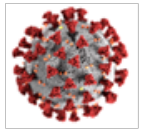
Evidence current as of 1/5/2020



Covid-19

Rapid Review for the EC

Tuesday, 28 April 2020

Review 7

Compiled by Dr Kamlin Ekambaram, Dr Luke Bush and Dr Lauren Lai King

The purpose of this regular review, is to present COVID-19 related questions in Emergency Medicine

We accept that available literature on the topics covered in these reviews may be scarce or incomplete, but shared discussion of novel front line strategies may be a tool to augment our clinical practice and develop future policy

Topic:

- **COVID-19 Associated Coagulopathy (CAC)**
- **VTE and D-dimer**
- **JACC Consensus Recommendations**

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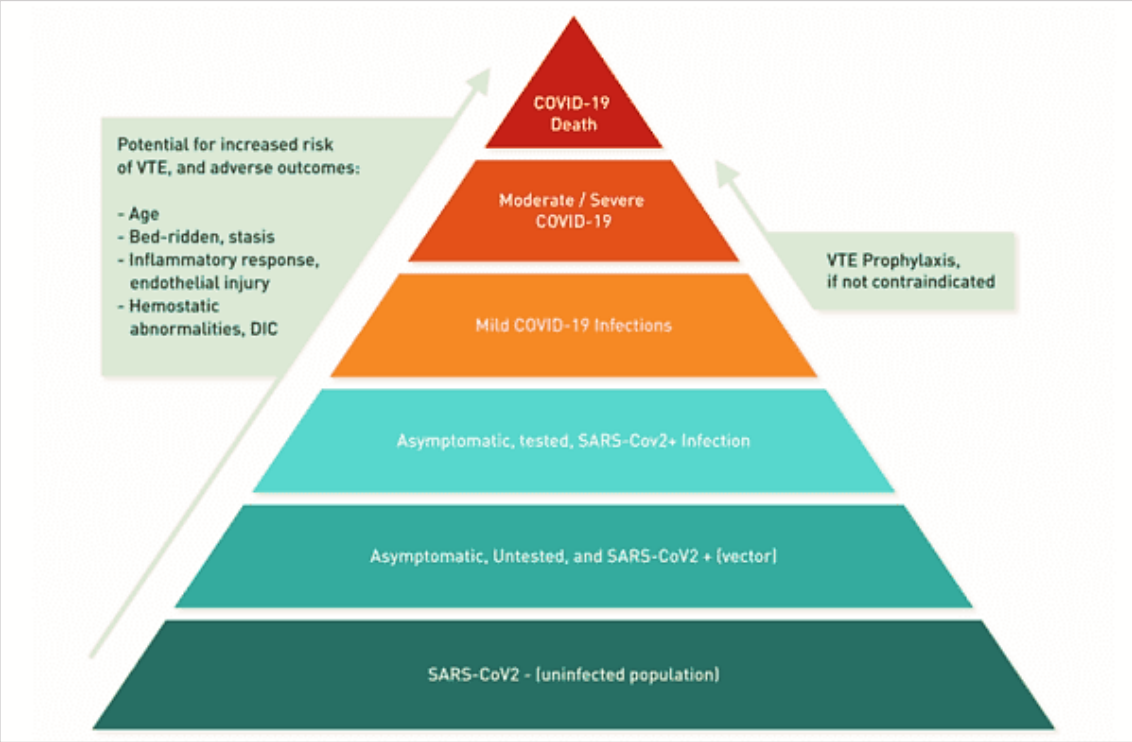
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Haematological Adverse Outcomes

