COVID!

Tom DeLoughery, MD MACP FAWM @bloodman
Oregon Health & Science University
DISCLOSURE

Current Relevant Financial Relationship(s)
None

OHSU
Talk

• Thrombosis incidence
• Mechanisms of thrombosis
• Testing
• Treatment

• Convalescent plasma
• Blood groups
COVID

- New infection
- Pneumonia primary feature
- Coagulation issues soon recognized as a major feature
Coagulopathy in COVID-19

• Very common!

• Most patients with
  – Abnormal coagulation
  – Very high D-dimers
  – Very high fibrinogen

• Thrombosis >>> bleeding
D-Dimer

- Marked elevation in all patients
- Major prognostic indicator
- May be a sign of thrombosis
- Cause
  - Widespread coagulation activation
  - Pulmonary thrombosis
D-Dimer

Fibrinogen → Fibrin Monomer → X-Linked Fibrin → D-Dimer

Thrombin

FPA

FPB
<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></td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Sex (male/female)</td>
<td>98/85</td>
<td>82/80</td>
<td>16/5</td>
<td></td>
<td>.035</td>
</tr>
<tr>
<td>With underlying diseases</td>
<td>75 (41.0%)</td>
<td>63 (38.9%)</td>
<td>12 (57.1%)</td>
<td></td>
<td>.156</td>
</tr>
<tr>
<td><strong>On admission</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</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>
</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>.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>.149</td>
</tr>
<tr>
<td><strong>D-dimer (µg/mL)</strong></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><strong>FDP (µg/mL)</strong></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>

Abbreviations: APTT, activated partial thromboplastin time; AT, antithrombin activity; FDP, fibrin degradation product; NCP, novel coronavirus pneumonia; PT, prothrombin time (PT).
Zhang, J Throm Haemo 18:1324, 2020
Thrombosis

• Rates of 17-69% reported even with prophylaxis
  – Much higher than literature
  – Venous thrombosis
  – Arterial thrombosis
  – Microthrombosis
Cui

- VTE = 25%
- Unknown prophylaxis
- D-Dimer predictive
- J Throm Hem 2020
<table>
<thead>
<tr>
<th>Cut-off (μg/mL)</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>PPV (%)</th>
<th>NPV (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.0</td>
<td>85.0</td>
<td>77.0</td>
<td>54.8</td>
<td>94.0</td>
</tr>
<tr>
<td><strong>1.5</strong></td>
<td><strong>85.0</strong></td>
<td><strong>88.5</strong></td>
<td><strong>70.8</strong></td>
<td><strong>94.7</strong></td>
</tr>
<tr>
<td>2.0</td>
<td>80.0</td>
<td>90.2</td>
<td>72.7</td>
<td>93.2</td>
</tr>
<tr>
<td>2.5</td>
<td>70.0</td>
<td>93.4</td>
<td>77.8</td>
<td>90.5</td>
</tr>
<tr>
<td>3.0</td>
<td>70.0</td>
<td>96.7</td>
<td>87.5</td>
<td>90.8</td>
</tr>
<tr>
<td>3.5</td>
<td>65.0</td>
<td>96.7</td>
<td>86.7</td>
<td>89.4</td>
</tr>
</tbody>
</table>

Table 3: Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of different D-dimer cut-off levels for predicting VTE in NCP patients.
Klok

- VTE = 27->49% (87% PE)
- Arterial = 3.7%
- All getting prophylaxis
- Coagulation abnormalities predicted thrombosis
- Thrombosis HR 5.4 death
- Throm Research 2020
France

- 16.7% thrombosis rate
- 96% CRRT thrombosis rate
  – < 24 hours!
- All getting prophylaxes

- ICU medicine in press
France II

- 26 consecutive ICU patients
- 69% thrombosis
  - PE 23% patients
- No benefit of standard prophylaxis
- JTH in press
Middledorf

- N = 199
- ICU: 26% @ 1wk, 47% @ 2 wks, and 59% @ 3 wks
  - ICU vs ward: 7.1
- 2.8%/day of ICU stay
- History of DVT not a risk factor

JTH
Venous Thrombosis Rates

• COVID: 17-65%
  – Increases with duration of ICU stay
• Non-COVID ICU
  – 14.6% Controls (2% PE)
  – 7.5% Prophylaxis (1%)
Wichmann

- First 12 mandated COVID autopsy
- Consecutive series
- Age - 73
- 75% male
- 4 (25%) die massive PE
- 3 more with DVT
Autopsy/Pathology

