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• In order to support the growth of the ECHO movement, Project ECHO® collects participation data for each teleECHO™ program. This data allows Project ECHO to measure, analyze, and report on the movement’s reach. It is used in reports, on maps and visualizations, for research, for communications and surveys, for data quality assurance activities, and for decision-making related to new initiatives.
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THROMBOSIS IN COVID-19 AN UPDATE

Masarret Fazili, MD
No conflicts of interest to declare
Disclosure

The content of this presentation does not relate to any product of a commercial entity; therefore, I have no relationships to report.
Objectives

• Participants will understand the proposed pathophysiology of venous thromboembolic disease in Covid-19.
• Participants will understand the role of lab testing and imaging to assess thromboembolic risk in patients with Covid-19.
• Participants will understand prophylaxis and treatment strategies for venous thromboembolic disease in Covid-19.
Covid-19 Pandemic

- US Case Count > 13 million
- US deaths > 250,000
- Utah Case Count > 190,000.
- Thrombotic complications are associated with 40% of deaths.
Hospitalized COVID-19 Patients and Venous Thromboembolism
A Perfect Storm

The coronavirus disease 2019 (COVID-19) pandemic caused by severe acute respiratory syndrome coronavirus 2 has taken the world by storm. As of May 4, 2020, there are >1.2 million confirmed cases in the United States and >66,000 deaths. Venous thromboembolism (VTE), which includes deep vein thrombosis (DVT) and pulmonary embolism (PE), is common in seriously ill patients with infection. Early reports suggested a VTE rate of approximately 27% in critically ill patients hospitalized with COVID-19.¹ This high rate of VTE, and, in particular, PE, is consistent with what has been reported in critically ill patients with pneumonias caused by other viruses, including H1N1 pneumonia and severe acute respiratory syndrome.²³

Article, see p 114

Alex C. Spyropoulos, MD
Jeffrey I. Weitz, MD
Incidence of VTE in ICU patients

- PE - 15.7%
- DVT - 10.6%

Metaanalysis - 30.40%

Incidence of VTE in Non-ICU patients

- NYC-c: 1.10%
- Boston-c: 3.10%
- NYC-c: 4.40%
- Spain-c (PE): 6.40%
- Italy-c: 6.60%
- Philadelphia-c: 9.50%
- Metaanalysis: 13%
- DVT 13%
- PE: 6%

Chest 2020, Dr. Sehgal
Rates of Arterial Thrombosis

- Limb arteries - 39%
- Cerebral arteries - 24%
- Great vessels - 19%
- Coronary arteries - 9%
- SMA - 8%

Bar chart showing rates:
- NYC: 0.40%
- Italy: 3.60%
- Netherlands: 3.70%
- Metaanalysis: 4%
- Italy/France: 9.60%
- NYC: 11%
### COVID-19 compared with other diseases

<table>
<thead>
<tr>
<th>Helms et al. (France)</th>
<th>Poissy et al. (France)</th>
</tr>
</thead>
<tbody>
<tr>
<td>77 COVID ARDS vs. 145 matched ARDS controls</td>
<td>PE Incidence in ICU</td>
</tr>
<tr>
<td>All Thrombosis 11.7% vs. 2.1%</td>
<td>COVID-19 (n=107) 20.6%</td>
</tr>
<tr>
<td>(OR 2.6)</td>
<td>Influenza (n=40) 7.5%</td>
</tr>
<tr>
<td></td>
<td>All ICU (n=196) 6.1%</td>
</tr>
</tbody>
</table>

Circulation 2020 142:184-186
SARS-CoV-2 and Coagulopathy

- Virus uses ACE-2 receptor, binding to spike glycoprotein on viral envelope
  - Found in many organs including lung, heart, brain, kidney and endothelium
- Impact of viral infection is pro-inflammatory response:
  - Endothelial injury, inflammatory and immune activation
  - Endothelitis contributes to vascular injury and risk of thrombosis
Severe COVID-19 generates an increase in pro-inflammatory cytokines and activates endothelial cells, neutrophils, mononuclear cells, and platelets leading to tissue factor-mediated activation of coagulation.\(^\text{a}\)\(^\text{a}\)

Coagulation proteases bind to specific receptors that mediate further pro-inflammatory responses.\(^\text{a}\)

The inflammatory response to COVID-19 results in activation of coagulation that itself may modulate further inflammatory activity.
OTHER POTENTIAL MECHANISMS OF THROMBOSIS

• Unique PE phenotype, Pulm Immuno-thrombosis, in-situ microvascular thrombosis

• Hypoxia

• Complement activation

• Increased Pro coagulant proteins, Fibrinogen, factor VIII, vWB, loss of protective anti-thrombin

