Thrombosis and Coagulopathy Guidance in COVID-19

The risk of thrombosis in COVID-19

Patients with COVID-19 are at risk of venous thromboembolism (VTE), which is a deep vein thrombosis (DVT) or pulmonary embolism (PE). It is still unknown if this risk is higher in comparison to non-COVID acutely ill patients.

How to interpret a D-dimer level in COVID-19

An elevated or rising D-dimer level is commonly seen in patients with COVID-19 (~50%) and is because of a profound inflammatory state. **An elevated D-dimer alone does not warrant investigation for VTE unless there is also a high clinical suspicion for DVT and/or PE.** Pulmonary embolism should be considered in admitted patients with COVID-19 who have unexplained worsening respiratory status/hypoxia, unexplained hypotension or tachycardia, or signs of DVT.

If the D-dimer is normal, this has the ability to rule out VTE. Although the false negative rate of D-dimer testing (i.e. DVT/PE is present but the result is normal) is unknown in COVID-19 patients, low rates of 1-2% using highly sensitive D-dimer assays have been reported in other high risk populations. Therefore, a normal level D-dimer level provides reasonable confidence that VTE is not present.

Prevention of thrombosis

All hospitalized patients with suspected or confirmed COVID-19 should receive pharmacologic thromboprophylaxis, preferably with low-molecular-weight heparin (LMWH).

LMWH prophylaxis should be held if the patient is bleeding or has a platelet count $<30 \times 10^9$/L. In patients where anticoagulation is contraindicated, use mechanical thromboprophylaxis (e.g. pneumatic compression devices). LMWH prophylaxis should be continued if there are other abnormal coagulation parameters (e.g. elevated PTT).

For prevention of VTE, LMWH should be given at prophylactic doses and follow weight-band dosing in SCM (i.e. tinzaparin 75 units/kg for patients >100 kg). LMWH prophylaxis is recommended over unfractionated heparin (UFH) to minimize complications such as HIT and health care provider exposure. UFH is recommended in patients who are in renal failure (creatinine clearance < 30 mL/min).

The role of therapeutic anticoagulation

While there have been reports of using therapeutic doses of LMWH to prevent VTE in patients with COVID-19, this is controversial. There is not enough data to support this practice outside of a clinical trial. Although therapeutic anticoagulation is recommended by some physicians in China because of high observed rates of thrombosis in critically ill patients with COVID-19, these observations occurred in a setting where thromboprophylaxis may not be routinely practiced.

Therapeutic LMWH (e.g. tinzaparin 175 units/kg) should be used if there is another indication for anticoagulation, or in the case of a suspected VTE when there is potential delay in imaging investigations.

If a patient with COVID-19 is already on DOAC or warfarin for another indication (e.g. past VTE, atrial fibrillation), then consideration should be made to switch to therapeutic LMWH/UFH while in hospital, especially in patients who are acutely ill. Parental anticoagulation is preferred over direct oral anticoagulants (DOACs) in patients with COVID-19 because of the concern for excess bleeding in seriously ill patients, and potential drug-drug interactions with off-label COVID-19 therapies. Atazanavir and lopinavir/ritonavir will increase drug concentrations of rivaroxaban and apixaban and decrease the active metabolite of clopidogrel and prasugrel. Rivaroxaban and apixaban should not be used with the

investigational product sarilumab. A list of all drug interactions with off-label COVID-19 therapies is available at: https://www.covid19-druginteractions.org/. In patients on warfarin, there may be difficulty maintaining stable INRs.

If a patient has suspected or confirmed HIT, fondaparinux is preferred over argatroban to minimize healthcare provider exposure, as long as the creatinine clearance is >30 mL/min.

Hematological and coagulation abnormalities

Elevations in d-dimer, fibrinogen is common, and reflects a profound inflammatory state. A markedly elevated D-dimer (>3-4 fold) is a poor prognostic indicator and is associated with increased mortality from COVID-19 infection. When coagulopathy/DIC is present, thrombosis is more common than bleeding in patients with COVID-19. Thrombocytopenia occurs less frequently and is generally mild (platelet counts 100-150 x 10^9/L). Lymphopenia has been reported in ~30-50% of patients with COVID-19. Anemia has not been frequently reported.

Coagulation monitoring

1) Baseline admission blood work: CBC, INR, PTT, fibrinogen, D-dimer level
2) Serial monitoring: Daily CBC, INR, PTT, fibrinogen and D-dimer until Day 4 of admission. If these are normal, then only check coagulation labs if there is a clinical deterioration, bleeding or thrombosis.

Coagulation factor replacement in the setting of coagulopathy/DIC with a low fibrinogen:

Fibrinogen 0.5-1.0 grams: RiaSTAP 2 grams Fibrinogen <0.5 grams: RiaSTAP 3 grams

Note: RiaSTAP (fibrinogen concentrate) is recommended over cryoprecipitate. If RiaSTAP is not available, Fybiga may be substituted and has the same dosing.

If there is acute **bleeding and coagulopathy**, then transfuse platelets if the platelet count is <50 x 10^9/L and transfuse fresh frozen plasma (FFP) 15 mg/kg (e.g. usually 4 units) if INR or aPTT ratios are prolonged >1.5. Coagulopathy does not need to be corrected if the patient is not bleeding, except for a low fibrinogen.

Tranexamic acid is contraindicated if there is evidence of DIC. Recombinant fVIIa is not recommended in patients with COVID-19.

Convalescent plasma from recovered individuals with COVID-19

Convalescent plasma should only be used in the setting of a research study.

Please page the hematologist or transfusion medicine physician on call if questions.

Recommendations adapted from:

American Society of Hematology COVID-19 Guidance: Anticoagulation
American Society of Hematology COVID-19 Guidance: VTE
Brigham & Women's Health COVID-19 Clinical Guidelines
Practical guidance for the prevention of thrombosis and management of coagulopathy and disseminated intravascular coagulation of patients infected with COVID-19.
Thachil, J, et al. ISTH Interim guidance on recognition and management of coagulopathy in COVID-19. J Thromb Haemost epub online March 25, 2020: doi: 10.1111/JTH.14810