• Uniformly show
  – Micro/macrovascular thrombosis in multiple organs
  – Minimal microangiopathy
  – Megakaryocytes in lungs
Arterial Thrombosis

• Increasing reports in young patients without risk factors
• Stroke, MI, aortic or visceral arterial thrombosis
Arterial Thrombosis

- Typical presentation – arterial event in young person
- Minimal to no respiratory symptoms
- Positive COVID testing
Stroke

- Increased incidence reported
- Rates of 1-2% in COVID patients
  - Higher on MRI??
- Unclear epidemiology
NYC Stroke

- 1.6% COVID patients with stroke
- 24% presented with stroke
- Mean age 69, 50% men
- OR 7.8 compared to flu patients
- Mortality 34% vs 14% no stroke
- JAMA Neurology 2020
COVID Toes
Heparin Resistance

• Increasing reports of high heparin requirements
  → 4000u/hr
• Breakthrough thrombosis
• High rates of CRRT/dialysis thrombosis
  → 90% in one study
Summary

• Thrombosis
  – Much increased in ICU patients
  – 7x
  – Mainly venous but arterial reported
  – Occurs despite standard prophylaxis
  – Widespread
Etiology

• Intense inflammation
  – Raises procoagulants
  – Convert endothelium to prothrombotic state

• Pulmonary inflammation

• Viral attack on endothelial cells

• Platelets

• Other cascades
Inflammation

• IL-6 stimulates prothrombotic changes
  – Increased fibrinogen
  – Increased factor 8
  – Increased VWF

• TNF/IL-1 convert endothelium to prothrombotic state
Stage I (Early Infection) - Viral response phase

Stage II (Pulmonary Phase) - IIA and IIB

Stage III (Hyperinflammation Phase) - Host inflammatory response phase

Severity of Illness vs. Time course

Clinical Symptoms:
- Mild constitutional symptoms
- Fever >99.6°F
- Dry Cough

Clinical Signs:
- Lymphopenia
- Shortness of Breath without (IIA) and with Hypoxia (IIB)
  (PaO2/FiO2 ≤ 300 mmHg)
- Abnormal chest imaging
- Transaminitis
- Low-normal procalcitonin

Complications:
- ARDS
- SIRS/Shock
- Cardiac Failure
- Elevated inflammatory markers (CRP, LDH, IL-6, D-dimer, ferritin)
  Troponin, NT-proBNP elevation
Evidence for Inflammation

- Antivirals +/- effectiveness
- Dexamethasone very effective
  - Only in patients requiring oxygen
- But maybe some inflammation good
  - Early dex harmful
  - Increasing reports of adverse outcomes with anti IL-6 therapy
Figure 2: Effect of allocation to dexamethasone on 28–day mortality by level of respiratory support received at randomization

<table>
<thead>
<tr>
<th>Respiratory support at randomization</th>
<th>Dexamethasone</th>
<th>Usual care</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No oxygen received</td>
<td>85/501 (17.0%)</td>
<td>137/1034 (13.2%)</td>
<td>1.22 (0.93–1.61)</td>
</tr>
<tr>
<td>Oxygen only</td>
<td>275/1279 (21.5%)</td>
<td>650/2604 (25.0%)</td>
<td>0.80 (0.70–0.92)</td>
</tr>
<tr>
<td>Invasive mechanical ventilation</td>
<td>94/324 (29.0%)</td>
<td>278/683 (40.7%)</td>
<td>0.65 (0.51–0.82)</td>
</tr>
<tr>
<td>All participants</td>
<td>454/2104 (21.6%)</td>
<td>1065/4321 (24.6%)</td>
<td>0.83 (0.74–0.92)</td>
</tr>
</tbody>
</table>

Trend across three categories: $\chi^2 = 11.49; p<0.001$
Potential Drivers

• Polyphosphates
  – Initiate contact pathway
• NETs
  – Powerful initiator of coagulation
• PAMP (Pathogen-associated molecular patterns)
NET

- Neutrophil extracellular traps
- DNA/Histones extruded from neutrophils
- Very prothrombotic
- Increased in sepsis, DIC, COVID
**NETosis** (slow cell death)
- Nuclear delobulation
- Disassembly of nuclear envelope

