as the epicenter of COVID-19 induced coagulopathy

Crit Care Med. 2020 May 27; 1097/CCM
3. Complement activation in COVID-19

Risitano et al Nat Rev Immun. 20, 343-344 2020
Complement-mediated microvascular injuries

Pulmonary

Dermal

C5b-9 deposition

Normal adjacent muscle

Magro et al. Transl Res. 2020 April 15
4. Dysregulated renin-angiotensin (RAS)

Vaduganathan et al. NEJM 382"1653-1659
Management: Current guidelines

- ASH (Expert Panel)
- ISTH
  - Recommendations are to give prophylactic anticoagulation to all patients (medical, surgical and obstetric) that are admitted with COVID-19.
  - Intermediate dose and therapeutic AC in ICU patients is controversial
  - Paucity of high quality data; individual institutional protocols have gone into effect.
Management

- For patients already on DOACs:
  - Continue DOACs as outpatient
  - Switch to shorter acting parenteral agents if admitted due to clinical status
  - Important to note significant drug interactions of DOACs with some of the treatments for COVID-19
Management: post discharge

• Routine post-discharge VTE prophylaxis not recommended

• Certain high-risk populations:
  - Modified IMPROVE-VTE score > 4 OR
  - Modified IMPROVE-VTE score > 2 and D-dimer > 2X normal OR
  - Age > 60 years, D-dimer > 2 times normal, and previous VTE or cancer

• Also consider individual patient risk factors, mobility, bleeding risks
Outpatient management of mild COVID-19

• No routine VTE prophylaxis is recommended
• Case by case discussion of the high risk patients should again be considered
### IMPROVE RISK SCORE

<table>
<thead>
<tr>
<th>VTE risk factor</th>
<th>VTE risk score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Previous VTE</td>
<td>3</td>
</tr>
<tr>
<td>Known thrombophilia&lt;sup&gt;a&lt;/sup&gt;</td>
<td>2</td>
</tr>
<tr>
<td>Current lower limb paralysis or paresis&lt;sup&gt;b&lt;/sup&gt;</td>
<td>2</td>
</tr>
<tr>
<td>History of cancer&lt;sup&gt;c&lt;/sup&gt;</td>
<td>2</td>
</tr>
<tr>
<td>ICU/CCU stay</td>
<td>1</td>
</tr>
<tr>
<td>Complete immobilization&lt;sup&gt;d&lt;/sup&gt; ≥ 1 d</td>
<td>1</td>
</tr>
<tr>
<td>Age ≥ 60 y</td>
<td>1</td>
</tr>
</tbody>
</table>

**Abbreviations:** CCU, cardiac care unit; ICU, intensive care unit; IMPROVE, International Medical Prevention Registry on Venous Thromboembolism; NIH, National Institutes of Health; VTE, venous thromboembolism.

<sup>a</sup>A congenital or acquired condition leading to excess risk of thrombosis (e.g., factor V Leiden, lupus anticoagulant, factor C or factor S deficiency).

<sup>b</sup>Leg falls to bed by 5 seconds, but has some effort against gravity (taken from NIH stroke scale).

<sup>c</sup>Cancer (excluding nonmelanoma skin cancer) present at any time in the past 5 years (cancer must be in remission to meet eligibility criteria).

<sup>d</sup>Immobilization is being confined to bed or chair with or without bathroom privileges.

- >4 OR
- 2-3 with D-dimer ≥2 X ULN

Spyropoulos et al. TH Jan 2020
Management: Testing

• All inpatients admitted with COVID-19 should get the following tests daily:
  - CBC with diff
  - PT, INR, PTT
  - D-dimer
  - Fibrinogen

• Institutional protocols are based on D-dimer levels
ANMC COVID19 Thromboprophylaxis Guidelines (5.14.2020)

**History:** Symptoms suggestive of arterial or venous thrombosis

**Physical exam:** Look for signs of arterial or venous thrombosis

**Labs:** Check PT, PTT, Fibrinogen and D-dimer daily

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**No concern for thrombosis and DIC ruled out**

- Other indications for therapeutic anticoagulation.
- High suspicion for DVT/PE but objective documentation cannot be obtained.
- Patients on dialysis with repetitive clotting of dialysis tubing.

**D dimer > 2.5 ug/ml (ANMC test)**

- Enoxaparin 0.5 mg/kg q12 hour (atten: Renal fx)
  OR
  UFH 60 U/Kg bolus then 12 U/kg/hr
  Target Anti-Xa 0.3 - 0.7 U/ml (preferably 0.3 - 0.5 U/ml)

**D dimer < 2.5 ug/ml (ANMC test)**

- **D-dimer (ug/ml)**
  - **Weight (Kg)**
  - **Drug**
  
    | D-dimer (ug/ml) | Weight (Kg) | Drug             |
    |-----------------|-------------|------------------|
    | < 1.0           | *           | Enoxaparin 40 mg Qday |
    | 1 - 2.5         | < 100       | Enoxaparin 30 mg BID |
    |                 | > 100       | Enoxaparin 40 mg BID |

**Confirmed diagnosis of thrombosis**

Treat for thrombosis per guidelines

**Post discharge:**
- Consider Apixaban 2.5 mg BID or Rivaroxaban 10 mg once daily for 30 days or until mobile.
- Educate patient about symptoms of DVT (swelling, pain, redness, warmth) and PE (SOB, CP, tachycardia, cough/hemoptysis)

*Please consult hematology for any questions*
THANK YOU!

QUESTIONS?