Practical guidance for the prevention of thrombosis and management of coagulopathy and disseminated intravascular coagulation of patients infected with COVID-19

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Background

Coronavirus Disease 2019 (COVID-19), caused by a novel coronavirus (SARS-CoV-2), is a highly contagious disease that appeared in Wuhan, Hubei province of China in December 2019. It has now spread to multiple countries through infected persons travelling mainly by air. Most of the infected patients have mild symptoms including fever, fatigue and cough. But in severe cases, patients can progress rapidly and develop the acute respiratory distress syndrome, septic shock, metabolic acidosis and coagulopathy including a disseminated intravascular coagulation (DIC).

There is little international guidance on how to manage thrombotic risk, coagulopathy, and DIC in patients with COVID-19 This brief paper provides concise pragmatic guidance on management of both thrombotic risk and DIC.
This is living guidance document that will be updated weekly.

Managing risk of hospital-associated venous thromboembolism

Hospital-associated venous thromboembolism (HA-VTE) includes VTE occurring in hospital and for up to 90 days post discharge.
COVID-19 infected patients are likely to be at increased risk of HA-VTE, especially if they become immobilised on critical care. At the moment it is unclear if hospitalized patients with COVID-19 have a greater risk of VTE than other medical patients who have chest infections and elevated D-dimer values (Darzi). Some have used an elevated D-dimer in a scoring system to identify those at increased risk of VTE (Spyropoulos).
Critically ill patients fulfil two out of three criteria of Virchows triad which states that reduced venous flow from immobility, prothrombotic changes and vessel wall changes increase the risk of VTE. Patients with severe COVID-19 are immobile, have an acute inflammatory state leading to a hypercoagulable state. There is also the possibility of endothelial cell activation/damage due to binding of the virus to ACE2 receptor. The optimal thromboprophylaxis in COVID patients is unknown. Drug-drug interactions between antiviral treatments and direct oral anticoagulants, and the difficulty in maintaining stable INRs in patients taking vitamin K antagonists while unwell, mean that patients on these drugs should be switched/bridged to low molecular weight heparins (LMWHs) or unfractionated heparins (UFH) with or without mechanical prophylaxis while unwell.

Recommendation1: 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).

i.e. Pharmacological thromboprophylaxis should be given to all immobilised and severely ill patients with COVID-19 patients unless otherwise contraindicated

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 immobilised patients would benefit from intermittent pneumatic compression in addition to pharmacological thromboprophylaxis.

Mechanical thromboprophylaxis should be used alone if platelets <30,000 or bleeding

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

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.

Management of COVID-associated coagulopathy

Descriptions of infection with Covid-19 from Wuhan, China described a coagulopathy in patients who were critically ill with Covid-19. It has long been recognised that activation of coagulation and/or fibrinolysis occur as part of the acute inflammatory response. Zhou et al performed a retrospective multicentre cohort study of 191 adults with laboratory confirmed COVID-19 from Wuhan Hospitals. Coagulopathy, defined as a 3 second extension of prothrombin time (PT) or a 5 second extension of activated partial thromboplastin time (APTT), was present in 50% of the non-survivors but only 7% of the survivors (p< 0.0001). Thrombocytopenia was a poor prognostic factor as in other groups of patients admitted to intensive care (Hunt). Platelet counts < 100^9 /l were noted in 20% non-survivors compared to 1% of survivors (<0.0001)

Multivariable regression showed increased odds of in-hospital death associated with very high D-dimer values (odds ratio 18.42, CI -2.6-128; p=0.0033). Higher values of D-dimers have been reported to be associated with 28-day mortality in patients with infection or sepsis in the emergency department (Rodelo et al)

Tang et al looked at coagulation screens, D-dimer & FDPs and antithrombin levels in 183 consecutive patients in Wuhan with an overall mortality of 11.5%[5]. Non-survivors had marked derangements in haemostatic defects at the time of admission in comparison to survivors with prolongation of APTT, PT, elevated D-dimers and fibrin degradation products (FDP). Progressive elevation of D-dimer and FDP was seen in non-survivors. Fibrinogen levels remained elevated in keeping with an acute phase response initially as opposed to a reduction that is commonly seen in DIC, mainly after day 7. In this cohort 71% of non-survivors met the International Society of Thrombosis and Haemostasis criteria of DIC compared to 0.4% of survivors. Higher D-dimer and FDP levels track with multi-organ dysfunction syndrome and poorer prognosis. (Wang et al, *JAMA* 2020). Median time to onset of DIC was 4 days into hospital admission but it is unclear at what stage of the illness patients were admitted.

Histological similarities have been shown to the Severe Acute Respiratory Syndrome-Coronavirus (SARS-CoV), the cause of a previous endemic between 2002-3, similarly causing ARDS. Localised pulmonary haemorrhage, pulmonary oedema, desquamation with hyaline membrane formation and an interstitial mononuclear inflammatory infiltrate have been seen. Localised pulmonary arteriolar thrombosis was seen with SARS but has not yet been described in the case reports of autopsies from patients with COVID-19 (Xu et al). Pulmonary vasculature thrombosis is likely to be a result of the severe hypoxia for hypoxia is a profound stimulant of coagulation (Ten et al). While therapeutic anticoagulation has been used empirically in some severe COVID-19 patients in Wuhan, it seems more logical to reduce the hypoxia if possible, rather than to submit patients to a therapy with no published efficacy and a high bleeding risk.

There is no proven benefit in correcting abnormal coagulation with replacement of missing coagulation factors (Hunt)

Recommendation 4: Abnormal coagulation results do not require correction in patients who are not bleeding.

