Management of thrombotic risk during the COVID-19 epidemic [Version 6.1 (24 April 2020)]

The problem
COVID-19 appears to provoke a hyper-inflammatory and pro-thrombotic state in many but not all patients. One observable manifestation is the frequent finding of hyper-fibrinogenaemia and very high levels of D-dimers. There is a suspicion that one of the reasons we are seeing progressive lung and renal failure in some patients is due to microvascular thrombosis (as opposed to venous thrombo-embolism). Widespread DIC criteria (low platelet count + high INR + low fibrinogen + elevated D-dimers) are not met in most cases, suggesting that the thrombosis and hyperfibrinolysis represents a localised miocrovascular imbalance of haemostasis. Hypertriglycerideaemia, may also be a feature of the hyperinflammatory syndrome and a co-factor in thrombosis.

The proposed solution
Increased doses of subcutaneous Dalteparin / Unfractionated Heparin (UFH) in placed of routine VTE doses based upon weight, renal function and D-dimer levels

1. INCLUSION CRITERIA
    a. COVID-19 hyper-inflammatory syndrome suspected or confirmed
    [Definition = classic history /classic CXR / swab or sputum +ve / ***normal*** WBC + neutrophil count + lymphopaenia / ***raised:*** CRP + fibrinogen + D-dimer + ferritin + LDH]

2. EXCLUSION CRITERIA for using the proposed dosing table:
    a. Platelet count <50 x 10^9/L
    b. Fibrinogen < 2.0g/L
    c. Anticoagulant drug naïve standard clotting time ratio(s) >2.0 [aPTTr and/or INR (PT)]
    d. If a patient has any acute / active bleed - defined as (see also suggest intervention plan IF acute bleeding occurs whilst on anticoagulants):
        i. otherwise unexplained drop in [Hb] ≥20g/L ***AND / OR***
        ii. otherwise unexplained haemodynamic instability ***AND / OR***
        iii. obvious macroscopic haemorrhage e.g. frank blood via nose, mouth, nasogastric tube or per rectum
    e. **If the patient has a suspected OR proven arterial OR venous thrombosis THEN USE** the dosing chart as for patients with D-dimer >3000ng/ml
    If any of the exclusion criteria are present – please discuss with the Haematology team urgently to individualise the anticoagulant plan

3. Estimate **ACTUAL BODY WEIGHT; IF <50 OR >150kg** discuss dosing with Haematology team

4. Review most recent eGFR and establish if ≥ ***OR*** <30 *&/OR* on intermittent RRT
    If eGFR ≥30 ml/min/1.73m^2 ***USE*** Dalteparin
    If eGFR <30 ml/min/1.73m^2 ***USE*** Unfractionated Heparin (UFH)

5. Review the most recent D-dimer level to determine the thrombosis risk category:
    If D-dimer <1000 ng/ml *THEN* enhanced thromboprophylaxis (Green column)
    If D-dimer 1000-3000 ng/ml *THEN* escalated thromboprophylaxis (Orange column)
    If D-dimer >3000 ng/ml *THEN* therapeutic anticoagulation (Red column)
    NOTE: D-dimers are renally cleared therefore accumulate with renal dysfunction AND are partially cleared by RRT. It is reasonable to view all COVID-19 patients with acute progressive AKI as being likely to benefit from full anticoagulation i.e. treat as being in the **RED** category. If uncertain how to interpret D-dimer levels please seek expert advice.

Dosing Table

			Anticoagulant dose *ALWAYS* give by subcutaneous injection		
Renal function	**Anticoagulant choice**	**Estimated ACTUAL body weight (kg)**	**D-dimer <1000ng/ml**	**D-dimer 1000-3000ng/ml**	**D-dimer >3000ng/ml**
eGFR ≥30 ml/min/1.73m^2	**Dalteparin**	<100kg	5000 units 12 hourly	7500 units 12 hourly	10,000 units 12 hourly
		≥100kg	7500 units 12 hourly	10,000 units 12 hourly	15,000 units 12 hourly
eGFR <30 ml/min/1.73m^2	**Unfractionated Heparin (UFH)**	<100kg	10,000 units 12 hourly	15,000 units 12 hourly	20,000 units 12 hourly
		≥100kg	15,000 units 12 hourly	20,000 units 12 hourly	30,000 units 12 hourly

IF <50 OR >150kg discuss dosing with Haematology team

Time of administration

- **On In-patient wards** give at 8am and 6pm
- **On ICUs** give at 2am and 2pm. Send daily bloods at 6am (4 hours post dose 2am dose to allow for therapeutic monitoring).

Monitoring

- All patients with complex disease [extremes of weight / on ICU] will need to have regular measurements of platelet count / INR / aPTTr / fibrinogen / D-dimer **AND** anti Xa.
- To be meaningful, anti Xa levels should be measured 4 hours after the THIRD dose.
- **Anti Xa targets**
  - For Dalteparin 0.3-1.2units/ml
  - For UFH 0.2-0.7units/ml
- The Haematology team will review all the results and advise the Medical Teams if any dose titration is required.

