COVID-19: thrombosis & thromboprophylaxis

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Dedicated to my brother Philip who died of COVID-19 this week
COVID-19

• Originated in China in Dec 2019
• 101 days since WHO were notified
• Nearly every country of the world affected by April 2020 except for Antartica & Polynesian islands
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Aim of this talk
- To look at COVID-19 in the context of what we already know
- Not looking at haemostasis in isolation, for it reflects other organ dysfunction e.g liver disease

- Adhere to hard evidence rather than beliefs
- Recognise that many publications about COVID-19 are poor quality
- Recognition that doctors in their altruism want to help & may over diagnose & over treat in times of stress
A reminder of concepts around haemostasis in sepsis, inflammation & hypoxia

The coagulation system evolved as an effector pathway of the immune response: laying down fibrin around bacteria to physically entrap them & prevent their dissemination.

Thus the end point of inflammation is thrombosis e.g Behcets disease, vasculitis …and anticoagulants do not improve outcome in these states Instead we treat the inflammatory process.

Hypoxia → hypoxia- inducible transcription factors which leads to a prothrombotic state (affect tissue factor & PAI-1 genes).
Admission for COVI-19 @GSTT

<table>
<thead>
<tr>
<th>Category</th>
<th>Clinical criteria for oxygenation</th>
<th>Suggested action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Green</td>
<td>$\text{SaO}_2 &gt; 94%$ on Room Air and RR≤20</td>
<td>Discharge for self-isolation as per PHE</td>
</tr>
<tr>
<td>Yellow</td>
<td>$\text{SaO}_2 &gt; 94%$ on FiO$_2$ 28-40%</td>
<td>Admit to medical ward</td>
</tr>
<tr>
<td>Amber</td>
<td>$\text{SaO}_2 ≤ 94%$ on FiO$_2$ 40% despite optimisation</td>
<td>Start 15L O$_2$ via non-rebreath mask CRT review in ED</td>
</tr>
<tr>
<td>Red</td>
<td>$\text{SaO}_2 ≤ 94%$ on 15L O$_2$ via non-rebreath mask</td>
<td>Urgent CRT review and prepare for intubation</td>
</tr>
<tr>
<td>Peri-arrest</td>
<td></td>
<td>Fast bleep CRT and MERIT</td>
</tr>
</tbody>
</table>

Management of Respiratory Failure
Suspected or Confirmed COVID-19

- **Conventional Oxygen Therapy (COT)**
  - $\text{O}_2$ Flow: 0.5 L/min
- **Targets**:
  - $\text{SpO}_2 ≥ 94\%$
  - $\text{HR} < 30/\text{min}$
  - $\text{SaO}_2 > 80\%$

- **Intubation + MV (High FiO$_2$)**
  - Volume Control ventilation
  - Tidal Volume: 8 ml/kg PBW
  - PEEP: $\geq 10$ cmH$_2$O
  - $\text{RR}$: Initially to ETCO$_2$ 4-6 kPa

- **If not intubated at presentation**
  - Low dose vasopressors

- **If intubated at presentation**
  - Low dose vasopressors

- **Aim to Switch to APRV (Call for advice)**
  - Initial settings:
    - $P_{aw}$ 20-28 cmH$_2$O
    - $P_{aw}$ 2-8 cmH$_2$O
    - $\text{T}_1 \text{aw}$ 3 \% $\text{T}_{aw}$ 0.5 \% Step D
    - $\text{P}_{aw}$ 0.5 \% Step C

- **Aim to Combine**
  - If targets not achieved

- **First Strategy**
  - Prone Position
  - Same ventilatory settings as above

- **Hypoxaemia refractory to prone position or APRV for ≥ 6 hours (or sepsis if life-threatening)**
  - Discuss with ECMO Consultant
  - ECMO candidate

- **Review Targets and Strategy**
What do we find in patients with COVID-19 pneumonia?

Changes of acute lung injury

Hyaline membrane formation was observed in some alveoli. The infiltrated immune cells in alveoli were majorly macrophages and monocytes. Moderate multinucleated giant cells, minimal lymphocytes, eosinophils and neutrophils were also observed. Most of infiltrated lymphocytes were CD4-positive T cells. Significant proliferation of type II alveolar epithelia and focal desquamation of alveolar epithelia were also indicated. The blood vessels of alveolar septum were congested, edematous and widened, with modest infiltration of monocytes and lymphocytes. Focal hemorrhage in lung tissue, organization of exudates in some alveolar cavities, and pulmonary interstitial fibrosis were observed. Part of the bronchial epithelia were exfoliated. Coronavirus particles in bronchial mucosal epithelia and type II alveolar epithelia were observed under electron microscope. Immunohistochemical staining showed that part of the alveolar epithelia and macrophages were positive for 2019-nCoV antigen.