• Marked Factor V activity (Am J of Hematology, Aug 24, 2020)

• Formation of APL (Science Translational Med Nov 18, 2020)

• Fibrin deposition to wall of infection, activation of neutrophil extracellular traps (NETosis)
Risk Factors for Thrombosis in COVID-19

<table>
<thead>
<tr>
<th>VTE</th>
<th>Arterial Thrombosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male Gender</td>
<td>Male Gender</td>
</tr>
<tr>
<td>Elevated D-dimer</td>
<td>Advancing Age</td>
</tr>
<tr>
<td></td>
<td>Hispanic Race</td>
</tr>
<tr>
<td></td>
<td>History of CAD</td>
</tr>
</tbody>
</table>

JAMA 2020 324;(8):799-801
Periods of VTE Risk for COVID-19 Patients

- **Outpatient (Low Risk Period?)**
  - VTE tied to immobility based on disease severity
  - ? Primary prevention

- **Hospitalization (High-Risk Period)**
  - Period of VTE risk tied to hospital acuity
  - Admission "Universal Prophylaxis" Standard to intermediate dose LMWH or UFH
  - ? Escalated heparin dose
  - Multimodal measures

- **Post-hospital discharge period (Intermediate Risk Period)**
  - Period of VTE risk tied to hospital discharge period
  - Extended thromboprophylaxis
  - DOAC for up to 30d in high risk groups

Patient-related (intrinsic)- and disease-specific (extrinsic incl COVID-19 related) VTE risk factors
How is thrombosis presenting?

• Presentation time is variable. Early in hospital stay vs 1-2 weeks into stay

• Median time from COVID positivity: 11 days (6-33)

• Mild COVID with delayed Thrombosis 3-4 weeks later
  • Most rare presentation
Biomarkers of COVID-19 Coagulopathy

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Trend in COVID-19</th>
<th>Clinical Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Platelets</td>
<td>20-30% have platelets 100-150</td>
<td>Not clearly associated with mortality</td>
</tr>
<tr>
<td>Lymphocytes</td>
<td>Often moderate to severe lymphopenia; 75-83% have ALC &lt; 1.5</td>
<td>Severe lymphopenia (ALC &lt; 0.5) and LDH elevation often seen in critical illness</td>
</tr>
<tr>
<td>PT (prothrombin time)</td>
<td>Mild prolongations (15-16 sec)</td>
<td>Prognostic (some association with mortality)</td>
</tr>
<tr>
<td>D-Dimer</td>
<td>Persistent, marked elevations (4-6x ULN) often seen in severe COVID</td>
<td>Prognostic (associated with mortality)</td>
</tr>
<tr>
<td>Fibrinogen</td>
<td>Typically elevated until late in disease course</td>
<td>Reductions can be seen late (10-14 days) into admission</td>
</tr>
</tbody>
</table>

Guan 2020; Fan 2020; Tang 2020; Bhatraju 2020
The laboratory characteristics of (severe) COVID-19 infection are risk factors for thrombosis:

- High fibrinogen levels in virtually all patients (with very low levels in severely ill patients briefly before death)
- Normal antithrombin levels

Conversely, a mildly to moderately reduced platelet count in the most severe patients and a mild prolongation of the prothrombin time in a minority of patients.

(very) elevated D-dimer levels, in particular in non-survivors
D-dimer and COVID-19

- D-dimer is a degradation product of fibrinolysis
  - Elevated in acute VTE and other conditions
    - COVID-19
    - Non-COVID-19 related respiratory illness
- Is elevated D-dimer due to COVID-19 hypercoagulability or a consequence of diffuse inflammation?
## D-dimer and COVID-19

Admitted to 2 hospitals in Wuhan; mortality 39%

<table>
<thead>
<tr>
<th>D-dimer</th>
<th>Non-survivors</th>
<th>Survivors</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;500 µg/L</td>
<td>4/54 (7%)</td>
<td>51/118 (43%)</td>
</tr>
<tr>
<td>500-1000 µg/L</td>
<td>6/54 (11%)</td>
<td>39/118 (33%)</td>
</tr>
<tr>
<td>&gt;1000 µg/L</td>
<td>44/54 (81%)</td>
<td>28/118 (24%)</td>
</tr>
</tbody>
</table>

Admitted to Tongji Hospital, Wuhan; mortality 41%

<table>
<thead>
<tr>
<th>D-dimer</th>
<th>Non-survivors</th>
<th>Survivors</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;2100 µg/L</td>
<td>34/97 (35%)</td>
<td>3/150 (2%)</td>
</tr>
</tbody>
</table>

Median D-dimer, µg/L (IQR)

<table>
<thead>
<tr>
<th></th>
<th>Non-survivors</th>
<th>Survivors</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(1,300-21,000)</td>
<td>(300-1,300)</td>
</tr>
</tbody>
</table>
Does a (very) high D-dimer point to a high risk of venous thromboembolism or is it just a marker of severe inflammatory pulmonary disease?

