Thrombosis in the Hospitalized COVID Positive Patient
Practical experiences and advice from the experts

Presented in Partnership with the Society of Hospital Medicine

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Presenter: Tracy Minichiello, MD

Expert Panel:
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Geoffrey Barnes, MD  Bill Dager, PharmD
Allison Burnett, PharmD  Steven Deitelzweig, MD
Mark Crowther, MD  David Garcia, MD

Note: Please follow all advisories from the Centers for Disease Control and Prevention
www.cdc.gov and your local public health organizations
Presenters

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## Disclosure for Conflicts of Interest

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<tr>
<th>Name</th>
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<td><strong>Arthur Allen</strong></td>
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<td>Boehringer-Ingelheim, BMS/Pfizer, Roche Diagnostics</td>
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<td>Personal Funding/Advisory Boards</td>
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<td>Preparation of Educational Materials and/or presentations</td>
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<td>Alexion, Bayer, Novo Nordisk, Pfizer, Sanofi, Spark, and Takeda</td>
<td>Research Support on his behalf</td>
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<td><strong>Steven Deitelzweig</strong></td>
<td>Portola, BMS, Pfizer</td>
<td>Research and Speakers Bureau</td>
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Allison Burnett, Bill Dager, David Garcia and Tracy Minichiello have no Conflicts of Interest.
Questions

➢ Is COVID 19 infection a hypercoagulable state?

➢ What DVT prophylaxis should patients with COVID 19 receive? Do recommendations change for those in the ICU?

➢ How do we evaluate COVID 19 patients for suspected VTE?

➢ What anticoagulation regimen is recommended for acute VTE in patients with COVID 19 and how should it be monitored?

➢ Should severely ill COVID 19 patients receive anticoagulation in the absence of an indication (i.e. AFIB, VTE etc.)?

➢ Should COVID 19 patients be discharged on VTE prophylaxis?
Case

69 year old man with HTN, remote CAD, obesity, weight 95kg presents with fever 102, fatigue, O2 sat 89% on room air. Labs with WBC 8/hgb 14/PLTs 105. PT mildly prolonged, D-dimer 950ng/ml. CXR is clear. He lives with his daughter who was recently diagnosed with mild COVID-19 infection. He is admitted to the COVID ward. O2 sats increase to 92% on 3 L O2.

Are these coagulation abnormalities expected in COVID 19?
COVID 19 Common Hematologic Abnormalities

• Elevation in d-dimer, fibrinogen and other inflammatory markers
• Thrombocytopenia less frequent and generally mild (platelet counts 100-150)
• Lymphopenia ~30-50% of patients
• Anemia has not been reported frequently

What are implications of Hematologic Abnormalities in COVID-19?

- Tang et al showed that abnormalities in coagulation are markers of severity of disease and track with prognosis. Non survivors had prolonged PT, elevated d-dimer and met ISTH criteria for DIC. D-dimer > 3 µg/ml associated with increased mortality.

- A meta-analysis of nine studies including COVID-19 patients with nearly 400 with severe disease found that platelet count was significantly lower in patients with more severe COVID-19 and more pronounced thrombocytopenia associated with increased mortality
Case

69 year old man with HTN, remote CAD, obesity, weight 95 kg presents with fever 102, fatigue, O2 sat 89% on room air. Labs with WBC 8/hgb 14/PLTs 105. PT mildly prolonged, D-dimer 950ng/ml. CXR is clear. He is admitted to the COVID ward. O2 sats increase to 92% on 3 L O2.

➢ What are the implications of these coagulation abnormalities? Is this DIC or something else?

➢ Should we be monitoring these and if so what and how often?

➢ Is COVID-19 a hypercoagulable state? If so, why?
Case

69 year old man with HTN, remote CAD, obesity, weight 95kg presents with fever 102, fatigue, O2 sat 89% on room air. Labs with WBC 8/hgb 14/PLTs 105. PT mildly prolonged, D-dimer 950ng/ml. CXR is clear. He is admitted to the COVID ward. O2 sats increase to 92% on 3 L O2.

Should he be started on pharmacologic DVT prophylaxis and if so what agent?
ISTH GUIDANCE – DVT PROPHYLAXIS

Prophylactic anticoagulation (LMWH) should be considered in ALL patients (including non-critically ill) who require hospital admission for COVID-19 infection, in the absence of any contraindications (active bleeding and platelet count less than 25 x 10^9/L)

• Thachil J et al. ISTH interim guidance on recognition and management of coagulopathy in COVID-19. JTH 2020 March 25

ASH COVID 19 DVT Prophylaxis Recommendations

All hospitalized patients with COVID-19 should receive pharmacologic thromboprophylaxis with LMWH or fondaparinux (suggested over unfractionated heparin to reduce contact) unless the patient is judged to be at increased bleeding risk. In patients with history of HIT, use fondaparinux. In patients where anticoagulants are contraindicated or unavailable, use mechanical thromboprophylaxis (e.g. pneumatic compression devices).

