COVID-19 Hypercoagulability

McMaster University Chair's Medical Grand Rounds

Thursday | May 14, 2020 | 8:00 – 9:00AM ET

Speaker:
Ted Warkentin, MD, BSc(Med), FRCPC, FACP, FRCP (Edin)

Moderators:
Mark Crowther, MD MSc, FRCPC, FRSC
Scott Kaatz, DO, MSc, FACP, SFHM

Presented in partnership between McMaster University and the Anticoagulation Forum
Attendance Code for McMaster employees only

CH 6809

e-mail to:
campb@mcmaster.ca
Disclosure Information
Theodore E. Warkentin, M.D.

I have the following financial relationships to disclose:
  Paid Consultant:  Ergomed, Instrumentation Laboratory, Octapharma;
  Speaker’s Bureau: Instrumentation Laboratory
  Research funding: Instrumentation Laboratory
  Other relevant financial or material interests:
    – medicolegal consulting/testimony

I WILL include discussion of investigational or off-label use of a product in my presentation.
  off-label treatment of COVID-19 hypercoagulability
Educational Objectives

At the end of my presentation, the participant will be able to:

• Describe the laboratory and clinical features of COVID-19 hypercoagulability;

• What is the significance of elevated fibrin D-dimers?

• Compare and contrast COVID-19 hypercoagulability with HIT and sepsis-associated DIC;

• Discuss implications for thrombosis prevention and treatment strategies
## HIT vs COVID-19

<table>
<thead>
<tr>
<th>HIT</th>
<th>COVID-19</th>
</tr>
</thead>
<tbody>
<tr>
<td>~0.5-1% hep-exposed</td>
<td>~0.5-1% get severe disease</td>
</tr>
<tr>
<td>Mild-mod thrombocytopenia</td>
<td>Mild-moderate thrombocytopenia</td>
</tr>
<tr>
<td>Coag act’n (↑PT, ↑dD)</td>
<td>Coag act’n (↑PT, ↑dD)</td>
</tr>
<tr>
<td>High fibrinogen DIC</td>
<td>High fibrinogen DIC (?)</td>
</tr>
<tr>
<td>~50% thrombosis rate</td>
<td>~50% thrombosis rate (ICU)</td>
</tr>
<tr>
<td>Venous &gt; Arterial clots</td>
<td>Venous &gt; Arterial clots</td>
</tr>
<tr>
<td>Limb ischemic syndromes</td>
<td>Limb ischemic syndromes</td>
</tr>
<tr>
<td>Rx: non-hep AC (therapeutic)</td>
<td>Rx: Heparin/LMWH (?)dose</td>
</tr>
</tbody>
</table>

*Draw parallels between HIT/sepsis & COVID-19*
INTRODUCTION

• COVID-19

**Coronavirus disease (2019)**

• Virus called SARS-CoV-2

• RNA virus binds to ACE-2 receptor (alveolar cells, cardiac myocytes, vascular endothelium, etc.)

• 1st case Wuhan 17 Nov 2019; pandemic 12 Mar 2020

• Viral pneumonia (ARDS)

• Significant mortality

• Hypercoagulability state; prothrombotic
PLATELETS
Clinical Characteristics of Coronavirus Disease 2019 in China


Wuhan (pop; 11,000,000) (Hubei province)
N=1099 patients
N=173 severe
N=67 (ICU ± vent’d ± died)
<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All Patients (N=1099)</th>
<th>Disease Severity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Nonsevere (N=926)</td>
</tr>
<tr>
<td>Lymphocyte count</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (IQR) — per mm³</td>
<td>1000 (700–1300)</td>
<td>1000 (800–1400)</td>
</tr>
<tr>
<td>Distribution — no./total no. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;1500 per mm³</td>
<td>731/879 (83.2)</td>
<td>584/726 (80.4)</td>
</tr>
<tr>
<td>Platelet count</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (IQR) — per mm³</td>
<td>168,000 (132,000–207,000)</td>
<td>172,000 (139,000–212,000)</td>
</tr>
<tr>
<td>Distribution — no./total no. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;150,000 per mm³</td>
<td>315/869 (36.2)</td>
<td>225/713 (31.6)</td>
</tr>
<tr>
<td>Median hemoglobin (IQR) — g/dl</td>
<td>13.4 (11.9–14.8)</td>
<td>13.5 (12.0–14.8)</td>
</tr>
</tbody>
</table>