**Non-lytic NETosis** (rapid release from live cells)
- Degranulation
- Expulsion of nuclear chromatin

**Granule**

**Cellular**
- Depolarization
- Chromatin decondensation

**Extracellular assembly of NET**

**Phagocytic cytoplasm**
- Plasma membrane rupture
- Release of NETs
Antiphospholipid Antibodies

- Increased incidence in COVID patients
  - Up to 90% lupus inhibitors
- Pathogenic or false positives?
- Further muddies waters on PTT monitoring of heparin
Pulmonary Inflammation

• Virus infection at alveolar level leads to local inflammation
• This spreads throughout the lung and system vasculature
• Path
  – Pulmonary inflammation with microthrombi
a

Normal state

Diseased state

Bronchial epithelial cell

SARS-CoV-2

Inflammation

Cytokine storm

IL-2, IL-2R, IL-6, IL-7, IL-8, IL-10, IP10, G-CSF, MCP1, MCP3

Neutrophil

Inflammatory cell

Pulmonary oedema

Vascular integrity

Anti-inflammatory

Anti-coagulation

1. Vascular leakage

2. Platelets

3. D-dimer

Inflammation

Coagulation
Proinflammatory cytokines and procoagulant factors

Venule

Hyaline thrombi

Arteriole

Macrophages and lymphocytes infiltrating vessel wall

Neutrophils

Macrophages

Clot formation

Vascular rupture and haemorrhage

Proinflammatory mediators

Cytokines and procoagulant enter capillary network
Endothelial Infection

• Increasing evidence virus can attack vascular endothelium
• Converts antithrombotic surface to prothrombotic
Figure: Pathology of endothelial cell dysfunction in COVID-19

Lancet: in press
Inactivation of Coagulation

PC---aPC

Activation of Coagulation

VII---VIIa

TF

TM

VII---VIIa

TF
Endothelial Damage

- ICU vs Ward patients
- vWF: 565% vs 278%
- P-selectin: 15.9 vs 11.2 ng/ml
- Mortality associated with increased thrombomodulin
- Goshua Lancet Haem 2020
Figure 1
Platelets

- COVID platelets
  - Unique transcriptome
  - Increased P-selectin/PDGF
  - Increased aggregation
  - Increased thrombopoietin
Novel Findings

• Transcriptome changes same in all COVID patient but different than other viral infections
• Platelets not decreased
• Antiplatelet agents being studied
Complement

- Complicated inflammatory cascade
- Active proteins lead to tissue damage
  - Lung, microvascular
- Increase C5a seen in COVID
- Early work with complement blockers
Contact Pathway

- Coagulation/inflammation overlap
- Contact blocker effective in sepsis
- Low risk of side effects
Raghunathan  Res Pract Thromb Haemost. 3:331, 2019
DeLoughery, EP Semin Thromb Hemost 45:502, 2019
Bottom Line

• COVID leads to a prothrombotic state via multiple mechanisms
• Unique compare to other infections
Testing

• Admit: INR, aPTT, platelets, D-dimer, fibrinogen,
• Daily platelets, D-dimers, fibrinogen
TEG

- Consistent findings
  - Shorten r time
  - Increase K time
  - Increased MA
  - Decreased lysis

- Hypercoagulability
Anticoagulation

- **Consensus**
  - Everyone in hospital for COVID gets thromboprophylaxis with LMWH (UFH if renal failure)

- **Controversy**
  - Everything else
Is Heparin Beneficial?

- Teng study showed heparin associated with increase survival esp with high d-dimers
- Prophylaxis not standard in China
- Unclear doses used
- Ayerbe showed RR of 0.55
28-day mortality (%)

- SIC+
- SIC
- D-D≤1ULN
- D-D>1ULN
- D-D>2ULN
- D-D>3ULN
- D-D>4ULN
- D-D>5ULN
- D-D>6ULN
- D-D>8ULN

Heparin users vs Heparin nonusers
Heparin

• Observational data

• But
  – Antithrombotic?
  – Antiinflammatory?
  – Antiviral?

• Italian studies underway
Heparin as Antiviral

- Heparin can be a decoy for virus binding
- Heparin binds to spike protein
- Heparin has anti-inflammatory properties
Pre-Existing Anticoagulation

• Circulation study suggested being on anticoagulation at admission beneficial
• Studies controlling for baseline conditions no benefit
Increase Dosing?

