Coagulopathy in COVID-19: Recommendations for Laboratory Testing and Thromboprophylaxis for patients with confirmed COVID-19

Lead Clinician	**:**	Dr Dewi Eden
Division	**:**	Haematology
Developed (date)	**:**	13/04/2020
Last updated	**:**	11/06/2020
Version	**:**	3
Last reviewed	**:**	N/A
Planned review	**:**	07/05/2021
Hyperlink (where applicable)	**:**	N/A
Keywords	**:**	Thromboprophylaxis, Tinzaparin, COVID-19, Coagulopathy, VTE
Comments	**:**	*This document outlines the guidelines for the laboratory testing and thromboprophylaxis of patients with confirmed COVID-19 at Shrewsbury and Telford Hospital NHS Trust.*

1 Overview

Background

A coagulopathy similar to, but distinct from, disseminated intravascular coagulation (DIC) is a common feature in patients with SARS-CoV-2 infection (COVID-19 disease), especially those with severe illness. Furthermore, widespread microvascular thrombosis has been described in the lungs at post mortem in COVID-19 pneumonia. The coagulopathy is likely induced by a "cytokine storm" due to a severe host inflammatory response and hypoxia may also play a role in the pathophysiology.

The coagulopathy is characterised by a markedly raised D-dimer level and a slight prolongation of the prothrombin time (PT). Initially, fibrinogen levels are often high or very high, followed by a decline to a mild to moderate hypofibrinogenaemia in deteriorating patients. Clinically significant thrombocytopenia is uncommon, and only occurs as a late feature in the most severely affected patients.

Clinically, the majority of patients with COVID-19 do not suffer from clinical bleeding. COVID-19 appears to induce a clinical pro-thrombotic state. Up to 5-10% of patients who require mechanical ventilation develop acute venous thromboembolism. VTE risk assessment is therefore of key importance for all hospitalised COVID-19 patients. There is evidence from China that prophylactic doses of LMWH may be associated with reduced mortality in severe coronavirus disease associated with coagulopathy.

There is, as yet, no published evidence for the optimal LMWH regime for prevention of thrombosis, but clinical trials are opening that address this question. However, there is an emerging evidence base but much of the guidance is based on best practice and clear scientific rationale. This guidance should be used for all Adult (non-pregnant) patients at Shrewsbury and Telford Hospital NHS Trust with confirmed COVID-19. We propose more intensive LMWH anticoagulation as a drug that has a proven effect in the prevention of thrombosis.

Do NOT adopt any other guidance or strategies that have been locally produced – if in doubt seek help from a Consultant Haematologist with an interest in Thrombosis.

2 Guideline detail

Management of COVID-19 Coagulopathy

General Principles

Clinically, COVID-19 coagulopathy is a prothrombotic state, with some resemblance to "chronic DIC" that is initially compensated and leads to thrombotic microangiopathy. The majority of patients with COVID-19 coagulopathy do not develop clinical bleeding. Blood products should not be administered purely to correct laboratory abnormalities but should be reserved for supportive management of bleeding, and in some cases for support for invasive procedures or surgery. Prevention, prompt diagnosis and management of thrombosis are of key importance. The following section gives guidance on prevention of VTE and assessment of balance of risks in the context of progressive COVID coagulopathy.

VTE Prophylaxis for patients with confirmed COVID-19 Disease

- All in-patients should have VTE risk assessment : on admission and if condition changes

- All in-patients should have LMWH prophylaxis with tinzaparin, irrespective of mobility, unless contraindicated.
- Choose the dose of prophylactic LMWH according to body weight and renal function.
- Mild prolongation of PT and/or APTT only, if due to COVID coagulopathy, is NOT a contraindication to LMWH prophylaxis.
- Use mechanical VTE prophylaxis alone if LMWH contraindicated and consider as an additional measure in patients who are completely immobile.
- If there is an unexplained 50% fall in platelet count in the absence of worsening coagulopathy, consider HIT (Heparin Induced Thrombocytopenia). Carry out a 4Ts score and seek haematology advice.
- Do not give additional prophylactic LMWH to patients with confirmed COVID-19 disease continuing oral anticoagulation prescribed prior to admission. If patient is already on full oral anticoagulation, maintain this during admission.