Distribution of other findings — no./total no. (%)

<table>
<thead>
<tr>
<th></th>
<th>All Patients (N=1099)</th>
<th>Disease Severity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Nonsevere (N=926)</td>
</tr>
<tr>
<td>CRP ≥10 mg/liter</td>
<td>481/793 (60.7)</td>
<td>371/658 (56.4)</td>
</tr>
<tr>
<td>Procalcitonin ≥0.5 ng/ml</td>
<td>35/633 (5.5)</td>
<td>19/516 (3.7)</td>
</tr>
<tr>
<td>LDH ≥250 U/liter</td>
<td>277/675 (41.0)</td>
<td>205/551 (37.2)</td>
</tr>
<tr>
<td>AST &gt;40 U/liter</td>
<td>168/757 (22.2)</td>
<td>112/615 (18.2)</td>
</tr>
<tr>
<td>ALT &gt;40 U/liter</td>
<td>158/741 (21.3)</td>
<td>120/606 (19.8)</td>
</tr>
<tr>
<td>Total bilirubin &gt;17.1 μmol/liter</td>
<td>76/722 (10.5)</td>
<td>59/594 (9.9)</td>
</tr>
<tr>
<td>Creatine kinase ≥200 U/liter</td>
<td>90/657 (13.7)</td>
<td>67/536 (12.5)</td>
</tr>
<tr>
<td>Creatinine ≥133 μmol/liter</td>
<td>12/752 (1.6)</td>
<td>6/614 (1.0)</td>
</tr>
<tr>
<td>D-dimer ≥0.5 mg/liter</td>
<td>260/560 (46.4)</td>
<td>195/451 (43.2)</td>
</tr>
</tbody>
</table>

Platelet Counts—log-normal distribution

Platelet Counts— log-normal distribution

Platelet count nadir (median)
Covid-19  ~168 (admission)

Platelet counts: Log-normal distribution in HIT

Type of HIT-associated thrombosis
- Nil (N=72)
- Venous (N=132)
- Venous and arterial (N=6)
- Arterial (N=24)

Median platelet count nadir, $55 \times 10^9$/L

Platelet fall <50%

Platelet Count Nadirs: HIT vs D-ITP

Platelet Count Nadir: Covid-19 vs Normal

Platelet Count Nadirs: Covid-19 Non-Survivors

- **Platelet count nadir (median)**
  - ~60 x10^9/L

- **Normal**
  - ~150-400

- **Covid-19 non-survivors**
  - ~50-<100

- **HIT**
  - Platelet count nadir (mdn)

- **Thrombosis**
Is Severe COVID-19 a “pancellular” activation disorder?

“endotheliitis” (Varga et al. *Lancet* 2020)
“netosis” (Barnes et al. *J Exp Med* 2020)
cytokine storm
platelet activation (DIC)

Neutrophil infiltration of lung capillaries in Covid-19
Platelet, Endothelial, Leukocyte Activation in HIT

Warkentin. (In preparation. For HIT chapter in Future edition of Hoffman Hematology)
D-DIMERS

DIC
Translation!

• D-Dimer
  – McMaster
    • Normal <500 μg/L
    • Moderate elevation ~2000 μg/L
    • Extreme elevation >20,000 μg/L
  – U.S. audience
    • Normal <0.5 mg/L
    • Moderate elevation ~2.0 mg/L
    • Extreme elevation >20.0 mg/L

• Fibrinogen
  – McMaster normal range 1.5 – 4.0 g/L
  – U.S. audience normal range 150 – 400 mg/dL
Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study

Fei Zhou*, Ting Yu*, Ronghui Du*, Guohui Fan*, Ying Liu*, Zhibo Liu*, Jie Xiang*, Yeming Wang, Bin Song, Xiaoying Gu, Lulu Guan, Yuan Wei, Hui Li, Xudong Wu, Jiuyang Xu, Shengjin Tu, Yi Zhang, Hua Chen, Bin Cao