D-dimer is a sensitive but not specific marker for venous thromboembolism.

Patients with (very) high D-dimer levels have a concentration-dependent higher 28-day mortality.\(^3,^{18}\)

Anecdotal reports seem to link very high D-dimer levels to an increased risk of venous thromboembolism but it is unclear whether D-dimer is just a marker of higher disease intensity or a link between coagulopathy, thromboembolic events and adverse outcome.
International Society of Thrombosis and Hemostasis (ISTH) sepsis-induced coagulopathy (SIC) scoring system [18]

<table>
<thead>
<tr>
<th>Item</th>
<th>Score</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Platelet count (× 10^9/L)</td>
<td>1</td>
<td>100–150</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>&lt; 100</td>
</tr>
<tr>
<td>INR</td>
<td>1</td>
<td>1.2–1.4</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>&gt; 1.4</td>
</tr>
<tr>
<td>SOFA score</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>≥ 2</td>
</tr>
<tr>
<td>Total score for SIC</td>
<td>≥ 4</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: INR international normalized ratio, SOFA sequential organ failure assessment
# Thrombosis Risk Factors

## 3334 Hospitalized Patients
- VTE Rate: 6% ATE Rate: 11%

<table>
<thead>
<tr>
<th>VTE</th>
<th>ATE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male Gender</td>
<td>Male Gender</td>
</tr>
<tr>
<td>Elevated D-dimer</td>
<td>History of CAD</td>
</tr>
<tr>
<td>Hispanic Race</td>
<td></td>
</tr>
<tr>
<td>↑Age</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>D-dimer (ng/dL)</th>
<th>VTE (HR)</th>
<th>ATE (HR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;230</td>
<td>1 (referent)</td>
<td>1 (referent)</td>
</tr>
<tr>
<td>231-499</td>
<td>1.25 (NS)</td>
<td>1.01 (NS)</td>
</tr>
<tr>
<td>500-1999</td>
<td>2.63</td>
<td>1.52</td>
</tr>
<tr>
<td>2000-4999</td>
<td>4.71</td>
<td>1.98</td>
</tr>
<tr>
<td>5000-9999</td>
<td>14.25</td>
<td>2.95</td>
</tr>
<tr>
<td>&gt;10,000</td>
<td>32.63</td>
<td>2.33</td>
</tr>
</tbody>
</table>

JAMA 2020 324;(8):799-801
D-DIMER

D-dimer cutoff of 1.5µg/mL had a Sensitivity of 85.0% and specificity of 88.5% for diagnosing VTE in COVID patients (JTH, Jun 2020)

D-dimer >2500 predicted PE (European Resp J, Oct 2020)

AC in pts with D-dimer > 4 ULN as it seems to be predictor of thrombosis (Lin et al)

Some institutions, escalated AC at D-dimer >3000 in ICU, or getting a baseline US
DIAGNOSIS OF VTE

- Challenging: restricted access, unstable patient, limited duplex US

- Improving risk stratification: utilize biomarkers, using patient phenotypes like ARDS

- Using US imaging, single limb, and stopping if clot identified

- Any role for Earlier screening.
Scientific and Standardization Committee communication: Clinical guidance on the diagnosis, prevention, and treatment of venous thromboembolism in hospitalized patients with COVID-19

Alex C. Spyropoulos, Jerrold H. Levy, Walter Ageno, Jean Marie Connors, Beverley J. Hunt, Toshiaki Iba, Marcel Levi, Charles Marc Samama, Jecko Thachil, Dimitrios Giannis... See all authors


Manuscript handled by: Marc Carrier
Final decision: Marc Carrier, 21 May 2020
DIAGNOSING PE IN COVID

RECOMMENDATIONS:

• Routine screening for VTE is not recommended by using bedside duplex US or based on an elevated D-dimer
• Perform venous CU if signs/symptoms of DVT are present
• Bilateral leg CU in absence of symptoms or signs of DVT (high Pre-test probability)
• Detection of DVT confirms diagnosis, allows treatment without more tests.
• Negative bilateral leg CU does not exclude PE.
• Perform CTPA for patients with abnormal CXR and no contraindication to CTPA.
• Perform a perfusion-only lung scan for patients with a normal portable CXR, negative bilateral leg CU, and a contraindication to CTPA.
VTE Px in non-ICU setting

