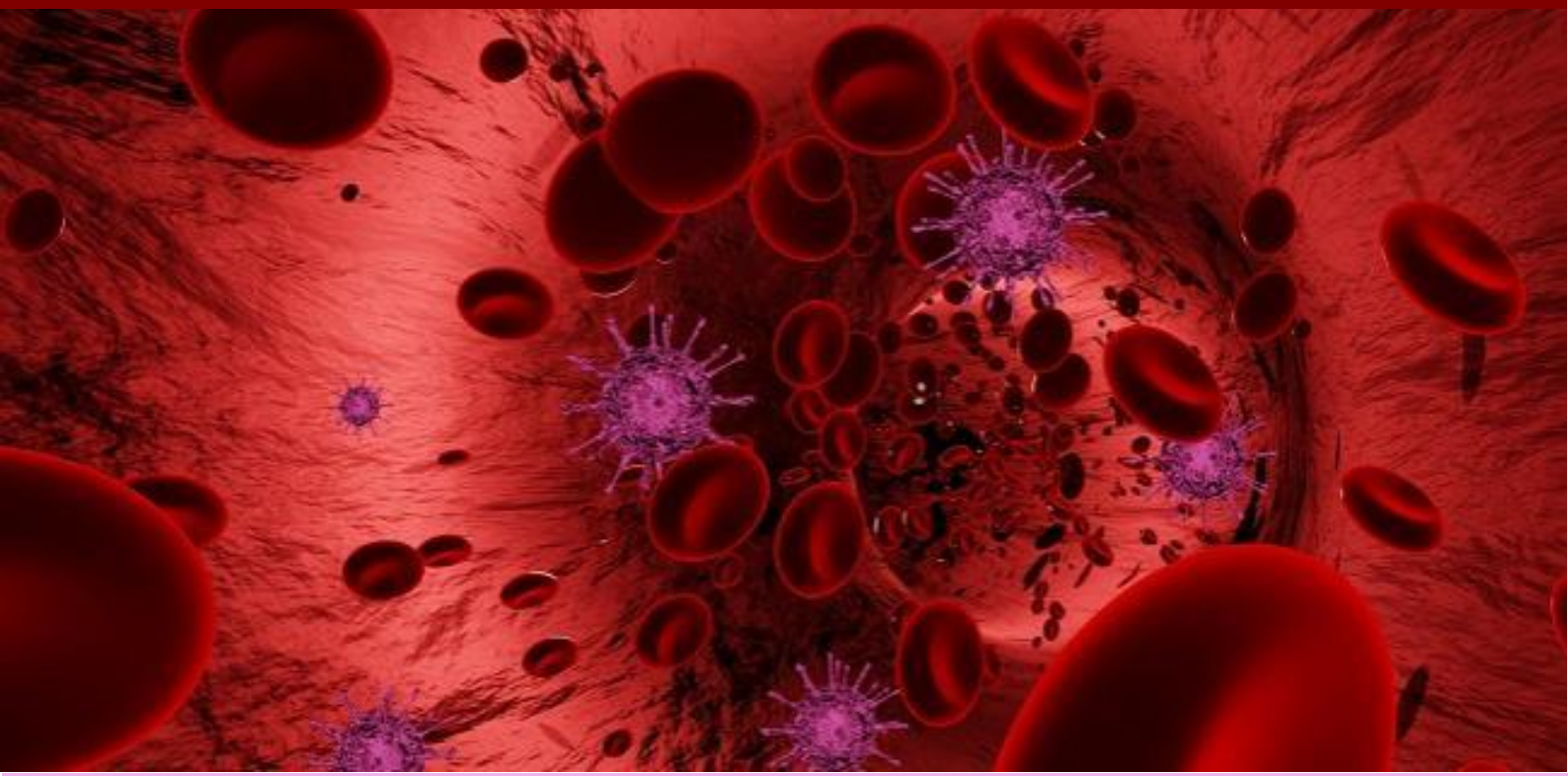
PREVENTION & TREATMENT OF VENOUS THROMBOEMBOLISM AND MANAGEMENT OF ANAEMIA & COAGULOPATHY IN COVID-19 INFECTION



A PRACTICAL GUIDE

Second Edition

MALAYSIAN SOCIETY OF HAEMATOLOGY
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Introduction

Coronavirus disease 2019 or COVID-19 is a highly contagious respiratory illness first identified in Wuhan, China in December 2019. It has since spread to multiple countries around the world and was declared a pandemic by the World Health Organisation (WHO) on 11 March 2020.