Increased risk of venous and arterial thrombotic complications

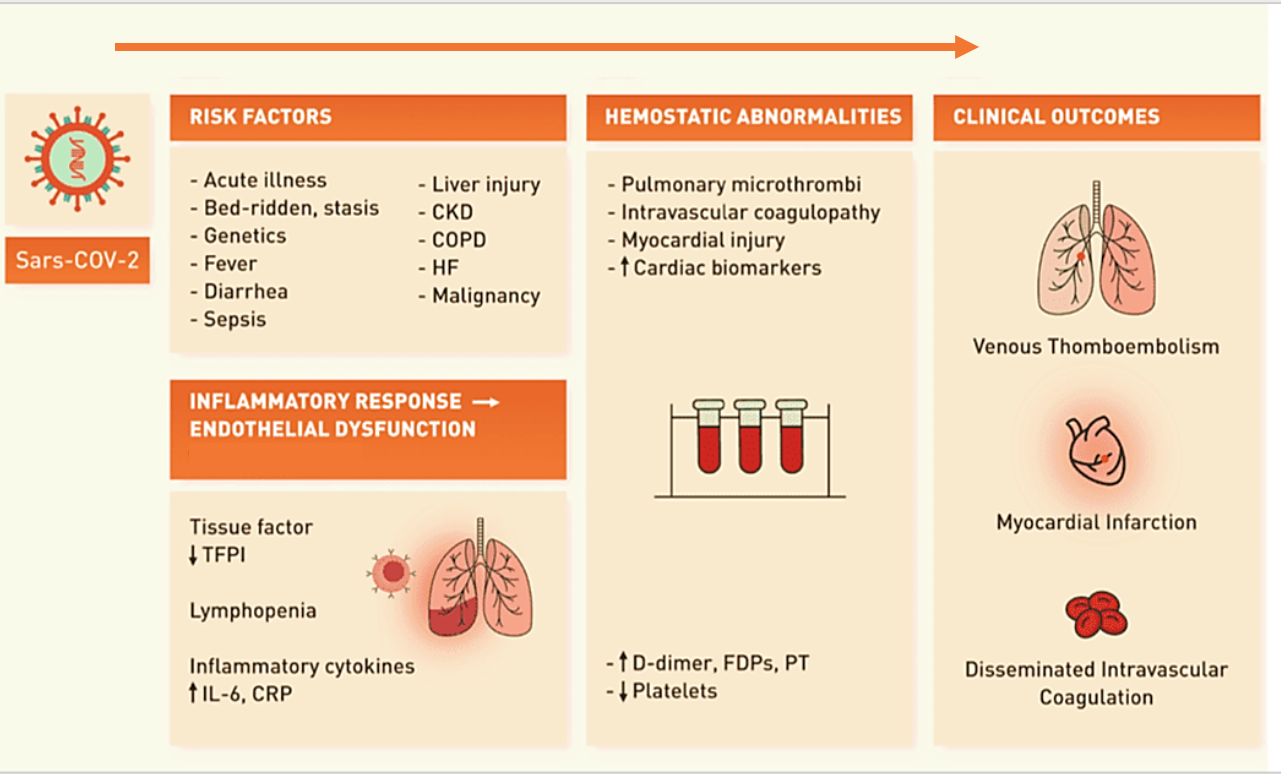
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It is becoming increasingly clear that morbidity and mortality from COVID-19 is not only related to the direct effects of the virus or the associated pneumonia. Identifying interventions that may have an impact on morbidity and mortality are important, as at this point we don't have any effective direct treatment for the disease.

Thrombotic complications are increasingly recognised as a significant contributor to the morbidity and mortality that is seen in COVID-19

There is some evidence and significant debate as to whether our current Heparin thrombo-prophylactic and therapeutic strategies adequately mitigate the effects of the coagulopathy associated with COVID-19.



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COVID-19-associated coagulopathy (CAC)

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Hospitalised patients with COVID-19 should be offered prophylactic LMWH unless contraindicated.

There is no evidence to suggest that in patients with CAC who are **not bleeding** that **blood product** administration improves outcomes

Whether **critically ill COVID-19** patients should receive **therapeutic-intensity** anticoagulation in the absence of confirmed or suspected VTE is currently **unknown.**

Any decision to use post-discharge thromboprophylaxis should consider the **individual patient's VTE risk factors**, including reduced mobility and bleeding risk as well as feasibility.



There is a well-established link between inflammation and an increased risk of deep vein thrombosis (DVT) (1).

A potential explanation is that vessel wall inflammation initiates thrombus formation, through the activation of endothelial cells, platelets, and leukocytes that trigger the coagulation pathway - "cytokine storm." (2)

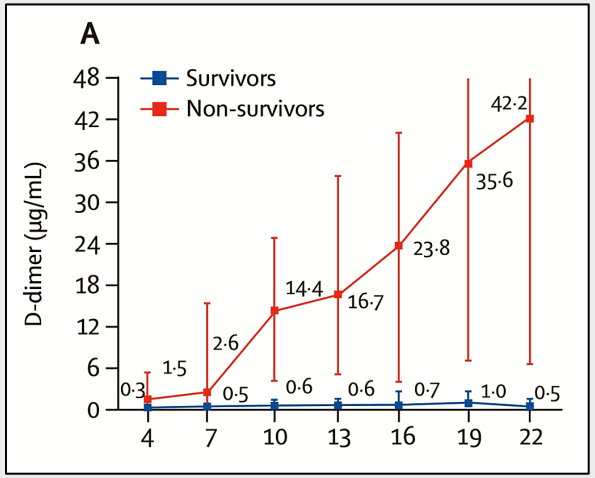
CAC is characterized by elevations in fibrinogen and D-dimer levels. The degree of aPTT elevation is often less than PT elevation (likely due to increased factor VIII levels), the thrombocytopenia is mild (platelet count ~100 x109/L), and microangiopathy is not present when compared to other sepsis induced DIC patterns.