Yao et al Zhonhua Bing 2020 March 15th translated from Chinese

Acute lung injury leads to a profound inflammatory state due to a cytokine storm/macrophage/endothelial activation

↑ IL-1, IL-6, IL-8, TNF-alpha

• ferritin
• CRP
• D-dimer
• Fibrinogen
What do we find in patients with COVID-19 pneumonia? Changes of acute lung injury

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Also noted in only one of three separate studies that hyaline thrombi were found in a minority of lung micro vessels. And that degeneration & necrosis of parenchymal cells, formation of hyaline thrombus in small vessels, and pathological changes of chronic diseases were observed in other organs ...with no evidence of coronavirus.

- ferritin
- CRP
- Procalcitonin
- Fibrinogen

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Tentative conclusion: This is NOT primarily a thrombotic process but thrombosis is occurring secondary to inflammation & hypoxia.
But

- New England Journal today: Coagulation & Antiphospholipid Antibodies in Patients with COVID-19, a letter from Zhang et al
  - Who reviewed this?!!
  - Anticardiolipin IgA not associated with thrombosis
  - What were the titres of the antibodies? Need to be moderate or high..
  - Transient antiphospholipid antibodies common in acutely ill
  - ...And if critically ill & an arteriopath you expect thrombotic events....
  - KEY Q: Are arterial events greater with COVID-19 than other non-COVID illnesses on Critical Care?
D-dimers are increased in inflammatory states, post operatively, pregnancy, going for a run and in ***non COVID pneumonias***

Taken from Yin et al JTH 2020 on line 3 4 20

### Table 1 Clinical and coagulation characteristics of COVID and non-COVID groups

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Normal range</th>
<th>COVID (n=449)</th>
<th>Non-COVID (n=104)</th>
<th>P values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>65.1 ± 12.0</td>
<td>58.4 ± 18.0</td>
<td></td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Sex ratio (male/female)</td>
<td>268/181</td>
<td>72/32</td>
<td></td>
<td>0.073</td>
</tr>
<tr>
<td>With underlying diseases</td>
<td>272 (60.6%)</td>
<td>64 (61.5%)</td>
<td></td>
<td>0.768</td>
</tr>
<tr>
<td>Receiving heparin</td>
<td>99 (22.0%)</td>
<td>22 (21.2%)</td>
<td></td>
<td>0.842</td>
</tr>
<tr>
<td>28-day mortality</td>
<td>134 (29.8%)</td>
<td>16 (15.4%)</td>
<td></td>
<td>0.003</td>
</tr>
<tr>
<td>Coagulation parameters</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PT (sec)</td>
<td>11.5–14.5</td>
<td>15.2 ± 5.0</td>
<td>16.2 ± 5.2</td>
<td>0.068</td>
</tr>
<tr>
<td>Platelet count (×109/L)</td>
<td>125–350</td>
<td>215 ± 100</td>
<td>188 ± 98</td>
<td>0.015</td>
</tr>
<tr>
<td>D-dimer (µg/mL)</td>
<td>&lt;0.5</td>
<td>1.94 (0.90–9.44)</td>
<td>2.52 (1.40–5.81)</td>
<td>0.140</td>
</tr>
</tbody>
</table>
Why are D-Dimer levels↑ & prognostic in COVID-19?

- Assumptions made that fibrinolytic activation in COVID-19 is product of thrombin generation
- i.e due to secondary fibrinolysis i.e thrombin stimulates t-PA release from the endothelium

References
1 Wu et al., JAMA Intern Med. doi:10.1001/jamainternmed.2020.0994. Published online March 13, 2020
Zhang et al, Allergy. 2020;00:1–12
Huang et al., The Lancet 2020; 395: 497–506
Zhou et al., The Lancet doi:10.1016/S0140-6736(20)30566-3. Published online March 9, 2020
Tang et al., J Thromb Haemost. 2020;00:1–4.
Why are D-Dimer levels ↑ & prognostic in COVID-19?
Hypothesis 1: a result of acute lung injury

- The hallmark of acute lung injury is intra-alveolar fibrin deposition
- (& later remodeling of fibrin → lung fibrosis)
- Urokinase –type plasminogen activator (uPA) produced locally regulates extravascular proteolysis, inhibited by PAI-1
- In SARS -infected mice a dose-dependent ↑ in lung urokinase with dose of SARS injected but locally swamped by PAI-1
- Pathways not clearly understood

Why are D-Dimer levels ↑ & prognostic in COVID-19? Hypothesis 2: produced by activated macrophages

