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Guidance on the Diagnosis and Management of COVID-19 Coagulopathy and on Prevention and Management of Venous Thromboembolism in COVID-19 Infection

From the LTHT Haemostasis and Thrombosis Team*:

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Quick reference

This guidance is intended for use for patients with symptomatic COVID 19 disease. It is not intended for use for those who have been swabbed for public health purposes or because they require a definitive diagnosis in the context of mild symptoms that would normally be managed at home even if that person is in hospital for another reason or if they have attended hospital and assessment has indicated the COVID-19 symptoms are trivial.

Even for hospitalised patients, COVID-19 disease runs a variable course with variable severity and pre-existing performance status and co-morbidities vary greatly between patients. It is important that this guidance is applied taking the holistic needs of individual patients into account. These decisions will require senior medical input and junior clinicians should escalate questions and concerns via the parent medical team in order to apply guidance appropriately.

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.

There is evidence that coagulation parameters and D-dimer in particular are of prognostic significance. Retrospective data from hospitalised patients with COVID-19 in Wuhan, China has shown that non-survivors had a significantly higher D-dimer on admission compared with survivors. D-dimers greater than 3-4 fold the upper limit of normal on

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first assessment may be of value in predicting likelihood of clinical deterioration, although prospective data are not available. **For those who go on to develop a coagulopathy that meets ISTH criteria for DIC, the Wuhan data indicate that the median time for this to occur is on day 4 after hospital admission** .

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 concern amongst clinicians that the high fibrinogen levels and severe inflammatory state associated with COVID-19 is likely to give rise to a degree of heparin resistance. 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.

The guidance below is based on discussion with colleagues locally and nationally on the front line (for prophylaxis) and also based on licensed treatment regimes.

Diagnosis of COVID-19 Coagulopathy	
Typical Features	Raised D-dimer[1] (may be marked, and is of prognostic value)
	Mildly prolonged prothrombin time[2] (look at PT, not INR)
	High fibrinogen level[3] (use Clauss fibrinogen, **not** derived)
	Later: mild/moderate hypofibrinogenaemia in severely affected[4] (Clauss)
	Usually platelets > 100, late thrombocytopenia in very severe disease
Diagnostic Tests	COVID-19 COAGULOPATHY TESTS
	Use the above tab on ICE*: on Adult Services: Intensive Care and ED Panels and on LTH Pathology: Haematology
	Set contains : FBC, Coagulation screen **Clauss** fibrinogen, D-dimer
	TEG/ROTEM **not** recommended (potential risk of aerosolisation)
Consult Clinical Haematology for diagnostic advice	If APTT or PT disproportionately prolonged with well-preserved Clauss fibrinogen and is unexplained **
	If platelets < 100 and platelet count has fallen > 50% from baseline without evidence of marked coagulopathy and thrombocytopenia is unexplained***
	If there is any clinical concern regarding interpretation if results

<u>Guide to Table</u>

[1]Important: Raised D-dimer is expected as a typical feature of COVID coagulopathy. D-dimer is used as a prognostic indicator in COVID-19 disease (please see below under monitoring). Do not investigate these patients for VTE purely because D-dimer is raised. Imaging for VTE is only indicated if there is also significant clinical suspicion of VTE on clinical assessment. If in doubt, please consult a senior medical colleague. No change is recommended to the usual pathway for VTE assessment for patients primarily presenting as? DVT or? PE, nor to the D-dimer cut off for exclusion of VTE (< 230ng/ml). Remember that D-dimer is used as an exclusion test in the VTE pathway for its <u>negative</u> predictive value.

[2] Usually 10-15% increase in early stages

[3] Normal range for Clauss fibrinogen is 1.5-4.5 g/l, [4] Around 1-1.5g/l for Clauss fibrinogen in most patients but may be lower in overt DIC

*Ensure the COVID status of the patient has been correctly selected on ICE

** Note that therapeutic doses of LMWH and sometimes prophylactic doses may cause or contribute to a prolonged APTT. In situations where the APTT is disproportionately prolonged, the Actin-FS APTT will help interpretation and has been added to the COVID coagulopathy set. If the Actin-FS APTT is normal in a non-bleeding patient, this rules out a significant coagulation factor deficiency.

***Thrombocytopenia is a late feature in Covid coagulopathy. Consider Heparin Induced Thrombocytopenia (HIT) if > 50% drop in platelet count in a patient on heparin or LMWH if coagulopathy is absent or non-severe or restricted to elevated D-dimer only. Always do a 4Ts score and seek clinical haematology advice

Guidance on Monitoring for COVID-19 Coagulopathy

It is recommended that clinicians should consider requesting a COVID-19 Coagulopathy test set for patients with proven or highly suspected COVID-19 disease who are acutely unwell at the following times during the course of assessment and subsequent in-patient management. Please use the COVID coagulopathy test set on ICE rather than requesting tests individually. This will ensure that the correct tests are performed in the laboratory. Note that derived fibrinogen will not give an accurate measure of plasma fibrinogen concentration in this condition. **Please also note that recommendations regarding the frequency and timing of testing should be tailored to suit the individual needs of the patient, taking account of, for example, decisions about ceiling of care which may evolve during the course of the patient's hospital stay, alongside the need to only carry out tests that would aid clinical management or care**

The purpose of monitoring for COVID-19 coagulopathy is to flag patients who are at risk of rapid respiratory deterioration. Furthermore, for severely affected patients with abnormal results at baseline, there is a risk of developing overt DIC with an associated risk of bleeding. Recognition of this should prompt review of and in some cases cessation of low molecular weight heparin prophylaxis or treatment. Monitoring should be tailored to individual patient needs and responsive to the pattern of previous results. Avoid taking blood samples that are unnecessary, for example in patients with stable results who are clearly improving clinically or for patients for whom decisions have been made to palliate.