British Guidance

• Recommendation 1: The risk of venous thromboembolism (VTE) must be assessed in all patients admitted to hospital, and prevention should be given to all high-risk patients according to international guidance on thromboprophylaxis in medical patients (NICE/ASH)
  • For CrCl > 30: Give LMWH or fondaparinux s.c. according to license
  • For CrCl < 30 or AKI: Unfractionated heparin 5000 units SC BD or TDS or dose-reduced LMWH
  • All completely immobilized patients would benefit from intermittent pneumatic compression in addition to pharmacological thromboprophylaxis
• Mechanical thromboprophylaxis should be used alone if platelets <30,000 or bleeding

Case

69 year old man with HTN, remote CAD, obesity, weight 95kg presents with fever 102, fatigue, O2 sat 89% on room air. Labs with WBC 8/hgb 14/PLTs 105. PT mildly prolonged, D-dimer 950ng/ml. CXR is clear. He is admitted to the COVID ward. O2 sats increase to 92% on 3 L O2.

- Should he be started on pharmacologic DVT prophylaxis and if so what agent?
- Should all COVID patients receive pharmacologic DVT prophylaxis (unless contraindicated)?
- What would you recommend in obesity? CrCl < 30 ml/min?
Case

On HD #4 he becomes more short of breath despite increasing nasal canula O2. On 6 L O2 his sats are in the mid 80s. He is transferred to the ICU and placed on heated high flow nasal canula O2. His D-dimer is now 2,000 ng/L.

He is on 40 mg SQ daily of LMWH. Should his anticoagulation regimen be adjusted?
Prevalence of VTE in Severe COVID 19

• Retrospective analysis of 81 patients with severe COVID PNA in ICU in China. All patients had imaging (not symptom driven)
• 20% had DVT
• No PHARMACOLOGIC VTE prophylaxis had been given
• Prolonged aPTT, low WBC count, age and elevated d-dimer were predictive
• D-dimer cut of > 3000 µg/ml associated with specificity of 95%, NPV of 95%

Thrombosis in COVID-19 Pneumonia

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

- 184 ICU COVID PNA pts
- 31% had thrombotic episode, symptomatic – majority PE (1/3 of PE sub segmental)
- Despite DVT prophylaxis
- Predictors: age, coagulopathy (PT> 3s, aPTT>5s)

https://doi.org/10.1016/j.thromres.2020.04.013
DVT Prophylaxis with LMWH and Mortality in COVID-19

449 patients with severe COVID-19; of which 99 received heparin (mainly with LMWH) at prophylactic doses. Anticoagulant therapy with LMWH (dosing 40-60 mg qd) associated with decreased mortality (40.0% vs 64.2%, P=0.029) in patients with D-dimer > six-fold of upper limit of normal or SIC score $\geq 4$.

- Tang, N et al. Anticoagulant treatment is associated with decreased mortality in severe coronavirus disease 2019 patients with coagulopathy https://doi.org/10.1111/JTH.14817
Case

On HD #4 he becomes more short of breath despite increasing nasal canula O2. On 6 L O2 his sats are in the mid 80s. He is transferred to the ICU and placed on heated high flow nasal canula O2. His D-dimer is now 2,000 ng/L.

- He is on 40 mg SQ daily of LMWH. Should his anticoagulation regimen be adjusted?
- What is your approach to DVT prophylaxis in the ICU patient with COVID 19? Does D-dimer guide you?
- Is there any role for monitoring anti-Xa levels?
Case

On HD #4 he becomes more short of breath despite increasing nasal canula O2. On 6 L O2 his sats are in the mid 80s. He is transferred to the ICU and placed on heated high flow nasal canula O2. His D-dimer is now 2,000 ng/L.

Should he be evaluated for PE and if so how?
British Guidance

Recommendation 2: Consider the possibility of pulmonary thromboembolism (PTE) in patients with sudden onset of oxygenation deterioration, respiratory distress, reduced blood pressure.

ASH COVID-19 PE Guidance

- How do we diagnose PE if we cannot perform CTPA or V/Q lung?

**Bedside assessment**

- Does a normal D-dimer level effectively rule out PE/DVT? **YES**
- If D-dimer levels change from normal to abnormal, or rapidly increase on serial monitoring, is this diagnostic of PE/DVT? **NO**
- If a patient is empirically started on anticoagulation for suspected PE, how long should they be anticoagulated? **3months**
- What if later investigation shows no evidence of PE? **it doesn’t matter**

Case

On HD #4 he becomes more short of breath despite increasing nasal canula O2. On 6 L O2 his sats are in the mid 80s. He is transferred to the ICU and placed on heated high flow nasal canula O2. His D-dimer is now 2,000 ng/L.

- Should he be evaluated for PE and if so how?
- Can you suggest an algorithm to approach these patients?
Critically Ill Patients

- Obi AT, Barnes GD... Henke PK. JVS:VLD 2020 (in press)
Non-Critically Ill Patients

• Obi AT, Barnes GD... Henke PK. JVS:VLD 2020 (in press)
Case

It is determined that he does not have acute PE. But this patient’s D-dimer is markedly elevated.