The haemorrhagic form of DIC appears to be rare in COVID-19. A brief review by Tang et al suggested that **CAC/DIC by ISTH criteria** was present in 71% of non-survivors when compared to 0.6% of survivors in Wuhan(3).

D-Dimer has been proposed as a marker of CAC by various authors. Tang et al suggested its use as a possible independent predictor of mortality with cut-offs around 3 – 4 times the upper limit of normal (ULN).

AND

tentatively showed that **therapeutic anticoagulation** with LMWH was associated with a decreased mortality when the d-dimer was > 6 x ULN.



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VTE and D-Dimer

Approximately a 1/3 of patients admitted to hospital with COVID-19 are having thrombotic complications (4,5)

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Where does that leave us now: Using D-dimer levels to guide practice and treatment of DVT and VTE disease is not reliable. A single value, unless negative, has little value and even increasing values are not necessarily associated with DVT and VTE.

In resource restricted environments, elevated levels do not warrant investigation in the absence of clinical manifestations, whilst negative values may still be helpful.

A high index of suspicion is required, relying on clinical features, aided by POCUS to assist, either finding a DVT, or showing interval changes on ECHO (acute unexplained right ventricular dysfunction) – these can assist in making a diagnosis where CT scan is not available or possible and thus guide further management decisions.

The **optimal preventative strategy, including risk assessment, dosage and duration of prophylaxis** warrant further investigation and in the interim some international and local centres are adjusting their prophylactic and therapeutic strategies based on d-dimer levels.

Our usual practice for hospitalised medical patients is to use **prophylactic LMWH** to decrease their risk of DVT and thromboembolic complications.

In COVID-19, this practice does not appear to decrease the risk to the same extent. There have been suggestions, that in moderate to severely ill COVID-19 patients, not at risk of bleeding, we should be adjusting prophylactic dosages.

Patients hospitalized for acute medical illness are at increased risk for VTE for up to 90 days after discharge. This finding should apply to COVID-19 patients, though sufficient data on incidence is not yet available (6).

Furthermore there is also an argument that even those with COVID-19 that are treated at home should be offered prophylactic LMWH depending on their VTE risk (7). At this point we await further evidence as to whether this will decrease morbidity or mortality.

D-Dimer is strongly associated with severe disease and mortality in COVID-19 (3,8)

We already know that d-dimer is elevated in inflammatory states(1) and there is also autopsy evidence in COVID-19 of pulmonary microvascular thrombosis (9-11). This and other findings suggest a **widespread thrombotic disease** which is still to be clearly defined (12) although a viral endothelitis is proposed (2).

Further research, likely available during the upcoming months, may help guide our local practice

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Heparin Guidance

Covid-19
Rapid Review for the EC

NHS
Imperial College Healthcare
NHS Trust

Until such time as there is clear thromboprophylaxis and therapeutic anticoagulation (TAC) guidance the following are reasonable measures in the EC*:

1. Start appropriate prophylactic dose for those being admitted to the ward
2. Initiate TAC in EC if PE/DVT is suspected.
3. Depending on resources available, for those going home who are at high risk for DVT/VTE, to consider LMWH or NOACs as an outpatient.

*In the absence of contraindications and at dosages as recommended by your institution.

	Disease Severity		
	Mild	**Moderate***	**Severe****
VTE Low Risk	None	Prophylactic LMWH	Prophylactic / TAC**
VTE Moderate Risk	None	Prophylactic LMWH	TAC
VTE High Risk	Prophylactic LMWH	Prophylactic LMWH	TAC

For Inpatients:
High Risk: D-Dimer >6x ULN (>3ug/L) = Therapeutic Anticoagulation (TAC)
Low Risk: D-Dimer <6x ULN (<3ug/L) = Prophylactic Dosing

For Outpatients (Deemed High Risk for DVT/PE Discharge Plan):
If no DVT/PE and on TAC during hospital stay + High risk (D-Dimer Still >6x ULN) –
> 2 weeks of AC post discharge
If no DVT/PE and on TAC during hospital stay + High risk (D-Dimer <6x ULN) –> No
AC post discharge
If confirmed DVT/PE, then normal provoked protocol –> AC for 3 – 6mos

Thromboprophylaxis and anticoagulation in COVID-19 infection

A striking feature of COVID-19 infection is the acute phase response (APR). Several pro-coagulant factors are positive acute phase reactants: Factor VIII, VWF, Fibrinogen and the APR is associated with an increased risk of thrombosis. Published data and local experience confirm that fibrinogen is often markedly elevated in the COVID patients.