Additional ICU related guidelines

Renal replacement therapy (RRT)

- All patients requiring RRT will be on UFH and ***MUST*** receive their subcutaneous doses as per schedule ***WHETHER OR NOT*** they are on RRT ***UNLESS*** they have been switched to continuous infusions of **Argatroban**
- As per the COVID-19 RRT protocol, give UFH 5000 units IV bolus before commencing treatment ***IF*** ACT <150s. Repeat ACT every 4 hours and give a repeat UFH 5000 units IV bolus ***IF*** ACT <150s. These boluses must be prescribed as PRN "heparin flushes".
- In addition, commence a continuous infusion of UFH via the circuit as follows:

D-dimer (ng/ml)	**<1000**	**1000-3000**	**>3000**
Starting dose of UFH infusion	1000units/hour	1500units/hour	2000units/hour

- Perform APTTr every 4 hours aiming for a target of 2.0-4.5.
  - If <2.0, increase dose by 1000units/hour
  - If >4.5, decrease dose by 500units/hour
- Once a stable / effective dose is established ***RECORD THIS CLEARLY*** and use it as the ***STARTING*** dose for the next RRT session
- ***IF*** despite optimal use of this regime ***AND*** VasCath flow / position ***EXCLUDED*** as a problem ***STOP*** all UFH ***AND COMMENCE*** systemic (into the patient) **Argatroban** as per protocol below ***BUT ONLY*** for the duration of RRT; when off RRT ***RE-COMMENCE*** UFH subcutaneous regime.

COVID-19 patients with proven (or strongly suspected) DVT / PE

- ***IF*** anticoagulant drug naïve (i.e. admission diagnosis) ***START THERAPY*** as if D-dimer >3000ng/ml
- ***IF*** occurs whilst on this enhanced prophylaxis regime ***CONSIDER*** starting on **Argatroban** (please discuss with Haematology)
- The clinical threshold to give thrombolysis in the context of a suspected / proven PE should arguably be ***LOWER*** than standard practice
  - ***HOWEVER*** as RV dysfunction is both common and multifactorial in COVID-19 patients, a CTPA to prove the diagnosis AND determine the clot burden should always be performed ***IF POSSIBLE***.
  - ***IF POSSIBLE*** please also seek the advice of Prof Madden's expert team before giving empirical thrombolysis.

Argatroban protocol

- Usual presentation is a **MULTI-DOSE** vial of Argatroban containing 250mg in 2.5ml. [Exembol Multidose 100 mg/ml concentrate for solution for infusion]
- Withdraw 0.5ml (50mg) and dilute in 49.5ml of 0.9% sodium chloride in a 50ml syringe to make a solution with a concentration of 1mg/ml.
- Place the opened vial in the drug fridge having written on the box the date first opened.
- Initial Infusion Rate 2mcg/kg/min. Dose titration table shown below and should be guided by aPTTr

aPTTr	Infusion Rate change	Next aPTTr
< 1.5	***INCREASE*** by 0.5mcg/kg/min	2 hours
1.5-3.0	***NO CHANGE***	2 hours After 2 consecutive aPTTr within target range, check with daily bloods
> 3.0 **ON RRT**	***HALF*** of the previous infusion rate	2 hours
> 3.0 **NOT ON RRT**	***STOP*** infusion until the aPTTr is 1.5-3.0; ***RESUME*** at half of the previous infusion rate	2 hours

- Conversion table showing ml/hr infusion rate for dose range and patient weight

DOSE (mcg/kg/min)	0.5	1.0	1.5	2.0	2.5	3.0	3.5	4.0
Actual body weight (kg)	*Infusion Rate (ml/hr) using dilution of 1mg/ml*							
50	1.5	3.0	4.5	6.0	7.5	9.0	10.5	12.0
60	1.8	3.6	5.4	7.2	9.0	10.8	12.6	14.4
70	2.1	4.2	6.3	8.4	10.5	12.6	14.7	16.8
80	2.4	4.8	7.2	9.6	12.0	14.4	16.8	19.2
90	2.7	5.4	8.1	10.8	13.5	16.2	18.9	21.6
100	3.0	6.0	9.0	12.0	15.0	18.0	21.0	24.0
110	3.3	6.6	9.9	13.2	16.5	19.8	23.1	26.4
120	3.6	7.2	10.8	14.4	18.0	21.6	25.2	28.8
130	3.9	7.8	11.7	15.6	19.5	23.4	27.3	31.2
140	4.2	8.4	12.6	16.8	21.0	25.2	29.4	33.6
150	4.5	9.0	13.5	18.0	22.5	27.0	31.5	36.0

- **Pharmacodynamics:** Argatroban, a synthetic L-arginine derivative, is a direct thrombin inhibitor that binds reversibly to thrombin. Argatroban exerts its anticoagulant effect independently of antithrombin III and inhibits fibrin formation; activation of coagulation factors V, VIII and XIII; activation of protein C; and platelet aggregation.
- **Pharmacokinetics:**
  - Steady-state levels typically achieved within 1-3 hours following initiation.
  - Anticoagulation parameters return to baseline generally within 2 to 4 hours after discontinuation of infusion. There is no reversal agent.
  - Predominantly inactivated by hepatic metabolism. Use with caution / dose reduce in severe hepatic impairment.
  - No significant clearance on RRT
- **NOTE:**
  - Argatroban will result in an elevated INR but this should not be used to titrate therapy.
  - Argatroban interferes with the Fibrinogen lab assay resulting in falsely low levels. If assessment of Fibrinogen required during therapy perform a TEG as the functional fibrinogen (CFF) assay should not be affected.

This guideline has been peer reviewed by: James Uprichard, Steve Austin, Pamala Kanagasabapathy, Andrew Hitchings and Joanne Peh.

References

1. April 6, 2020. Disseminated pulmonary microvascular thromboembolism in COVID-19: a mechanistic link between coagulopathy and respiratory failure? anne sofie andreasen, MD, PhD, EDIC | Department of Anesthesiology and Intensive Care, Herlev and Gentofte Hospital, Denmark Comments on https://jamanetwork.com/journals/jamainternalmedicine/fullarticle/2763184
2. Dosing loosely based upon https://www.dbth.nhs.uk/wp-content/uploads/2017/10/Dalteparin_Dosing_Tables.pdf [in particular, taking treatment doses in pregnancy as the guide in patients with D-dimer >3000].