- COVID-19 pneumonia lung histology characterized by many macrophages
- Macrophages generate plasmin & metalloproteinases (MMPs)
- Fibrin degradation also occurs by an alternative pathway- fibrin (ogen) binding to CD11b/CD18 I internalized into the lysosome where cathepsin D degrades it

Severe COVID-19

ACE2 receptor on
Pulmonary epithelium & endothelium

In a minority
COVID-19 pneumonia
Massive inflammatory response
Cytokine storm/macrophage activation

Prothrombotic state due to effects of IL1, IL-6
Severe COVID-19

ACE2 receptor on Pulmonary epithelium & endothelium

In a minority COVID-19 pneumonia
Massive inflammatory response
Cytokine storm/macrophage activation

Prothrombotic state due to effects of IL1, IL-6

Does a pre-existing inflammatory state make COVID-19 pneumonia more likely?
e.g atherosclerosis, diabetes, obesity
Hypertrophic adipocytes (like atherosclerosis & diabetes) induce an inflammatory state.

Obesity is common: BMI > 25 in 75% of UK patients with severe COVID-19 infection
(Source @ICNARC)
High background risk of VTE in critically ill patients

- Hospital-associated VTE – VTE occurring in hospital & up to 90 days post discharge
- But lack of current data and variation in severity of illness to qualify for critical care beds across the world
- What is the current VTE risk in critical care?
  - 1982 Cade 1982 119 patients DVT in 29% vs 13% UFH 5,000 BD by day 6
  - 1999 MEDENOX 1102 pts placebo arm 15% had DVT/PE by day 14

Risk factors
- Increasing age
- Acute infective illness
- Use of venous lines
- Underlying patient risk factors
- Immobility
- Etc etc
Benefits of heparinoid thromboprophylaxis for 6-14 days over placebo in medical patients

<table>
<thead>
<tr>
<th>Study</th>
<th>RRR</th>
<th>Thromboprophylaxis</th>
<th>Patients with VTE (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MEDENOX¹</td>
<td>63%</td>
<td>Placebo</td>
<td>14.9*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Enoxaparin 40 mg</td>
<td>5.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Placebo</td>
<td>5.0*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dalteparin</td>
<td>2.8</td>
</tr>
<tr>
<td>PREVENT²</td>
<td>45%</td>
<td>Placebo</td>
<td>10.5⁺</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dalteparin</td>
<td>5.6</td>
</tr>
<tr>
<td>ARTEMIS³</td>
<td>47%</td>
<td>Placebo</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Fondaparinux</td>
<td></td>
</tr>
</tbody>
</table>

RRR = relative risk reduction

Does LMWH/UFH reduce risk?

Alhazzani et al Crit Care Med 2013; 41: 2088
- Systematic review 7,226 pts in RCTs
- ↓ sympt/asympt DVT RR 0.51 (95% CI 0.41-0.64); p <0.0001)
- ↓ PE RR 0.52 (95% CI 0.28-0.92); p= 0.04
- No difference in bleeding or mortality

Which is better?

Lim et al Crit Care Med 212;40: 328
- Compared LMWH vs UFH in same group
- LMWH ↓ DVT & PE> UFH
- For PE RR 0.52: 95% CI 0.28,0.97) p=0.04
- No difference in bleeding or mortality
Extended thromboprophylaxis in medical patients

Trials Of Extended Thromboprophylaxis In Acute Medically Ill Patients

VTE events (symptomatic and proximal asymptomatic)

<table>
<thead>
<tr>
<th>Trial</th>
<th>Placebo</th>
<th>Enoxaparin</th>
<th>Enoxaparin</th>
<th>Apixaban</th>
<th>Enoxaparin</th>
<th>Rivaroxaban</th>
<th>Enoxaparin</th>
<th>Betrixaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>EXCLAIM</td>
<td>0.3</td>
<td>0.8</td>
<td>2.5</td>
<td>4</td>
<td>0.4</td>
<td>7.03</td>
<td>0.57</td>
<td>5.3</td>
</tr>
<tr>
<td>ADOPT</td>
<td>0.2</td>
<td>0.5</td>
<td>3.1</td>
<td>2.7</td>
<td>4.4</td>
<td>5.7</td>
<td>4</td>
<td>1.1</td>
</tr>
<tr>
<td>MAGELLAN</td>
<td>0.4</td>
<td>0.2</td>
<td>0.5</td>
<td>5.7</td>
<td>0.001</td>
<td>0.02</td>
<td>0.57</td>
<td>0.67</td>
</tr>
<tr>
<td>APEX</td>
<td>0.57</td>
<td>0.01</td>
<td>0.8</td>
<td>2.5</td>
<td>0.006</td>
<td>0.04</td>
<td>0.01</td>
<td>0.04</td>
</tr>
</tbody>
</table>