Risk Assessment: Consider the factors:

Risk assess all patients in the usual manner

1. Thrombotic risk for patients with confirmed COVID-19 disease is usually high regardless of mobility - but multiple risks may change the management strategy
    a. Thrombotic Risk:
        - Personal history of VTE or arterial thromboembolic disease in the past
        - Active cancer or if received chemotherapy/radiotherapy in the last 6 months
        - Known thrombophilia's
        - BMI > 30
        - Immobility
        - Recent major surgery within 4 weeks
        - D-dimer> 3000 (0-500ng/mL)
2. Assess bleeding risk against criteria (accepting that lower platelet counts are tolerated)
    a. Bleeding Risk
        - Any contraindication to LMWH
            - Conditions include: acute bacterial endocarditis, after major trauma, epidural anaesthesia, haemophilia or other significant haemorrhagic disorders, peptic ulcer, recent cerebral haemorrhage, recent surgery to eye, recent surgery to nervous system, spinal anaesthesia, history of heparin-induced thrombocytopenia.
        - Evidence of active bleeding including from lungs/respiratory tract or gastrointestinal tract
        - Platelet count <30
        - Recent stroke in preceding 4 weeks

Management

Patients with confirmed COVID-19 disease who are well with minimal symptoms, no risk factors from above and require admission to hospital should receive **standard prophylaxis**.

Those patients with confirmed COVID-19 who are considered higher risk due to factors included in the risk criteria above will require the **enhanced prophylaxis** dosing of LMWH during their inpatient stay.

Those patients with confirmed COVID-19 disease, whose ONLY risk factor from the criteria above is immobility/have reduced mobility, should be given the **enhanced prophylaxis** based on their weight for 1 week at least during their inpatient stay. They will also benefit from mechanical VTE prophylaxis. When clinically better they should receive **standard prophylaxis** for 1 week at least and until fully mobile. If these patients are ready for discharge before they are able to complete this regime they would revert to the standard prophylaxis dosing detailed below. (See discharge planning)

If the patient with confirmed COVID-19 disease has a platelet count that is less than 30×10^9/L or there is active bleeding then use mechanical prophylaxis alone.

If patient with confirmed COVID-19 disease is already on an oral anticoagulant for treatment and are unable to continue on their oral anticoagulant then this can be discontinued and **therapeutic treatment dosing** of tinzaparin can be started unless contraindicated. If on warfarin then start tinzaparin when INR<2. If on a DOAC then start tinzaparin when the next dose of DOAC would have been due. Plan to restart original anticoagulation as per usual process before discharge unless clinical circumstances have changed.

Dosing of LMWH Prophylaxis

Dosing in the table below is for prophylactic tinzaparin, which is the LMWH of choice for VTE prophylaxis in SaTH.

Standard Prophylaxis (based on current guidelines)		
Weight	**Creatinine Clearance >20ml/min**	**Creatinine Clearance <20ml/min**
Less than 30kg	Discuss with the Haematology Consultant for advice	
31-54kg	3500units ONCE daily	Use unfractionated Heparin 5000units BD
55-120kg	4500units ONCE daily	Use unfractionated Heparin 5000units BD
more than 120kg	50 units/kg ONCE a day. Round doses to the nearest 1000 units.**	Use unfractionated Heparin 5000units BD
Previous HIT or hypersensitivity to LMWH	Consider Fondaparinux 2.5mg once a day or discuss with the Haematology Consultant for advice	
Enhanced Prophylaxis		
Weight	**Creatinine Clearance >20ml/min**	**Creatinine Clearance <20ml/min**
Less than 30kg	Discuss with the Haematology Consultant for advice	
31-54kg	3500units TWICE daily*	Discuss with the Haematology Consultant for advice
55-100kg	4500units TWICE daily*	
More than 100kg	50units/kg TWICE daily* (rounded to the nearest 1000units)**	
Previous HIT or hypersensitivity to LMWH	Discuss with the Haematology Consultant for advice	

* TWICE daily dosing is unlicensed.
**the following prefilled syringes are graduated to enable the correct dose to be given; 8000units/0.4ml, 10,000units/0.5ml, (these strengths are unlicensed for prophylaxis dosing)

Monitoring

Full coagulation screening in suspected COVID19 infected inpatients should be done on admission and then repeated if admitted to critical care; it should ideally include the following:

- FBC
- PT (INR) and APTT
- Fibrinogen
- D dimer

It is recommended that the coagulation screen should be repeated for all patients who remain unwell with confirmed COVID-19 at day 4 or if clinical deterioration occurs. It is also relevant to consider re-testing at these points for any patients receiving full dose therapeutic or enhanced prophylactic doses of LMWH, in order to prevent harm from continued administration of anticoagulation to a patient who is developing a worsening coagulopathy and may therefore be at risk of bleeding (see guidance below on stopping parameters for LMWH in prophylaxis).

Coagulation screening must be repeated on admission to critical care and should be at least daily thereafter for patients continuing to be appropriate for and requiring HDU or ITU care.

When patients are recovering and no longer require Level 2 or 3 care, and their coagulopathy is also resolving, monitoring can be tailed down unless clinical deterioration occurs.

Platelet Count:
If platelets fall below 30 – LMWH dose may need discontinuing – discuss with Haematology consultant.
If platelets rise above 600 – LMWH dose may need adjusting – discuss with Haematology consultant

Coagulation
PT/APTT
Fibrinogen: if fibrinogen is <1.0 may need a reduction in tinzaparin dose or <0.5g/l may need discontinuation of tinzaparin. Discuss further with Haematology consultant

D-Dimer
If this rises above 3000 the patient will fall into a higher risk category therefore tinzaparin dose may need adjusting.