Pneumonia and sepsis are often complicated by DIC, but although COVID patients do have abnormalities of coagulation, they are not typical of DIC. The most marked abnormality is an elevation of d-dimer but without a parallel fall in platelets or prolongation of clotting times. This suggests that local rather than disseminated thrombin generation and fibrinolysis is taking place.

The site of thrombin and fibrin formation appears to be the lungs, based on limited post-mortem data and clinical observations from CT scans and ventilation parameters (V/Q mismatch). Some patients have overt pulmonary emboli, but in others it is presumed to be microvascular thrombi.

The above is consistent with limited evidence from China indicating that patients receiving prophylactic dose UFH/LMWH had significantly better survival than those who did not.

In response to these findings the COVID-19 Treatment Guidelines Working Group, with expert input from haematology, makes the following recommendations for medical patients admitted with suspected or confirmed COVID-19 in Level 1 and 2 beds, unless such agents are contraindicated:

D-Dimer	Weight	LMWH
<1000	<100kg	Enoxaparin 40mg OD
	100-150kg	Enoxaparin 40mg BD
	>150kg	Enoxaparin 60mg BD
1000-3000	<100kg	Enoxaparin 40mg BD
	100-150kg	Enoxaparin 80mg BD
	>150kg	Enoxaparin 120mg BD
>3000	<100kg	Tinzaparin 175 units/kg OD

As per usual practice, all doses may need adjusting based on renal function. In the absence of bleeding, coagulopathy is not a contraindication to heparin unless platelets fall below 30 for prophylaxis or below 50 for therapeutic heparin.

JACC Consensus Recommendations On Antithrombotic Therapy During COVID-19 Pandemic

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Table 6. Summary of Consensus Recommendation on Antithrombotic Therapy During the COVID-19 Pandemic