- Universal strategy of routine thromboprophylaxis with standard – dose UFH or LMWH after careful assessment of bleeding risk

- LMWH as preferred agent

- Prophylaxis should be modified based on extremes of body weight, severe thrombocytopenia or worsening renal function
VTE Px in ICU setting

- Routine thromboprophylaxis with prophylactic dose UFH or LMWH after careful assessment of bleeding risk
- Intermediate/escalated dose LMWH only in critically ill patients, adjusted for weight, renal fx
- Recommend against using D-dimer to trigger dose escalation outside clinical trials
- Treatment dose heparin not to be used for primary prevention until results of controlled trials available. Inadequate evidence if Rx dose superior to Px dose, unnecessary exposure of pts to risk of bleeding
- Consider Multi-modal thromboprophylaxis with IPC
VTE Rx in hospitalized COVID patient
ISTH SCC GUIDANCE

• Use established guidelines for Rx of confirmed VTE
• LMWH preferred, consider concomitant meds, renal fx and PLT counts.
• Consider change to treatment dose in patients without established VTE but high suspicion, deteriorating Pulm status or ARDS and diagnostic testing not possible.
• Duration of treatment should be at least 3 months.
VTE Prophylaxis of Hospitalized or ICU COVID-19 Patients
Northwell Health

Bleed risk Factors
APROVE Bleed Score < 7 or clinical gestalt

- VTE surveillance portable
- tEEUS/beside TTE as per clinical gestalt but not recommended
- UFH Q8 hrs preferred
- Known whether elevated coagulopathy/DIC or not. Use ISTH DIC calculator

ICU Patient

CrCl > 15ml/min

BMI > 30
- Lovenox 40mg SQ BID + IPCs

BMI < 30
- Lovenox 40mg SQ QD + IPCs

CrCl < 15ml/min or RRT

BMI > 30
- UFH 7500 U SQ Q6*** or Q12 + IPCs

BMI < 30
- UFH 5000 U SQ Q8 + IPCs

1. Not to be used for Pediatric and OB/GYN order sets

EXTENDED THROMBOPROPHYLAXIS

IMPROVE Score, not adequate to ID patients yet
Inadequate evidence so far, we do not know who will benefit
VTE risk at 30 days low, 0-0.6% from early data. Risk may not be as high.
There is a fine margin of risk vs benefit
Actively researching just this question with guidance to come
Currently advise against it
COVID-19: Antenatal Management

**EGA @ Diagnosis**

- **< 28 weeks**
  - Detailed survey @ 18-22w **OR** Growth US 6 weeks after diagnosis
  - Lovenox 40mg QD x 2 weeks

- **28-35\(^{+6}\) weeks**
  - Growth US 6 weeks after diagnosis **OR** @ 36-38 weeks
  - Weekly NST/AFI* @ ≥32 weeks until normal growth and fluid assured
  - Lovenox 40mg QD x 2 weeks

- **≥ 36 weeks**
  - Weekly NST/AFI*
  - Growth US if clinically indicated
  - Deliver @ 39 weeks
  - Unfractionated heparin 5000u BID x 2 weeks or until delivery
  - Restart Lovenox 40mg QD x 2 weeks after delivery

---

*Begin 10 days post-diagnosis or symptom onset + at least 24h w/o fever or significant symptoms. Individualize approach if symptoms worsen, fetal movement decreases, etc.*
## International recommendations

<table>
<thead>
<tr>
<th></th>
<th>Antepartum</th>
<th>Intrapartum</th>
<th>Postpartum</th>
</tr>
</thead>
<tbody>
<tr>
<td>UK - RCOG</td>
<td>Risk based</td>
<td>Treat all</td>
<td>Treat all (10 days)</td>
</tr>
<tr>
<td>Australia</td>
<td>Treat all</td>
<td>Treat all</td>
<td>Treat all</td>
</tr>
<tr>
<td>ISUOG</td>
<td>Risk based</td>
<td>Treat all</td>
<td>Treat all</td>
</tr>
<tr>
<td>ISIDOG (Infectious disease in OB/GYN)</td>
<td>Treat all</td>
<td>Treat all</td>
<td>Treat all</td>
</tr>
<tr>
<td>France (CNGOF)</td>
<td>Risk based</td>
<td>Risk based</td>
<td>Risk based</td>
</tr>
<tr>
<td>Swiss Society of GYN and OB</td>
<td>Treat all</td>
<td>Treat all</td>
<td>Treat all</td>
</tr>
<tr>
<td>Swedish Society of OB/GYN</td>
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<td>Treat all</td>
<td>Treat all</td>
</tr>
<tr>
<td>COVID Collaborative Group (Spain)</td>
<td>Treat all</td>
<td>Treat all</td>
<td>Treat all</td>
</tr>
<tr>
<td>ACOG/SMFM</td>
<td>No recommendation</td>
<td>No recommendation</td>
<td>No Recommendation</td>
</tr>
</tbody>
</table>
Conclusions