• N=191 in-patients with Covid-19 (2 hospitals)
  • 54 died, 137 discharged
• Main risk factors for death on admission (per Abstract)
  • Older age (1.10 per year increase; p=0.0043)
  • Higher SOFA score (5.65; p<0.0001)
  • d-Dimer >1µg/mL on admission (18.42; p=0.0033)
<table>
<thead>
<tr>
<th></th>
<th>Total (n=191)</th>
<th>Non-survivor (n=54)</th>
<th>Survivor (n=137)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anaemia</td>
<td>29 (15%)</td>
<td>14 (26%)</td>
<td>15 (11%)</td>
<td>0.0094</td>
</tr>
<tr>
<td>Platelet count, \times 10^9 per L</td>
<td>206.0 (155.0-262.0)</td>
<td>165.5 (107.0-229.0)</td>
<td>220.0 (168.0-271.0)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>&lt;100</td>
<td>13 (7%)</td>
<td>11 (20%)</td>
<td>2 (1%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Albumin, g/L</td>
<td>32.3 (29.1-35.8)</td>
<td>29.1 (26.5-31.3)</td>
<td>33.6 (30.6-36.4)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>ALT, U/L</td>
<td>30.0 (17.0-46.0)</td>
<td>40.0 (24.0-51.0)</td>
<td>27.0 (15.0-40.0)</td>
<td>0.0050</td>
</tr>
<tr>
<td>&gt;40</td>
<td>59/189 (31%)</td>
<td>26 (48%)</td>
<td>33/135 (24%)</td>
<td>0.0015</td>
</tr>
<tr>
<td>Creatinine &gt;133 µmol/L</td>
<td>8/186 (4%)</td>
<td>5 (9%)</td>
<td>3/132 (2%)</td>
<td>0.045</td>
</tr>
<tr>
<td>Lactate dehydrogenase, U/L</td>
<td>300.0 (234.0-407.0)</td>
<td>521.0 (363.0-669.0)</td>
<td>253.5 (219.0-318.0)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>&gt;245</td>
<td>123/184 (67%)</td>
<td>53 (98%)</td>
<td>70/130 (54%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Creatine kinase, U/L</td>
<td>21.5 (13.0-72.4)</td>
<td>39.0 (19.5-151.0)</td>
<td>18.0 (12.5-52.1)</td>
<td>0.0010</td>
</tr>
<tr>
<td>&gt;185</td>
<td>22/168 (13%)</td>
<td>11/52 (21%)</td>
<td>11/116 (9%)</td>
<td>0.038</td>
</tr>
<tr>
<td>High-sensitivity cardiac troponin I, pg/mL</td>
<td>4.1 (2.0-14.1)</td>
<td>22.2 (5.6-83.1)</td>
<td>3.0 (1.1-5.5)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>&gt;28</td>
<td>24/145 (17%)</td>
<td>23/50 (46%)</td>
<td>1/95 (1%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Prothrombin time, s</td>
<td>11.6 (10.6-13.0)</td>
<td>12.1 (11.2-13.7)</td>
<td>11.4 (10.4-12.6)</td>
<td>0.0004</td>
</tr>
<tr>
<td>&lt;16</td>
<td>171/182 (94%)</td>
<td>47 (87%)</td>
<td>124/128 (97%)</td>
<td>0.016*</td>
</tr>
<tr>
<td>&gt;16</td>
<td>11/182 (6%)</td>
<td>7 (13%)</td>
<td>4/128 (3%)</td>
<td>..</td>
</tr>
<tr>
<td>D-dimer, µg/mL</td>
<td>0.8 (0.4-3.2)</td>
<td>5.2 (1.5-21.1)</td>
<td>0.6 (0.3-1.0)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>≤0.5</td>
<td>55/172 (32%)</td>
<td>4 (7%)</td>
<td>51/118 (43%)</td>
<td>&lt;0.0001*</td>
</tr>
<tr>
<td>&gt;0.5 to ≤1</td>
<td>45/172 (26%)</td>
<td>6 (11%)</td>
<td>39/118 (33%)</td>
<td>..</td>
</tr>
<tr>
<td>&gt;1</td>
<td>72/172 (42%)</td>
<td>44 (81%)</td>
<td>28/118 (24%)</td>
<td>..</td>
</tr>
<tr>
<td>Serum ferritin, µg/L</td>
<td>722.0 (377.2-1435.3)</td>
<td>1435.3 (728.9-2000.0)</td>
<td>503.2 (264.0-921.5)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>&gt;300</td>
<td>102/128 (80%)</td>
<td>44/46 (96%)</td>
<td>58/82 (71%)</td>
<td>0.0008</td>
</tr>
<tr>
<td>IL-6, pg/mL</td>
<td>7.4 (5.3-10.8)</td>
<td>11.0 (7.5-14.4)</td>
<td>6.3 (5.0-7.9)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Procalcitonin, ng/mL</td>
<td>0.1 (0.1-0.1)</td>
<td>0.1 (0.1-0.5)</td>
<td>0.1 (0.1-0.5)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>&lt;0.1</td>
<td>114/164 (70%)</td>
<td>19/51 (37%)</td>
<td>95/113 (84%)</td>
<td>&lt;0.0001*</td>
</tr>
<tr>
<td>≥0.1 to &lt;0.25</td>
<td>30/164 (18%)</td>
<td>16/51 (31%)</td>
<td>14/113 (12%)</td>
<td>..</td>
</tr>
<tr>
<td>≥0.25 to &lt;0.5</td>
<td>6/164 (4%)</td>
<td>3/51 (6%)</td>
<td>3/113 (3%)</td>
<td>..</td>
</tr>
<tr>
<td>≥0.5</td>
<td>14/164 (9%)</td>
<td>13/51 (25%)</td>
<td>1/113 (1%)</td>
<td>..</td>
</tr>
</tbody>
</table>
QUESTION