Management of bleeding in COVID-19

In **minor bleeding** monitor FBC and coagulation screen &/or TEG/ROTEM

TEG/ROTEM should only be used if risk assessment shows they do not cause risk of aerosolisation of blood or they can be used in a Safety hood.

If **major bleeding**, (an arbitrary definition of major haemorrhage is bleeding which leads to a systolic blood pressure less than 90mm Hg and/or heart rate more than 110 beats per minute.)

1) ***Fresh frozen plasma (FFP)*** should be given early in the resuscitation process at an initial dose of 12 – 15 ml/kg (pragmatically 1 bag for every 20 kg, or 4 units in an adult), after base line coagulation studies taken but before results available. Further FFP should be guided by laboratory or near patient tests with a transfusion trigger of PT > 1.5; or if the results are not available with rapid turnaround, a further 4 units of FFP may be transfused prior to moving on to 'goal-directed' therapy.
2) ***Platelet transfusion:*** dose of one adult therapeutic dose (1 apheresis pack or 4 pooled units) for platelet count < 50 x 10^9/L in complex trauma especially with head injury. (BCSH guidelines for the use of platelet transfusion, 2003). There is no evidence for the need to maintain a platelet count higher than 75 x 10^9/L
3) ***Fibrinogen replacement.*** Hypofibrinogenaemia is common in massive haemorrhage and fibrinogen is the first factor to fall to critical levels; fibrinogen levels of < 1 g/L are likely after 1 - 1.5 times blood volume replacement (Hiippala et al, 1998, Hirshberg et al, 2003) and bleeding will be exacerbated by a plasma fibrinogen of < 1.5g/L. FFP alone is unlikely to be sufficient to improve fibrinogen levels (4 units raising the fibrinogen by approximately 1 g/L in an adult). If bleeding continues and fibrinogen levels are <1.5g/L (or equivalent level suggested by TEG/ROTEM), fibrinogen should be replaced in the form of cryoprecipitate (two 5 unit pools raising the fibrinogen by approximately 1 g/L in an adult). Fibrinogen concentrate (if licensed) is used extensively as an alternative to cryoprecipitate, usually given at a dose of 3 to 4 gms
4) ***Tranexamic acid (TA).*** Multiple trials have shown that 1gm of TXA followed by another gram are efficacious and safe in patients with bleeding. Importantly, for a drug that affects haemostasis, there were no increased thrombotic events: and a trend to a lower rate of arterial events in those receiving TA. Adult patients with major haemorrhage, in whom antifibrinolytics are not contraindicated, ***and who do not have DIC*** should be given tranexamic acid as soon as possible in a dose of 1g over 10 minutes followed by a further dose of 1gm if bleeding persists or restarts in the next 24 hours

5) Other agents

a) *Recombinant activated factor VIIa (rVIIa)* is approved for use specific inherited bleeding disorders. It has also been used widely 'off label' in patients with massive transfusion after major surgery or trauma without a pre-existing coagulopathy. Despite early reports suggesting great benefit, these findings were not replicated in further studies, and a recent Cochrane meta-analysis on the off-license use of rFVIIa (Simpson et al) showed only modest reductions in total blood loss or red cell requirements (equivalent to less than one unit of red cell transfusion). For other endpoints there were no consistent indications of benefit and no trial has been powered to study effect on mortality. Levi et al reviewed safety of the 4468 patients entered into trials of rVIIa and found an increased rate of arterial thromboembolism: those in over 65 years had a rate of 9% vs. 3.6%, p=0.003;. ***rVIIA is not recommended in patients with COVID-19.***

b) *Prothrombin complex concentrate (PCC).* There is a paucity of data reporting the utility and safety of PCC in managing bleeding in this setting. This agent agent may be prothrombotic and is not recommended ***patients with*** COVID-19.

Recommendation 5. For patients with major bleeding give empirical FFP and red cells followed by blood products determined by repeat coagulation screens, using PT/INR >1.5 or APTT > 1.5 as an indication to give FFP 15-25mg/Kg. For fibrinogen <1.5g/l give cryoprecipitate or fibrinogen concentrate, if platelets <50x 109/l give a pool of platelets. If the patient does not have DIC then also give tranexamic acid 1gm IV.

Management of disseminated intravascular coagulation in COVID-19

DIC is common in many patients in ITU as part of multiorgan failure. It is uncertain whether COVID-19 has unique characteristics to cause DIC. As DIC is usually only seen in severely ill patients, this seems unlikely. It seems more plausible that DIC develops in patients with COVID-19 after they become hypoxic, and/or have secondary bacterial infection. The diagnosis of DIC is easiest using the ISTH DIC score calculator. A score < 5 means DIC is not present and the score should be recalculate every 1-2 days as necessary. The best management of DIC is to identify and treat underlying condition, which with COVID-19 is difficult. Lastly Recovery from DIC is dependent on endogenous fibrinolysis breaking down the disseminated thrombi. This process will be inhibited by tranexamic acid which is an antifibrinolytic

Recommendation 6: Manage bleeding with blood product replacement as per managing major bleeding as above: i.e. if PT/INR or APTT ratios are greater than 1.5 then give FFP 15-25mg/Kg; if fibrinogen is <1.5g/l then give a source of fibrinogen- either cryoprecipitate or fibrinogen concentrate; if platelet are < 50x 10$_9$/l then give platelets

Recommendation 7: Do not use tranexamic acid in COVID-associated DIC

Lastly if overt thromboembolism or organ failure due to clot (i.e. purpura fulminans) consider low dose anticoagulation with unfractionated heparin pump to switch off stimulus to coagulation activation. Be mindful that there has been no mortality benefit of therapeutic anticoagulation and so run aPTT target < 1.5 or anti-Xa levels at a low rate in DIC. (Levi et al., *Blood,* 2018)

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