- No direct evidence about risk in pregnant patients
- Case reports of VTE in COVID pregnant patients
- Most International Societies recommend antepartum, intrapartum and postpartum prophylaxis
- No recommendations from ACOG, SMFM
- We will continue with current recommendations
- Use of a risk-based approach is more complicated
TAKE HOME POINTS

• Thromboprophylaxis for all, stick to evidence-based Prophylaxis
• Routine screening for VTE not recommended
• Monitoring of coag parameters to risk stratify, triage
• Negative D dimer: negative predictive value
• D-dimer as threshold to trigger AC other than in setting of trial not recommended.
• No data for therapeutic anticoagulation w/o overt thrombosis
• Agent selection: Consider co-morbidities
• Parenteral AC preferred, LMWH preferably
• Using anti-Xa for therapeutic UFH monitoring
TAKE HOME POINTS

• Reasonable to de-escalate thromboprophylaxis tx out of ICU
• Recommend against use of thrombolytics outside of a trial
• AC stewardship. Treat for full 3 months in presumed VTE. No need to test later
• Change to DOAC if feasible on D/c
• Clinical trials underway aimed at optimizing Rx during hosp, on d/c and in ambulatory setting.
• >1000 papers
• 188 review articles
• 23 systematic reviews
• 7 meta analysis
• 37 ongoing clinical trials
## Management strategy

<table>
<thead>
<tr>
<th>COVID-19†</th>
<th>Coagulation tests</th>
<th>Standard-dose VTE PPX</th>
<th>Escalated-dose* VTE PPX</th>
<th>Therap. dose anti-coagulation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Outpatient</td>
<td></td>
<td>Consider†</td>
<td></td>
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</tr>
<tr>
<td>Inpatient</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ward</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ICU</td>
<td>X</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Confirmed VTE</td>
<td>X</td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Presumed PE†</td>
<td>X</td>
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<td></td>
<td>X</td>
</tr>
<tr>
<td>ARDS</td>
<td>X</td>
<td></td>
<td>X</td>
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</tbody>
</table>

Suggested approach to COVID-19 patients and coagulopathy. All admitted patients should have baseline PT, aPTT, fibrinogen, D-dimer, and platelet
Algorithm for Anti Coagulation in Covid-19
Journal of Intensive Care, Sep 14, 2020

Patient with COVID-19

Obtain baseline prothrombin time, d dimer, fibrinogen, platelet count

Assess Bleeding risk

Low/acceptable
Encourage mobilization + Initiate thromboprophylaxis with UFH/LMWH
*consider higher dosing for patients at higher risk (obese, active malignancy, immobility, surgery/spontaneous echo contrast on US)

High
Encourage mobilization + Sequential Compression device (SCD) when not ambulating + Hold thromboprophylaxis

Active routine screening for venous/arterial thrombosis (cutaneous, pulmonary, deep venous, stroke, line thrombosis, acute coronary syndromes): Clinico-radiological surveillance
Trend d Dimer
Screen positive or very high clinical suspicion of occult microthrombosis

Consider therapeutic anticoagulation (AC) with either UFH/LMWH titrated to aPTT/anti-Xa levels. Reassess bleeding risk routinely
(Insufficient evidence to recommend initiation of therapeutic AC based on d-dimer cutoffs only)

Transition to Vitamin K antagonist/UFH/Direct oral anticoagulant on discharge (*Beware of drug interactions with antivirals/antiplatelets)
Insufficient data on long term outcomes in patients (3-6 months in the absence of risk factors beyond COVID-19/modifications needed in the setting of additional risk factors)
References

13. Zang et al, D-dimer levels on admission to predict in hospital mortality in COVID patients, JTH, Vol18, Issue 6
23. Spyropoulos et al, SSCC, clinical guidance on the diagnosis, prevention and treatment of VTE in hospitalized patients with COVID, JL of Thrombosis and Haemostasis/ Vol 18, issue 8