Discharge Planning:

VTE prophylaxis is indicated throughout the hospital admission for patients with COVID-19 disease in accordance with the criteria above and extension of this prophylaxis following discharge for 2 weeks should be considered unless they fall into the following categories:

- If the illness has been mild and full mobility has been regained prior to discharge then **no further prophylaxis** will be needed on discharge.
- A longer duration of 4 weeks is appropriate for those who have required mechanical ventilation during their admission.
- A longer duration of 4 weeks is appropriate for those who are expected to have significant on-going reduced mobility. The holistic needs of the patient should be taken into account in making this decision.
- Those patients with confirmed COVID-19 disease whose ONLY risk factor from the criteria above is immobility/have reduced mobility who are ready for discharge before they have completed their 1 week of enhanced dosing should be reviewed and converted to the appropriate treatment based on an assessment of their mobility.(see bullet points above)

For extended out of hospital prophylaxis for patients recovering from confirmed COVID-19 disease, dosing should revert to “standard prophylaxis”. If the patient cannot self-inject, and extended prophylaxis is required an oral agent may be used if appropriate and the course length will be in line with the criteria above. Dosing for each DOAC is as stated below.

- Rivaroxaban 10mg daily (*unlicensed for medical prophylaxis in the UK but licensed in US)
- Apixaban 2.5mg twice daily (unlicensed for medical prophylaxis)

In patients with moderate (CrCl 30-49ml/min) or severe renal impairment (CrCl 15-29ml/min) – no dose adjustment is needed for rivaroxaban nor apixaban.
If CrCl <15ml/min – both agents are not recommended. Discuss further with Haematologist.

3 Review date

This policy will be reviewed after 1 year unless there are significant changes at either national policy level, or locally.

4 Monitoring Compliance

This guidance will be monitored by the clinical audit process

5 References

- Guidance from University Hospital Birmingham NHS Trust - Coagulopathy in COVID-19: Recommendations for Laboratory Testing and Thromboprophylaxis
- Guidance adopted from Leeds Teaching Hospitals NHS Trust - Guidance on the Diagnosis and Management of COVID-19 Coagulopathy and on Prevention and Management of Venous Thromboembolism in COVID-19 Infection
- Guidance adopted from Countess of Cheshire Hospital NHS Trust – Guidance for thromboprophylaxis for suspected or confirmed COVID-19 patients in adult ICU COCH.
- BTS Guidance on Venous Thromboembolic Disease in patients with COVID-19: V1.0 20 April 2020
- Chelsea and Westminster Hospital: Guidance on Thromboprophylaxis, Thrombosis and Coagulopathy Management in COVID-19 April 2020
- Intensive Care Society/NIHR Applied Research Collaboration North Thames/UCL-Rapid dissemination summary: COVID-19: a synthesis of clinical experience in UK intensive care settings April 2020
- Imperial College Health Care Covid Treatment Group: Thromboprophylaxis and anticoagulation in COVID-19 infection April 2020: Guidance on VTE prevention for patients with suspected or confirmed COVID-19 April 2020
- Royal Liverpool University Hospital: Guidance on VTE Prevention for patients with suspected or confirmed Covid-19 infection April 2020
- Tang N, Li D, Wang X, Sun Z. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. J Thromb Haemost. 2020;00:1–4. https://doi.org/10.1111/ jth.14768
- Tang N, Li D, Wang X, Sun Z. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. J Thromb Haemost. 2020;18:844–847. https://doi.org/10.1111/jth.14768
- Pasi KJ et al. Trial Protocol. Thromboprophylaxis in COVID-19 (TRIC): an open label randomized controlled trial of standard dose versus intensive low molecular weight heparin. Queen Mary University of London, 9 April 2020.
- Thachil, J., Tang, N., Gando, S., Falanga, A., Cattaneo, M., Levi, M., Clark, C. and Iba, T. (2020), ISTH interim guidance on recognition and management of coagulopathy in COVID-19. J Thromb Haemost. Accepted Author Manuscript. doi:10.1111/jth.14810
- https://thrombosisuk.org/covid-19-thrombosis.php
- Levi, M., Toh, C.H., Thachil, J. and Watson, H.G. (2009), Guidelines for the diagnosis and management of disseminated intravascular coagulation. British Journal of Haematology, 145: 24-33. doi:10.1111/j.1365-2141.2009.07600.x
- Lee, A.Y.Y., Connors, J.M., Baumann Kreuziger, L., Murphy, M.F., Gernsheimer, T., Lin, Y. on behalf of the American Society of Hematology (2020). COVID-19 and Coagulopathy. https://www.hematology.org/covid-19/covid-19-and-coagulopathy

6 Associated Documentation

None