What is the explanation for ↑dD in Covid-19?
↑ d-Dimer

• Two general explanations for ↑d-Dimer
  • Localized thrombosis
    • DVT, PE, etc.
    • Pulmonary microthrombosis
  • Systemic activation of hemostasis (“DIC”)
Pathologic Thrombin Generation

- Tissue factor + Factor VIIa
- Factor IXa (factor VIIIa) + Factor Xa (factor Va)
- Cross-linked (X) fibrin
- Soluble fibrin
- Fibrinogen → fDP's
- FDP's → X-FDP's (D-dimer)
- PLASMIN
- Plasminogen activator
- Plasminogen
- Platelet activation

Warkentin (Ch. 22.6.5). Oxford Textbook of Medicine, 2010
QUESTION

Can ↑d-D distinguish between DIC and (non-DIC) thrombosis?
Pulmonary Microthrombosis in Covid-19

↑ d-Dimer

• Two general explanations for ↑d-Dimer
  • Localized thrombosis
    • DVT, PE, etc.
    • Pulmonary microthrombosis
  • Systemic activation of hemostasis (=DIC)
Hemostasis Tests (on Admission)

- Hemostasis abnormalities in COVID-19
  - Thrombocytopenia
  - ↑d-Dimer (dD)
  - ↑PT (INR)
  - ↑PTT
  - ↑Fibrinogen
    - Beware—high fibrinogen does not rule out DIC; rather, confers adverse prognostic risk factor in DIC!!
  "High fibrinogen DIC"
1. Risk assessment: does the patient have an underlying disorder known to be associated with overt DIC?
   - If Yes: Proceed
   - If No: Do not use this algorithm

2. Order global coagulation tests
   - Platelet count: 150-450 0, 1, 2
   - D-dimer: < 0.5 0, 2, 3
   - PT / INR: 0.8-1.2 0, 1, 2
   - Fibrinogen: 150-400 0, 1

3. Score global coagulation test results:
   - Platelet count:
     - ≥100 = 0
     - 50-99 = 1
     - <50 = 2
   - Fibrin-specific marker (D-dimer):
     - no/mild increase = 0
     - 1.0-3.0 mg/L = 2
     - >3.0 mg/L = 3
   - Prolonged INR:
     - ≤1.2 = 0
     - 1.3, 1.4 = 1
     - ≥ 1.5 = 2

4. Calculate score:
   - If ≥ 5: Compatible with overt DIC
   - If < 5: Suggestive (not affirmative) for non-overt DIC

TOTAL [Maximum, 8 points]

Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia

Ning Tang¹ | Dengju Li² | Xiong Wang¹ | Ziyong Sun¹

Abstract

**Background:** In the recent outbreak of novel coronavirus infection in Wuhan, China, significantly abnormal coagulation parameters in severe novel coronavirus pneumonia (NCP) cases were a concern.