The majority of patients infected with the causative virus, SARS-CoV-2 present with mild symptoms including fever, sore throat, cough and lethargy. However, the severe cases rapidly progress to respiratory and multiorgan failure with metabolic acidosis and coagulopathy, including disseminated intravascular coagulation (DIC)[1].

As this is a novel disease, there are very few international guidance to the management of thrombosis and disseminated intravascular coagulation in COVID-19. This brief report is based on existing guidelines in VTE and DIC management as well as advice from the UK thrombosis group and ASH guidelines[2–4]

There are emerging data to show a high incidence of thrombotic complications in critically ill ICU patients with COVID-19, as high as 31% (27% confirmed VTE and 3.7% arterial thrombotic events)[5].

COVID-19 AND COAGULOPATHY

COVID-19 is associated with an increased risk of both arterial and venous thrombotic events. Venous thromboembolism (VTE), including extensive deep vein thrombosis (DVT) and pulmonary embolism (PE), is very common in acutely ill patients with COVID-19, seen in up to one-third of patients in the intensive care unit (ICU), even when prophylactic anticoagulation was used[6]. Less common clinical manifestations include thrombosis of central lines and catheters and arterial occlusive events (cerebrovascular events, limb ischemia, etc).

The most common pattern of laboratory coagulation abnormalities observed in patients hospitalized with COVID-19 is elevations in D-dimer and fibrinogen levels, and mild prolongation of prothrombin time (PT) / activated partial thromboplastin time (aPTT) which is usually correlated with a parallel rise in markers of inflammation (e.g. CRP, ferritin)[7]. Unlike the pattern seen in classic DIC from bacterial sepsis or trauma, prolongation of the aPTT and/or PT is minimal, thrombocytopenia is mild (platelet count ~ 100 x10/L) and laboratory results supporting microangiopathy are infrequent.

COVID-19 related coagulopathy is characterized by more thrombotic than haemorrhagic events. Although bleeding is less common than clotting in patients with COVID-19 it may occur especially in the setting of anticoagulation. Coagulopathic features are associated with a more serious form of COVID-19 and severe outcome[8]. A high D-dimer value are associated with high mortality, likely reflecting coagulation activation from infection / sepsis, cytokine storm and impending organ failure[9].

Patients who die from COVID-19 are more likely to have DIC compared to survivors. Massive PE was the cause of death in about one third of the cases. Autopsy studies showed that severe endothelial injury (endothelialitis), widespread thrombosis with microangiopathy and alveolar capillary microthrombi, and increased angiogenesis were significantly more prominent in the lungs of the patients who died of COVID-19[10].

Careful and dynamic thrombotic risk assessment should be performed in all COVID-19 patients, whether hospitalized or not. This assessment includes classic thrombotic risk factors, but also biological parameters such as D-dimer and CRP. Laboratory findings that are atypical for COVID-19, such as severe thrombocytopenia (platelet count <50 $x10^9$/L), prolonged aPTT out of proportion to the PT, or a markedly reduced fibrinogen, should be evaluated as done for individuals without COVID-19.

PREVENTION OF VENOUS THROMBOEMBOLISM

Hospital-Acquired Venous Thromboembolism (HA-VTE) is VTE occurring in hospital and up to 90 days post-discharge. It is not clear whether COVID-19 patients are at a greater risk of HA-VTE compared with other medically ill patients with pneumonia[5]. Clearly, critically ill patients who are managed in the Intensive Care Unit (ICU) are at greatest risk[11].

All 3 components of the Virchow's triad play a role in the development of HA-VTE in critically ill patients with COVID-19.

1. **Blood** – inflammatory cytokines induce a hypercoagulable state
2. **Vessel** – endothelial injury from indwelling catheters and possibly from the binding of the virus itself (endothelialitis)
3. **Flow** – immobilisation reduces blood flow

In view of the increased risk of thrombosis, all hospitalised patients should receive thromboprophylaxis throughout their hospital admission.