- Is there a role for full intensity anticoagulation in the treatment of severely ill COVID-19 patients in the absence of indication for AC? Should elevated D-dimer prompt full dose anticoagulation?
- What would be the rational behind the use of heparin?
- Is there a role for tPA?
ASH COVID-19 ANTICOAGULATION IN SEVERE COVID 19 IN ABSENCE OF CONFIRMED VTE?

• No-only prophylactic AC unless there is an indication for full therapeutic-intensity anticoagulation.

• Although therapeutic anticoagulation is recommended by some physicians in China because they have observed high rates of thrombosis in seriously ill people with COVID-19, these observations occurred in a setting where routine thromboprophylaxis may not be routinely practiced.

[Source: https://www.hematology.org/covid-19/covid-19-and-vte-anticoagulation]
ASH COVID-19 ANTICOAGULATION IN SEVERE COVID 19 IN ABSENCE OF CONFIRMED VTE

➢ Are there any clinical scenarios in which empiric therapeutic anticoagulation would be considered in COVID-19 patients?

- Intubated patients who develop sudden clinical and laboratory findings highly consistent with PE, especially when CXR and/or markers of inflammation are stable or improving.

- Patients with physical findings consistent with thrombosis, such as superficial thrombophlebitis, peripheral ischemia or cyanosis, **thrombosis of dialysis filters, tubing or catheters**, or retiform purpura (branching lesions caused by thrombosis in the dermal and subcutaneous vasculature).

- Patients with respiratory failure, particularly when D-dimer and/or fibrinogen levels are very high, in whom PE or microvascular thrombosis is highly suspected and other causes are not identified (e.g., ARDS, fluid overload).

Case

- If he had been found to have acute PE what anticoagulation regimen would you recommend?
- If on IV UFH how would you monitor it?
- Any concerns about use of DOACS? Should DOACs be used for ANY hospitalized patient with COVID 19? What about warfarin?
• British Guidance - Recommendation 3: Consider switching to LMWH in patients taking direct oral anticoagulants (DOACs) or vitamin K antagonist (e.g warfarin) for stroke prevention in atrial fibrillation or previous VTE.

• Consider using pre-filled LMWH syringe sizes
  • Any hard outcome benefits of measuring Anti-Xa for dosing adjustments is unclear and is another trip into the patients room

• DOACs can interfere with Anti-Xa measurements for heparin infusions

• aPTT may be elevated in COVID19 – Anti-Xa monitoring may be preferred
  • For guidance on transitioning from the aPTT to Anti-Xa – see the Anticoagulation Forum Centers of Excellence [https://acforum-excellence.org/Resource-Center](https://acforum-excellence.org/Resource-Center)
## Interactions with Experimental COVID-19 Therapies

Charts updated 9 April 2020

Please check [www.covid19-druginteractions.org](http://www.covid19-druginteractions.org) for updates.

Please note that if a drug is not listed it cannot automatically be assumed it is safe to coadminister. No recommendation to use experimental therapy for COVID-19 is made. Drug interaction data for many agents are limited or absent; therefore, risk-benefit assessment for any individual patient rests with prescribers.

### Anti-coagulant, Anti-platelet and Fibrinolytic

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[www.covid19-druginteractions.org](http://www.covid19-druginteractions.org)
Case

Over the next 4 days his O2 requirement decreases. He is transferred back to the floor on 4 L O2 with saturation of 93%. On HD #15 he is ready for discharge.

- Should he be discharged on pharmacologic DVT prophylaxis?
- If so, which agent?
Extended Duration Prophylactic Anticoagulation

**EXCLAIM**[^a]

- **VTE Events Incidence** (P=0.042, ARR=1.53%)
  - 0.30% Placebo
  - 0.80% Extended-Duration Enoxaparin (P<0.05)

**MAGELLAN**[^b]

- **VTE Events Incidence** (P=0.02, RRR=23%)
  - 0.40% Enoxaparin Group
  - 1.10% Extended-Duration Rivaroxaban (P=0.001)

**APEX**[^c]

- **VTE Events Incidence** (P=0.006, RRR=24%)
  - 0.60% Enoxaparin Group
  - 0.70% Extended-Duration Betrixaban (P=0.55)

[^a]: Evidence from EXCLAIM study showing a significant decrease in VTE events with extended-duration Enoxaparin.
[^b]: Results from MAGELLAN study indicating a 23% relative risk reduction with extended-duration Rivaroxaban.
[^c]: Data from APEX study showing a 24% relative risk reduction with extended-duration Betrixaban.
Resources

- Centers for Disease Control
  www.cdc.gov/coronavirus/2019-nCoV

- Anticoagulation Centers of Excellence Resource Center
  acforum-excellence.org/Resource-Center

- ASH Guidance

- British Guidance on VTE prevention

- ISTH COVID 19 Resources
  https://academy.isth.org/isth/#!*listing=3*browseby=2*sortby=1*label=19794*featured=16717

- ISTH Management of Coagulopathy

- ISTH Webinar on COVID

- MGH COVID 19 Resources

- Liverpool COVID-19 Drug Interactions
  https://covid19-druginteractions.org
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