**Objectives:** To describe the coagulation feature of patients with NCP.

**Methods:** Conventional coagulation results and outcomes of 183 consecutive patients with confirmed NCP in Tongji hospital were retrospectively analyzed.

**Results:** The overall mortality was 11.5%, the non-survivors revealed significantly higher D-dimer and fibrin degradation product (FDP) levels, longer prothrombin time and activated partial thromboplastin time compared to survivors on admission ($P < .05$); 71.4% of non-survivors and 0.6% survivors met the criteria of disseminated intravascular coagulation during their hospital stay.

**Conclusions:** The present study shows that abnormal coagulation results, especially markedly elevated D-dimer and FDP are common in deaths with NCP.
Adverse Risk Factors (Emphasis of Coagulation Testing)

<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 values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>54.1 ± 16.2</td>
<td>52.4 ± 15.6</td>
<td>64.0 ± 20.7</td>
<td>&lt;.001</td>
<td></td>
</tr>
<tr>
<td>Sex (male/female)</td>
<td>98/85</td>
<td>82/80</td>
<td>16/5</td>
<td>.035</td>
<td></td>
</tr>
<tr>
<td>With underlying diseases</td>
<td>75 (41.0%)</td>
<td>63 (38.9%)</td>
<td>12 (57.1%)</td>
<td>.156</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>On admission</th>
<th>Normal range</th>
<th>Mdn(IQR)</th>
<th>P values</th>
</tr>
</thead>
<tbody>
<tr>
<td>PT (sec)</td>
<td>11.5-14.5</td>
<td>13.6 (13.0-14.3)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td></td>
<td></td>
<td>15.5 (14.4-16.3)</td>
<td></td>
</tr>
<tr>
<td>APTT (sec)</td>
<td>29.0-42.0</td>
<td>41.2 (36.9-44.0)</td>
<td>.096</td>
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<tr>
<td></td>
<td></td>
<td>44.8 (40.2-51.0)</td>
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</tr>
<tr>
<td>Fibrinogen (g/L)</td>
<td>2.0-4.0</td>
<td>4.51 (3.65-5.09)</td>
<td>.149</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5.16 (3.74-5.69)</td>
<td></td>
</tr>
<tr>
<td>D-dimer (µg/mL)</td>
<td>&lt;0.50</td>
<td>0.61 (0.35-1.29)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2.12 (0.77-5.27)</td>
<td></td>
</tr>
<tr>
<td>FDP (µg/mL)</td>
<td>&lt;5.0</td>
<td>4.0 (4.0-4.3)</td>
<td>&lt;.001</td>
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<tr>
<td></td>
<td></td>
<td>7.6 (4.0-23.4)</td>
<td></td>
</tr>
<tr>
<td>AT (%)</td>
<td>80-120</td>
<td>91 (83-97)</td>
<td>.096</td>
</tr>
<tr>
<td></td>
<td></td>
<td>84 (78-90)</td>
<td></td>
</tr>
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</table>

**Adverse Risk Factors (Emphasis of Coagulation Testing)**

TABLE 1 Coagulation parameters of NCP patients on admission

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</tr>
<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;.001</td>
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</tr>
<tr>
<td>D-dimer (µg/mL)</td>
<td>&lt;0.50</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;.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;.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>.096</td>
</tr>
</tbody>
</table>

Does normal or elevated fibrinogen rule out DIC?

Fibrinogen Values in DIC

Per ISTH DIC criteria:  
Median (25%ile-75%ile) = 203  (115 – 334 mg/dL)

Per JMHW criteria:  
Median (25%ile-75%ile) = 191  (120 – 345 mg/dL)

Per JAAM criteria:  
Median (25%ile-75%ile) = 254  (150 – 365 mg/dL)


Levi & ten Cate (Blood Rev 2002) = “the sensitivity of a low fibrinogen level for the diagnosis of DIC was only 28%”
Symmetrical Peripheral Gangrene (SPG) in a Patient with DIC and Fibrinogen Nadir = 480 mg/dL
45-yr-old female with *Klebsiella pneumoniae* septicemia and acute-on-chronic liver disease

Fibrin D-Dimer rise to >20,000!!