All fully immobilised patients would also benefit from intermittent pneumatic compression (mechanical) in addition to pharmacological thromboprophylaxis with LMWH. Mechanical compression should be used alone if platelet count falls below 30 x 10^9/L or if the patient is bleeding[3,4]. For patients who are already on oral anticoagulants (DOACs or warfarin) for atrial fibrillation (AF) or previous VTE, consider switching to therapeutic low molecular weight heparin (LMWH) (see table 2).

Recommendation 1

The risk of VTE must be assessed in all patients admitted to hospital and thromboprophylaxis must be given for all high-risk patients according to established guidelines (MOH 2013, ASH, NICE)[2,4].

Recommendation 2

Pharmacological thromboprophylaxis (LMWH is the preferred choice) should be given to all COVID-19 patients who are symptomatic with pneumonia and those who are critically ill.

DIAGNOSIS OF VENOUS THROMBOEMBOLISM

Patients with COVID-19 infection often present with respiratory symptoms such as chest pain and haemoptysis that overlap with the nonspecific presentation of acute PE. Considering the high incidence of thrombotic complications, clinicians must have a low threshold for considering the presence of VTE in COVID-19 patients.

Unexpected respiratory worsening, unexplained tachycardia, hypotension, PE-specific ECG changes, and symptoms indicative of deep vein thrombosis of the extremities should trigger targeted diagnostic testing.

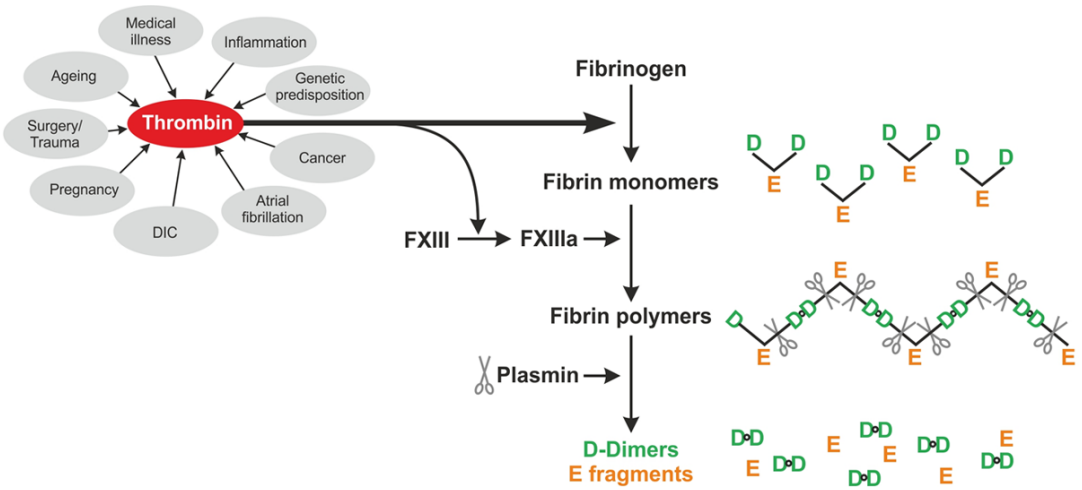
It is recommended however, to only order diagnostic tests for PE when it is clinically suspected, and not apply screening strategies. The specificity of D-dimer tests is very low in hospitalised patients especially in patients admitted with COVID-19 infection.

What is D- Dimer?

D-dimer is a fibrin degradation product of cross-linked fibrin and is elevated when there is breakdown of clots in the body (Figure 1)[12]. It is also an acute phase reactant and therefore increased in most hospitalised patients due to inflammation or infection making it not a specific marker for thrombosis[2]. Hence, D-dimer is not recommended to be used in the diagnosis of VTE. On the contrary if there is a very high clinical suspicion of VTE, diagnostic imaging i.e. Ultrasound Doppler of the lower limbs or Computed Tomography Pulmonary Angiogram (CTPA) should be carried out.

If diagnostic imaging is not available or if patient is too ill to be sent to the imaging unit, empirical therapeutic anticoagulation should be started and imaging should be carried out as soon as it is available or if patient remains symptomatic.