	Patients with Mild COVID-19 (outpatient)
	For outpatients with mild COVID-19, increased mobility should be encouraged. Although indiscriminate use of pharmacological VTE prophylaxis should not be pursued, assessment for the risk of VTE and of bleeding is reasonable. Pharmacologic prophylaxis could be considered after risk assessment on an individual case basis for patients who have elevated risk VTE, without high bleeding risk.*
	There is no known risk of developing severe COVD-19 due to taking antithrombotic agents (i.e. antiplatelet agents or anticoagulants). If patients have been taking antithrombotic agents for prior known thrombotic disease, they should continue their antithrombotic agents as recommended.
	For outpatients on vitamin K antagonists who do not have recent stable INRs, and are unable to undergo home or drive-through INR testing, it is reasonable to transition the treatment DOACs if there are no contraindications and no problems with drug availability and affordability. If DOACs are not approved or available, low-molecular weight heparin can be considered as alternative.*
	Patients with Moderate or Severe COVID-19 without DIC (hospitalized)
	Hospitalized patients with COVID-19 should undergo risk stratification for VTE prophylaxis.
	For hospitalized patients with COVID-19 and not in DIC, prophylactic doses of anticoagulation can be administered to prevent VTE.*¥† If pharmacological prophylaxis is contraindicated, it is reasonable to consider intermittent pneumatic compression.
	For hospitalized patients with COVID-19 and not in DIC, there is insufficient data to consider routine therapeutic or intermediate-dose parenteral anticoagulation with UFH or LMWH.*‡
	Routine screening for VTE (e.g. bilateral lower extremity ultrasound) for hospitalized patients with COVID-19 with elevated D-Dimer (>1,500 ng/mL) cannot be recommended at this point&
	Patients with Moderate or Severe COVID-19 and suspected or confirmed DIC (hospitalized)
	For patients with moderate or severe COVID-19 and in DIC but without overt bleeding, prophylactic anticoagulation should be administered.*¥§
	For hospitalized patients with COVID-19 with suspected or confirmed DIC, but no overt bleeding, there is insufficient data to consider routine therapeutic or intermediate-dose parenteral anticoagulation with UFH or LMWH.*β
	For patients with moderate or severe COVID-19 on chronic therapeutic anticoagulation, who develop suspected or confirmed DIC without overt bleeding, it is reasonable to consider the indication for anticoagulation and weigh with risk of bleeding when making clinical decisions regarding dose adjustments or discontinuation. The majority of authors of this manuscript recommended reducing the intensity of anticoagulation in this clinical circumstance, unless the risk of thrombosis considered to be exceedingly high. ‖
	For patients with moderate or severe COVID-19 and an indication for dual antiplatelet therapy (e.g. percutaneous coronary intervention within the past 3 months or recent myocardial infarction) and with suspected or confirmed DIC without overt bleeding, in the absence of evidence, decisions for antiplatelet therapy need to be individualized. In general, it is reasonable to continue dual antiplatelet therapy if platelet count >50,000, reduce to single antiplatelet therapy if 25,000<platelet count<50,000; and discontinue if platelets <25,000. However, these guidelines may be revised upward or downward depending on the individualized relative risk of thrombotic complications vs. bleeding.
	For patients who were admitted and are now being discharged for COVID-19, routine screening for VTE risk is reasonable for consideration of pharmacological prophylaxis for up to 45 days post-discharge. Pharmacological prophylaxis should be considered if there is elevated risk for thrombotic events, without high bleeding risk. *# Ambulation and physical activity should be encouraged.
	Patients with COVID-19 presenting with ACS
	For presentations concerning for STEMI and COVID-19, clinicians should weigh the risks and severity of STEMI presentation with that of potential COVID-19 severity in the patient, as well as risk of COVID-19 to the individual clinicians and to the healthcare system at large. Decisions for primary percutaneous coronary intervention or fibrinolytic therapy should be informed by this assessment.*
	Patients without COVID-19 who have previously-known thrombotic disease
	There is no known risk of developing severe COVD-19 due to taking antithrombotic agents. Patients should continue their antithrombotic agents as recommended.
	To minimize risks associated with healthcare worker and patient in-person interactions, follow-up with e-visits and telemedicine is preferable in most cases.
	Patients without COVID-19 who develop new thrombotic disease
	To minimize risks associated with healthcare worker and patient in-person interactions, in-home treatment or early discharge should be prioritized.
	To minimize risks associated with healthcare worker and patient in-person interactions, follow-up with e-visits and telemedicine is preferable in most cases.
	Patients without COVID-19 but with co-morbid conditions (e.g. prior VTE, active cancer, major cardiopulmonary disease), who are homebound during the pandemic
	Recommendations include increased mobility, and risk assessment for the risk of VTE and risk of bleeding is reasonable. Administration of pharmacologic prophylaxis could be considered after risk assessment on an individual case basis for patients who have elevated risk for thrombotic events, without high bleeding risk.

*Indicates recommendations as reached by consensus of at least 66% of authors determined via Delphi method. ¥Although high-quality data are lacking, some panel members (55%) considered it reasonable to use intermittent pneumatic compression in patients with severe COVID-19, in addition to pharmacological prophylaxis. Specific areas of concern included limited data on use in the prone position as well as potential high incidence of preexisting asymptomatic DVT. †If VTE prophylaxis is considered, enoxaparin 40mg daily or similar LMWH regimen (e.g. dalteparin 5000U daily) can be administered. Subcutaneous heparin (5000U twice to three times per day) can be considered for patients with renal dysfunction (i.e. creatinine clearance <30 mL/min). ‡While the majority of the writing group did make this recommendation, 31.6% of the group were in favor of intermediate-dose anticoagulation [e.g. enoxaparin 1mg/kg/day, or enoxaparin 40mg BID, or UFH with target aPTT of 50-70] and 5.2% considered therapeutic anticoagulation. &The majority of the investigators recommended against routine VTE screening (68%); however, the remaining members of the group (32%) recommended to consider such testing. §The majority of the investigators recommended prophylactic anticoagulation (54%). A minority of investigators (29.7%) voted for intermediate-dose parenteral anticoagulation in this setting, and 16.2% considered therapeutic anticoagulation. ‖While the majority of investigators voted to reduce the intensity of anticoagulation if the indication were not acute (62%), this survey question did not meet prespecified cut-off of 66%. #The majority of the writing group recommended prophylaxis with DOACs (51%) and minority (24%) recommended LMWH, if available and appropriate. ACS: acute coronary syndrome; DOAC: direct oral anticoagulant, LMWH, low-molecular weight heparin; STEMI, ST-segment elevation myocardial infarction; UFH, unfractionated heparin; VTE, venous thromboembolism.

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