Disturbed procoagulant-anticoagulant balance

1. Risk assessment: does the patient have an underlying disorder known to be associated with overt DIC?
   - If Yes: Proceed
   - If No: Do not use this algorithm

   “Klebsiella pneumoniae pneumonia/septicemia”

2. Order global coagulation tests

<table>
<thead>
<tr>
<th>Test</th>
<th>Normal</th>
<th>Pt “X”</th>
</tr>
</thead>
<tbody>
<tr>
<td>Platelet count</td>
<td>150-450</td>
<td>&lt;10</td>
</tr>
<tr>
<td>D-dimer:</td>
<td>&lt; 0.5</td>
<td>&gt; 20.0</td>
</tr>
<tr>
<td>Prothrombin time:</td>
<td>11-15 sec</td>
<td>18 sec</td>
</tr>
<tr>
<td>Fibrinogen:</td>
<td>150-400</td>
<td>720→480 mg/dL</td>
</tr>
</tbody>
</table>

3. Score global coagulation test results:
   - Platelet count: 
     - >100 = 0
     - <100 = 1
     - <50 = 2
   - Elevated Fibrin related markers (Fibrin split products & D-dimer):
     - no increase = 0
     - increase to 1.0-3.0 = 2
     - strong increase (>3.0) = 3
   - Prolonged PT:
     - <3 sec = 0
     - >3 but <6 sec = 1
     - >6 sec = 2
   - Fibrinogen level:
     - >100 mg/dL = 0
     - <100 mg/dL = 1

4. Calculate score:
   - If ≥ 5: Compatible with overt DIC
   - If < 5: Suggestive (not affirmative) for non-overt DIC

   TOTAL [Maximum, 8 points] 6

Diagnosis = “DIC”
CONCEPT

DIC occurring with high fibrinogen is a dangerous situation (+++ substrate)

(e.g., sepsis with prodrome; HIT; severe COVID-19 infection?)
QUESTION
Is COVID-19 coagulopathy static or progressive?
PT Progressively Rises in Non-Survivors

![Graph showing PT values over days for survivors and non-survivors]
dD Progressively Rises in Non-Survivors

FDPs Progressively Rise in Non-Survivors

![Graph showing FDP levels in survivors and non-survivors over days after admission.](image)

Fibrinogen Progressively Falls in Non-Survivors


![Graph showing fibrinogen levels in survivors vs. non-survivors over time.](image-url)
Antithrombin (AT) Levels Are Lower in Non-Survivors

Evolution to DIC

• ISTH DIC criteria met in 16/183 (8.7%) patients
  • Survivors– DIC occurred in 1/162 (0.6%)
  • Non-Survivors– DIC occurred in 15/21 (71.4%)

• DIC strongly associated with non-survival

QUESTION

Is COVID-19 infection associated with DIC?  YES*

* per Tang et al. J Thromb Haemost

But contradicted by others...
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 Merdjii¹,⁶, Raphaël Clerc-Jehl¹,², Malika Schenck⁷, Florence Fagot Gandet⁷, Samira Fafi-Kremer²,⁸, Vincent Castelain⁷, Francis Schneider⁷, Lélia Grunebaum⁹, Eduardo Anglés-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)

4 ICU’s in France

- 150 ICU COVID-19 ARDS
- PE in 25/150 (16.7%) despite prophylaxis
- No patient met DIC criteria
- ↑Fbg ↑vWF
- 50/57 lupus anticoagulant

Covid-19 ARDS had lower dD levels vs. non-Covid-19 ARDS controls!

QUESTION
Is COVID-19 associated with increased risk of thrombosis?
Prevalence of venous thromboembolism in patients with severe novel coronavirus pneumonia

Songping Cui¹  |  Shuo Chen¹  |  Xiunan Li¹  |  Shi Liu²  |  Feng Wang³,⁴,⁵,⁶

Hospital in Wuhan, China

- 81 severe COVID-19 pneumonia (ICU)
- VTE in 20/81 (25%)
- dD cutoff 1.5 μg/mL (1500 μg/L) Se 85%, Sp 88%
Academic hospital in Hamburg, Germany (n=12)

- Consecutive autopsies with fatal COVID-19 infection (mandated by state)
- DVT in 7/12 patients; fatal PE in 4
- VTE had not been suspected antemortem

Incidence of thrombotic complications in critically ill ICU patients with COVID-19