Figure 1.



COVID-19 and D-Dimer

Though elevated D-dimer levels are associated with poorer prognosis in patients with COVID-19, there is no clear recommendation to tailor patient treatment strategy based on D-dimer levels. It is also not useful to include or exclude VTE in patients with COVID-19 infection. Current data do not support the routine use of high D-Dimer levels in isolation to guide decisions regarding investigation and anticoagulation.

Recommendation 3

Consider the possibility of pulmonary embolism in patients with sudden deterioration of oxygen saturation, respiratory distress and hypotension.

Recommendation 4

D-dimer has a poor negative predictive value and is not recommended for the inclusion or exclusion of VTE in the hospitalised setting and in patients with COVID-19 infection.

TREATMENT OF VENOUS THROMBOEMBOLISM

The optimal treatment of VTE in hospitalized COVID-19 patients has not been studied yet. Currently, management follows standard VTE guidelines.

In critically ill patients, parenteral anticoagulation is advised over oral anticoagulation. In acutely ill patients on general wards, initial LMWH treatment may have advantages (in terms of drug-drug interactions and risk of rapid clinical deterioration) over oral treatment, although oral anticoagulation is suitable for clinically stable patients without contraindications[13].

Direct Oral Anticoagulants (DOACs) provide advantages over vitamin K antagonists (VKAs), especially in the post-hospital setting, as they are safer, and do not involve the need for routine monitoring.

Recommendation 5

Parenteral anticoagulation is preferred over oral anticoagulation in critically ill patients with COVID-19 infection. The anticoagulant of choice is LMWH.

DURATION OF ANTICOAGULATION

Without VTE

Patients who have no evidence of VTE should receive anticoagulation throughout their hospital stay. There is currently no clear evidence to support outpatient anticoagulation post-discharge as it is still being investigated.

The decision to extend thromboprophylaxis up to 45 days post-discharge are based on several studies in medically ill patients. Consider extending thromboprophylaxis in the presence of any of the following factors[14] :

- Age ≥75 years
- Past history of VTE or cancer
- ICU-stay
- Obesity
- Lower limb paresis

However, this is not a standard of practise at the moment and decision should be made on a case to-case basis. If the decision is to extend anticoagulation post-discharge, the US Food and Drug Administration (FDA) has approved rivaroxaban for this purpose in medically ill patients.

For pregnant patients with COVID-19 post-Caesarean section, thromboprophylaxis with LMWH should be continued for 6 weeks.

With VTE

Venous thromboembolism in COVID-19 patients is considered to be provoked by a reversible risk factor, so generally, a treatment duration of 3 months is advised.

For patients who were started empirically on treatment dose of anticoagulation for suspected VTE but no diagnostic imaging was able to be performed, we recommend to continue therapeutic anticoagulation for at least 6 weeks post-discharge.

Recommendation 6

Consider extending thromboprophylaxis up to 45 days post-discharge especially in patients who were critically ill and managed in ICU and those who have continued risk of VTE.

Recommendation 7

For pregnant mothers with COVD-19 post-Caesarean section, thromboprophylaxis with LMWH should be continued for 6 weeks.

Recommendation 8

The recommended duration of anticoagulation for VTE in patients with COVID-19 infection is 3 months.

Recommendation 9

For patients who were started on empirical therapeutic anticoagulation for unconfirmed suspected VTE, the duration of anticoagulation should extend to at least 6 weeks post-hospital discharge.

Recommendation 10

Direct oral anticoagulants are preferred over Vitamin K antagonists in the post-hospital discharge setting.

CHOICE OF ANTICOAGULANTS AND RECOMMENDED DOSING

The anticoagulant of choice for the prevention and treatment of VTE in COVID-19 infection is LMWH. In Malaysia, the LMWH that is widely available is Enoxaparin.

Enoxaparin is partly metabolised and cleared by both the reticuloendothelial system and kidneys. Fondaparinux, a synthetic pentasaccharide is eliminated unchanged only through the kidneys, hence is not recommended in critically ill patients whose kidney function are usually also compromised.[2,3] In patients with renal impairment (CrCl <30 mL/min) prescribe reduced dose LMWH or unfractionated heparin (UFH) subcutaneously; fondaparinux is contraindicated.