• Many protocols increase heparin dosing for
  – ICU patients
  – D-Dimers 1.5- 3 x normal
• LMWH 40mg bid
• Multiple RCT in process
Therapeutic Dosing

• Some centers starting therapeutic dosing with D-Dimer 3-6x normal
  – High pretest probability of thrombosis
Thrombotic Risk

- Low – not in hospital
- Intermediate – in hospital but not requiring oxygen/vent
- High – obese or requires oxygen/vent
- Very high risk – obese + oxygen/vent, ECMO, high D-dimers or fibrinogen

Susan, Crit Care 2020
Risk

- Low – nothing
- Intermediate – standard LMWH
- High – double LMWH
- Very high – therapeutic LMWH

- Susan, Crit Care 2020
Outpatient Prophylaxis

• Some advocate after discharge prophylaxis for 30-45 days due to perceived high risk of thrombosis

• 10% readmissions for thrombosis
Heparin Resistance

• Etiology
  
• Increased inflammatory proteins
  – Increased fibrinogen, etc absorb heparin
  – Interference with PTT
  – Heparinase?

• Prothrombotic drive
Heparin Resistance

• Solution
  – Use LMWH as much as possible
  – If using UFH, use heparin levels
  – Breakthrough: increase LMWH by 25% or use argatroban
Suggested Protocol

1. Prophylaxis for everyone with COVID admitted to hospital –
   - LMWH preferred
   - Enoxaparin 40mg daily is standard
   - BMI >40, enoxaparin 40mg BID
   - For renal failure
     - Unfractionated heparin 5000u BID or
     - Enoxaparin 30mg daily
Suggest Protocol

2. Screen for DVT at admit to ICU and every 4-5 days in ICU
   - Low threshold for empiric treatment of thrombosis (sudden deterioration, D-Dimer > 3.0)
     - Enoxaparin 1mg/kg BID (preferred)
     - Renal failure: unfractionated heparin with goal 0.35-0.7

3. Double Prophylaxis for ICU patients
   - Enoxaparin 40mg bid
Suggested Protocol

4. Outpatient prophylaxis for patients who are likely to be immobile for a month either:
   - 40mg enoxaparin or
   - 10mg rivaroxaban
Guidelines

• Multiple ones!
  – ACCP, ISTH, AC Forum, BSH, etc
• Contentious issues:
  – Dosing of prophylaxis
  – Initiation of therapeutic dosing
  – Screening
Dosing of Prophylaxis

- **Pro** increase dosing:
  - High rates of thrombosis on standard dosing
  - Low risk of bleeding

- **Con**
  - No data
  - Is thrombosis driven by inflammation?
  - Not risk free
Initiation of Therapeutic Anticoagulation

- **Pro**
  - High rates of thrombosis
  - Difficult to get sick people to imaging

- **Con**
  - No data
  - Risk of bleeding
  - Can obtain testing if you try hard enough
Screening Dopplers

• **Pro**
  – High rates of thrombosis
  – Patients are unable to complain of symptoms

• **Con**
  – No data for screening
  – Exposes patients to risk of anticoagulation
Use of Convalescent Plasma

• Incredible hope and speculation about this
• Multiple trials/protocols in process
Convalescent Plasma

- Very old idea
- Antibodies in donor convalescent plasma can decrease infection in recipient
- Two types
  - Plasma
  - Hyperimmune globulin
Hyperimmune Globulin

- Long track records of effectiveness
- Process
  - Patients know to have high titers
  - Plasmapheresis
  - Fractionation to isolate IGG
  - Concentrate given to patient
Convalescent Plasma

- Patient documented to have infection
  - Ideally with high titers of ab
- Unit of whole blood drawn or plasmapheresis
- Plasma spun off and frozen
Issues

- Plasma raises IgG by ~5%
- Lack of antibody testing
  - Are high titers neutralizing?
- Many anecdotes but negative RCT studies in other disease
- One trial stopped because patients already had antibodies
Netherland Trial

- 86 patients (~10 days into illness, ~2 days in hospital)
  - 79% already had neutralizing antibodies
  - Titers same as plasma
  - Trial stopped
Plasma: Bottom Line

• ~ 10,000 received plasma outside of trials
• Many units no titer testing was done
• Need RCT data
Blood Groups

- Multiple (7) studies showing
  - Group O protective: 0.80
  - Group A risk factor: 1.20
  - Both serology and genetic studies
Blood Groups

• Type O protective?
  – Lower levels of von Willebrand factor

• Anti-A binds virus spike protein
  – Group A at risk
COVID Thrombosis

• Very high rate of thrombosis
  – ICU patients
    • Venous thrombosis
    – Arterial thrombosis
• Low suspicion for diagnosis and treatment
• Need RCT to report!