F.A. Klok\textsuperscript{a,*}, M.J.H.A. Kruip\textsuperscript{b}, N.J.M. van der Meer\textsuperscript{c}, M.S. Arbous\textsuperscript{d}, D.A.M.P.J. Gomers\textsuperscript{e}, K.M. Kant\textsuperscript{f}, F.H.J. Kaptein\textsuperscript{a}, J. van Paassen\textsuperscript{d}, M.A.M. Stals\textsuperscript{a}, M.V. Huisman\textsuperscript{a,1}, H. Endeman\textsuperscript{e,1}

3 Dutch ICUs (n=184)

- All given LMWH proph.
- 31% thrombosis by d15
- 25 PE (28% subseg’l)
- 3 DVT, 3 ATE
- $\uparrow$PT(>3s) $\uparrow$PTT(>5s)

Fig. 1. Cumulative incidence of venous and arterial thrombotic complications during the course of intensive care unit admission of patients with proven COVID-19 pneumonia.
Confirmation of the high cumulative incidence of thrombotic complications in critically ill ICU patients with COVID-19: An updated analysis

F.A. Klok\textsuperscript{a,*}, M.J.H.A. Kruip\textsuperscript{b}, N.J.M. van der Meer\textsuperscript{c,d}, M.S. Arbous\textsuperscript{e}, D. Gommers\textsuperscript{f}, K.M. Kant\textsuperscript{g}, F.H.J. Kaptein\textsuperscript{a}, J. van Paassen\textsuperscript{e}, M.A.M. Stals\textsuperscript{a}, M.V. Huisman\textsuperscript{a,1}, H. Endeman\textsuperscript{f,1}

3 Dutch ICUs (n=184)

- Updated data (7→14d)
- 57% thrombosis by d25
- 65 PE (29% subseg’l)
- 3 DVT, 7 ATE (5 CVA’s)
- HR 0.29 if adm. AC

What is this graph reminiscent of?
Natural History of Isolated HIT

Cumulative Thrombotic Event Rate (%)

Days After Isolated HIT Recognized

52.8%

QUESTION
Is DIC in COVID-19 associated with limb ischemic necrosis?
Massive outpouring as actor loses leg in COVID-19 fight

More than $300,000 raised for Hamilton’s Nick Cordero and family following news of amputation

It’s hard to suggest there could be much good news for Nick Cordero coming out of a weekend in which the Hamilton actor lost his leg as a casualty of his battle with COVID-19. Even though the surgery apparently went well.

For a singer and dancer — not to mention the father of a 10-month-old son — this is life-altering.

Yet at the same time he was recovering from his surgery, a Go Fund Me page was exploding with donations and providing a glimmer of optimism. By Sunday afternoon, more than $300,000 US had been donated. And the total was climbing.

Even so, it couldn’t overshadow the shocking news that arrived Saturday morning in an Instagram post from his wife.

“The right leg will be amputated today,” Amanda Kloots said.

It was a stunning turn. The Westdale Secondary grad was a perfectly healthy 41-year-old Tony Award-nominated Broadway and TV star less than three weeks ago. Now he’s unconscious in the intensive care ward of a Los Angeles hospital on a ventilator. And then this.
COVID-19 & Limb Ischemia

Acute limb ischemia in patients with COVID-19 pneumonia.


- 20 pts with acute limb ischemia requiring surgical revascularization (Jan-Mar 2020)
  - Acute artery thrombosis
  - Treated surgically (intra-/postop heparin)
  - “Virus-associated hypercoagulable state”
Microthrombosis with DIC and Natural Anticoagulant Depletion

Ischemic limb gangrene with pulses

Protein C and antithrombin are both made in the liver!!

COVID-19 & Limb Ischemia

- 7 pts adm. to Wuhan hospital Feb 4-15, 2020
- Adm: N plt, ↑dD (~7.0), ↑↑fbg (~600), ↑inr
- Limb ischemia: Plt↓ (~85), ↑↑dD (>20), ↑↑fbg
- Not in shock (lactate <2.0); not on vasopressors
- Treated with LMWH 100 U/kg bid
Observational Research
Case Analysis
Platelets and Routine Hemostasis Markers over 1-mo Course