It is important to risk stratify patients individually taking into consideration the thrombotic versus the bleeding risk when deciding the intensity of anticoagulation one should receive. Higher intensity anticoagulation may be preferred in patients judged to have a higher thrombotic risk if the bleeding risk is low. However, there is no clear evidence to date to suggest that much higher doses should be used in patients who are acutely ill without thrombosis.

The recommended anticoagulation and dosing for both prophylaxis and treatment of VTE is shown in table 1.

Table 1: Anticoagulants and Recommended Dosing[15,16]

ANTICOAGULATION	DOSE RECOMMENDATION			
	Non-Critically Ill Patients		Critically Ill Patients	
	Prophylaxis	Treatment	Prophylaxis	Treatment
LMWH Enoxaparin	40 mg OD	1 mg/kg BD	1 mg/kg OD or in 2 divided doses	1 mg/kg BD
Fondaparinux (Monitor for renal impairment)	2.5 mg OD	5 mg OD: <50kg 7.5 mg OD: 50-100kg 10 mg OD: >100 kg	2.5 mg OD	5 mg OD: <50 kg 7.5 mg OD: 50-100 kg 10 mg OD: >100 kg
DOACs				
Rivaroxaban	10 mg OD	15 mg BD x21/7 then 20 mg OD	Not recommended in patients who receive medication that interfere with P450 enzyme activity. Contraindicated in pregnancy. Watch for renal impairment especially with dabigatran.	
Apixaban	2.5 mg BD	10 mg BD x7/7 then 5 mg BD		
Dabigatran	150 mg BD	150 mg BD		
Unfractionated Heparin (In general, not recommended as standard VTE prophylaxis / Safe in renal impairment)	5000 IU BD (S/C)	80 IU / kg bolus then adjust according to APTT ratio	5000 IU BD (S/C)	80 IU/kg bolus then adjust according to APTT ratio

Note:
- Avoid DOACs and Fondaparinux for all patients with Creatinine Clearance < 30mls/min. Adjust Enoxaparin dose according to guidelines.
- Patients on extracorporeal circuits or with recurrent catheter thrombosis may need intermediate intensity anticoagulation dose

MANAGEMENT OF ANAEMIA, BLEEDING AND DISSEMINATED INTRAVASCULAR COAGULATION IN THE CRITICALLY ILL

Anaemia is associated with increased morbidity and mortality and should be addressed and corrected in critically ill patients with COVID-19 infection. The cause of anaemia is multifactorial and is most commonly due to anaemia of inflammation and iron deficiency due to frequent phlebotomy[19,20].

More than 70% of adult patients in general, will develop anaemia on their second day in ICU[17,18]. The 3-pillar principles of Patient Blood Management (PBM) should be applied and will bring great benefit in this group of patients[19,20]. The treatment of anaemia should be instituted early with subcutaneous erythropoietin and intravenous iron, and we recommend this once Hb falls below 12 g/dL (see Table 2)[17].

Vitamin K deficiency is common in the critically ill due to a variety of causes such as inadequate dietary intake, malabsorption and antibiotic therapy. Vitamin K is an essential co-factor for the synthesis of factors II, VII, IX, X, Protein C and Protein S. Patients in ICU should receive Vitamin K supplementation either through enteral feeding or intravenously to prevent bleeding (see Table 2)[21].

Minor bleeding can be managed with tranexamic acid. In major bleeding (systolic blood pressure <90 mmHg and heart rate >110 beats/min), activate the Massive Transfusion / Haemorrhage Protocol.

1. Packed red cells to replace blood loss – initial 2 units safe Group O red cells if blood group not known
2. Fresh frozen plasma (FFP) to replace clotting factors – initial FFP at a dose of 12-15 mL/kg or 4 units; further dose guided by coagulation results to keep PT <1.5 x normal[22–24]
3. Cryoprecipitate to replace fibrinogen – 1 unit/ 10 kg body weight to keep fibrinogen levels >1.5 g/L[22–24]
4. Platelet transfusion to replace platelet consumption – 1 pool of platelets or 4 units of random platelets to keep platelet count >50 $x10^9$/L[22–24]

Tranexamic acid (1 g over 10 minutes and further dose of 1 g if still bleeding) is effective and safe in patients with major bleeding in the absence of DIC. The diagnosis of DIC is easiest made by using the ISTH DIC score calculator https://reference.medscape.com/calculator/dic-score.