MARINER trial (low dose rivaroxaban) excluded as only measured symptomatic & fatal VTE
Criteria for extending prophylaxis

- **Age ≥ 75 y or**
- **Past history of cancer or VTE or**
- **EXtra risk factors***
  - *Known risk factors for VTE including: D-dimers ≥ 2 upper limit of normal range, Intensive Care Unit stay, or 2 other factors such as past history of superficial VT, obesity, varicose veins, chronic venous insufficiency, lower extremity paresis, hormone therapy, thrombophilia (congenital or acquired), concomitant use of erythropoiesis stimulating agents*
  - **planned admission >2 days, but none of the admission criteria listed in the moderate risk group consider on a case by case basis**
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Anticoagulant treatment is associated with decreased mortality in severe COVID-19 patients with coagulopathy
Tang et al, JTH 2020, preprint

- Retrospective study in Tongji Hospital, 449 patients with severe COVID-19 infection, 99 (22%) received heparin
Anticoagulant treatment is associated with decreased mortality in severe COVID-19 patients with coagulopathy
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Why were only a few on heparin?
(routine VTE risk assessment & thromboprophylaxis is clearly not used, hence high rates of thromboembolism seen)
Which heparin?
What dose?
Unanswered Qs in thrombosis & thromboprophylaxis in COVID-19 infection

Rates of thromboembolism

• What are the current rates of VTE in critically ill patients?
• Are the rates of thrombosis higher than other patients on critical care especially can we compare with non-COVID-19 viral pneumonia?

Thromboprophylaxis

• Is weight adjusted thromboprophylaxis better than empirical dosing? (Many trial excluded high weight individual AND obesity rates have ↑ since trials)
• Would a higher dose of thromboprophylaxis be beneficial without significantly increasing bleeding risk?
• Should we add in intermittent pneumatic compression?
• Should we give extended thromboprophylaxis?
Management of fresh VTE in COVID-19

Diagnosis: how to detect PE when can’t use D-dimer?
• This is not a new problem!
• Need to maintain high clinical suspicion esp. if becomes more clinically hypoxic suddenly
• Would manage with 3/12 anticoagulation (would start with LMWH while in critical care then switch to DOAC on discharge) according to current guidelines

Catheter-associated thrombosis
• Six weeks Rx according to current guideline
• Expecting to see it frequently

NB despite thromboprophylaxis we will see VTE in at least 7%, probably more, of all critically ill patients whether COVID-19 or not
Objective: To provide basic guidance for common haematological issues in patients with confirmed or suspected COVID-19 who are being cared for in an ICU environment.

Routine haematological management

1. **Check haemoglobin**
   - If <70g/l give single unit red cell transfusion and re-check

2. **Check platelet count**
   - If <20x10^11 give one pool of platelets and re-check

3. **Check coagulation results**

4. **Check thromboprophylaxis**
   - Check if special circumstances apply (see special circumstances)
   - If special circumstances apply: end steps on this card
   - OTHERWISE —

5. **Check creatinine clearance**
   - If >30ml/min prescribe LMWH per Thromboprophylaxis dose LMWH (see thromboprophylaxis doses)
   - If ≤30ml/min prescribe unfractionated heparin 5000iu S/C TDS

General principles

- Minimise phlebotomy use
- Avoid excessive blood sampling; take arterial samples not more than four hourly
- Use approved COVID order sets on EPR
- Choice of agent: LMWH is preferred; fondaparinux if no supply of LMWH available

Special circumstances

- **AF or previous VTE**
  - If AF or previous VTE which was >90 days ago, no special circumstances apply
  - If VTE ≤ 90 days ago, prescribe treatment dose LMWH

Active bleeding
- Correct abnormal results
- Planned procedures:
  - See Target parameters for procedures

Thromboprophylaxis dosing

<table>
<thead>
<tr>
<th>Actual weight (kg)</th>
<th>Dalteparin</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;49</td>
<td>2500iu OD</td>
</tr>
<tr>
<td>50-99</td>
<td>5000iu OD</td>
</tr>
<tr>
<td>100-139</td>
<td>7500iu OD</td>
</tr>
<tr>
<td>140-180</td>
<td>5000iu BD</td>
</tr>
</tbody>
</table>

Target parameters for procedures

- **Central line/arterial line insertion**
  - Platelets transfusion required if <20x10^11; experienced operator if ≤50x10^11
  - Do not remove until platelets >50x10^11; if urgent removal is indicated, platelet transfusion required

- **Chest drain or tracheostomy insertion**
  - INR <1.5 / APTT <1.5
  - Fibrinogen >1.5g/l
  - Platelet count >60x10^11