Symptom onset  Admission  Intubation  Extubation  PE During Line Removal

INR...normal.....
PTT...37.....
Fbg...............566
Plt ...130....105

Platelet count fall 350 to 200 (43% drop)
Serial D-Dimer Values over 1-mo Course

- Days after symptom onset: 0, 5, 10, 15, 20, 25, 30
- Symptom onset
- Admission
- Intubation
- Extubation
- PE During Line Removal

Graph: (3/30/20 0958 - 4/22/20 1257)

D-Dimer rise from ~0.5 to 3.5
QUESTION

So, what is being recommended re: anticoagulation?
At presentation:
(a) Plt (CBC), (b) PT (INR), (c) dD, (d) Fbg

Monitoring
Serial (a) Plt, (b) PT (INR), (c) dD, (d) Fbg

Management: LMWH preferred over UFH
Higher bioavailability (vs UFH) with inflammation
Less risk of HIT (?)
COVID-19 is not inherently prohemorrhagic
Individualize treatment decisions

Association of Treatment Dose Anticoagulation with In-Hospital Survival Among Hospitalized Patients with COVID-19

Ishan Paranjpe, BS, Valentin Fuster, MD, PhD, Anuradha Lala, MD, Adam Russak, MD, Benjamin S. Glicksberg, PhD, Matthew A. Levin, MD, Alexander W. Charney, MD, PhD, Jagat Narula, MD, PhD, Zahi A. Fayad, PhD, Emilia Bagiella, PhD, Shan Zhao, MD, PhD, Girish N. Nadkarni, MD, MPH

- **Mnt Sinai Health (NYC)**
- **Mar14-Apr11**
- **Observational**
- **N=395 ventilator**
- **AC (therapeutic-dose)**
  ↓**mortality (29% vs 62%)**

Paranjpe et al. *J Am Coll Cardiol* 2020 May 5 [Epub ahead of print]
Dosing of LMWH (medical pts)

• **Prophylactic (standard dosing); e.g., AC Forum for Covid-19 patient on regular ward**
  - Enoxaparin (Lovenox)—40mg/d (30mg/d CrCl<30)
  - Dalteparin (Fragmin)—5000 U/d

• **Prophylactic—weight-adjusted (McMaster thrombosis service)**
  - Dalteparin (weight-adjusted)
    - <50kg 2,500U
    - 50-99kg 5,000U
    - 100-139kg, 7,500U
    - >140kg 10,000

• **Intermediate (Germany [Andreas Greinacher])**
  - Dalteparin
    - "elevated d-Dimers" 5,000U twice-daily
    - ICU, previous VTE, active cancer, etc. 5,000U twice-daily

• **Intermediate (AC Forum)**
  - Enoxaparin 40mg twice-daily (0.5 mg/kg twice-daily) patient admitted to ICU
  - (AC Forum does not currently recommend using d-Dimer to guide dosing)

• **Therapeutic (selected situations) [ENTER INTO RCT, e.g., ATTACC trial]**
  - Enoxaparin (Lovenox)—1mg/kg bid (1mg/kg OD CrCl<30)
  - Dalteparin (Fragmin)—200U/kg OD (100U/kg bid)
QUESTION

What about post-discharge anticoagulation?

• AC Forum (paraphrasing): Consider VTE prophylaxis and if deemed reasonable, we recommend use of an adequately studied and/or approved agent, per total duration used in trials, e.g.,:
  • Betrixaban 35-42d
  • Rivaroxaban 31-39d
  • Enoxaparin 6-14d
Summary

• Covid-19 ARDS is prothrombotic (hypercoagulability)
  • High frequency of thrombosis
  • Venous predominance (but important arterial events, e.g., stroke, limb artery thrombosis)
  • Activation of hemostasis (↓plt ↑PT ↑PTT ↑dD ↑fibrinogen)—prognostic features

• Unique features
  • May represent “high fibrinogen DIC state”
  • Even without classic DIC, ↑fibrinogen ↑vWF, etc., may contribute to prothrombotic effect
  • Inflammatory state may lead to heparin underdosing
  • Like HIT, antithrombotic prophylaxis in Covid-19 might require therapeutic-dose anticoagulation (not currently widespread)
Attendance Code for McMaster employees only
CH 6809
email to:
campb@mcmaster.ca

Thanks to
Mark Crowther
Scott Kaatz
Andreas Greinacher
Menaka Pai
Patricia Liaw
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