A score ≥5 suggest DIC. Recovery from DIC is dependent on endogenous fibrinolysis breaking down disseminated thrombi. Tranexamic acid prevents fibrinolysis hence it is not recommended in DIC[22,23].

Off-label use of recombinant activated factor VII (rFVIIa) in major bleeding has not shown to be beneficial in a recent large meta-analysis[25]. Furthermore, rFVIIa as well as Prothrombin

Complex Concentrate (PCC) are prothrombotic and associated with an increased risk of thrombosis, both arterial and venous[22,25,26].

In DIC with organ failure due to thrombosis, consider low dose anticoagulation with IVI UFH to switch off thrombin generation; which is the stimulus to coagulation activation[22,27].

Table 2: Guide to Managing Haematological Problems in Critically ill Patients with COVID-19 in ICU

Practical Guide for Managing Haematological Problems in Patients with COVID-19 in ICU

Routine Haematological Management

1. Check Haemoglobin
- If Hb <12 g/dL → Consider S/C EPO (4,000 IU 3x/week) and I/V iron (100 mg 3x/week) at alternate day dosing
- If Hb <7 g/dL → Consider single unit red cell transfusion if other measures that increase oxygen delivery have failed

2. Check Platelet count
- If Plt <20 x 10^9/L → Consider one pool of platelets

3. Check coagulation results
- Routine IV Vitamin K supplementation 10 mg 2x/week

4. Check thromboprophylaxis
- Check if special circumstances apply (see special circumstances)
- If none, go to no. 5

5. Check creatinine clearance
- If CrCl >30 mL/min → prescribe LMWH as per thromboprophylaxis dose (if BW <60 kg → Enoxaparin 40 mg OD; if BW ≥60 kg → Enoxaparin 1 mg/kg OD)
- If CrCl ≤30 mL/min → prescribe S/C UFH 5000 IU BD or reduced dose LMWH (Enoxaparin 20 mg OD or 40 mg EOD)

General Principles

Minimise phlebotomy
- Avoid excessive blood sampling

Special Circumstances

AF or previous VTE
- If AF or previous VTE >90 days ago, no special circumstances apply
- If VTE ≤90 days ago, prescribe treatment dose LMWH (Enoxaparin 1 mg/kg BD)

Active bleeding
- Correct abnormal results
- Consider I/V iron

Planned procedures
- See targets for procedures

Targets for Procedures

Central line / arterial line insertion
- Plt >20 x 10^9/L

Central line / arterial line removal
- Do not remove until Plt >50 x 10^9/L

Chest drain or tracheostomy insertion
- INR <1.5 or APTTr <1.5
- Fibrinogen >1.5 g/dL
- Platelet count >50 x 10^9/L

EPO - Erythropoeitin
LMWH - Low molecular weight heparin
UFH - Unfractionated heparin
I/V - Intravenous
S/C – Subcutaneous

Recommendation 11

Anaemia is common in the critically ill. Measures should be taken to prevent or reduce anaemia by minimising phlebotomy and using paediatric collection tubes. Early recognition of anaemia and treatment with erythropoietin and intravenous iron can reduce morbidity and mortality.

Recommendation 12

Abnormal laboratory coagulation results do not require correction unless associated with bleeding or prior to invasive procedures. Routine Vitamin K supplementation is recommended to prevent bleeding in the critically ill.

Recommendation 13

In patients with major bleeding, the use of blood and blood components must be guided by the clinical condition of the patient as well as the coagulation results (PT, APTT, fibrinogen) and blood counts (haemoglobin and platelet count).

Recommendation 14

Recombinant activated factor VII and PCC are prothrombotic and are not recommended in the management of major bleeding in COVID-19.

Recommendation 15

Do not use tranexamic acid in COVID-19 with DIC.

Recommendation 16

Consider low dose UFH in COVID-19 associated DIC with organ failure due to thrombosis.

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