- Test as soon as possible, during initial medical assessment for patients with typical symptoms of COVID-19 disease. (Discharge of patient not recommended if D-dimer > 700ng/ml as data suggest that a D-dimer more than 3 times the upper limit of normal may predict a poor prognosis).
- **Consider** requesting the COVID coagulopathy set daily thereafter to aid prognostic assessment and progress, **only if initial D dimer > 700ng/ml or other baseline tests are deranged**. **The holistic needs of the patient should be taken into account when deciding on the frequency of testing.**
- It is recommended that the COVID coagulopathy screen should be repeated for all patients who remain unwell as a result of COVID-19 disease at day 4* or if clinical deterioration occurs unless a decision has been made that the patient would not be suitable for escalation to level 2 or level 3 care. 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 and treatment sections pages 4 and 6).
- Request a COVID coagulopathy screen on admission to HDU or ICU and at least daily thereafter for patients continuing to be appropriate for and requiring HDU or ICU care.
- Always ensure when requesting tests that the COVID status of the patient has been correctly selected on ICE.

- 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.

*Day 4 was the median time for development of overt DIC in the Wuhan studies.

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 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 two sections give guidance on prevention and management of VTE and assessment of balance of risks in the context of progressive COVID coagulopathy.

VTE Prophylaxis for Patients with COVID-19 Disease

Thromboprophylaxis in Patients with 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 enoxaparin, 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.
Do not administer prophylactic LMWH if platelets < 25 or Clauss fibrinogen < 0.8g/l or active bleeding occurring.
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 continuing oral anticoagulation prescribed prior to admission.

Dosing of LMWH Prophylaxis
Dosing in the Table below is for prophylactic enoxaparin (Inhixa) which is the LMWH of choice for VTE prophylaxis in LTHT.

Standard Prophylaxis		
Weight	**Cr clearance > 30ml/min**	**Cr clearance < 30ml/min***
< 50kg	**20mg s/c od**	**20mg s/c od with caution**
50-100kg	**40mg s/c od**	**20mg s/c od**
100-150kg	**40mg s/c bd**	**40mg s/c od**
➢ **150kg**	**60mg s/c bd**	**60mg s/c od**
Enhanced Prophylaxis		
< 50kg	**20mg s/c bd**	**20mg s/c od**
50-100kg	**40mg s/c bd**	**40mg s/c od**
100-150kg	**60mg s/c bd**	**60mg s/c od**
➢ **150kg**	**80mg s/c bd**	**80mg s/c od**

Please calculate the Cockcroft Gault creatinine clearance:
http://www.leedsformulary.nhs.uk/chaptersSubDetails.asp?FormularySectionID=99&SubSectionRef=99.02&SubSectionID=A100&drugmatch=4988#4988

*For patients on continuous renal replacement therapy (for example continuous veno-venous haemofiltration), follow dosing guidance above for Cr clearance > 30ml/minute**. Check a LMWH antiXa level as well as a coagulation screen and Clauss fibrinogen if there are any concerns for clinical bleeding.**

There is concern amongst clinicians that COVID-19 disease induces heparin resistance because of the degree of the inflammatory response. It is becoming common practice in critical care units to use enhanced prophylactic regimes. To date there is no clear evidence published to support this. However, there is no doubt that the coagulopathy associated with COVID-19 is associated with marked fibrin formation, leading to very high D-dimer levels. The main site of fibrin formation is most likely in the lungs. The optimal prophylactic LMWH regime is unknown but is subject currently to research.

In LTHT the multidisciplinary team recommend **considering enhanced prophylaxis** with intermediate dose prophylaxis as defined in the Table above for **those patients requiring critical care that have confirmed or highly suspected COVID-19 disease.** It is also **suggested** that enhanced LMWH prophylaxis should be considered for patients who are acutely unwell due to COVID-19 and who are being managed outside of HDU or ICU who have two or more additional patient related or admission related risk factors that are independent of the acute COVID-19 disease, using the VTE risk assessment tool on PPM+. The holistic needs of the patient should be taken into account in making this decision. If in doubt, and especially for older patients, junior clinicians should seek senior advice regarding enhanced prophylaxis. In older patients, it is especially important to calculate the Cockcroft Gault creatinine clearance as the eGFR may overestimate their creatinine clearance.

Please note that LTHT are not currently recommending the use of prophylactic LMWH regimes that adjust the dose of LMWH according to D-dimer results. Clinical trials on patients with COVID-19 disease have commenced in April 2020 that address whether or not such regimes are more effective compared with standard prophylaxis or intermediate dose enhanced prophylaxis as we have recommended. **This guideline will be updated in the light of results of clinical trials.**

VTE Prophylaxis is generally indicated throughout the hospital admission and extension of prophylaxis following discharge for 2-4 weeks should be considered, unless the illness has been mild and full mobility has been regained. The longer duration of 4 weeks is appropriate for those who have required mechanical ventilation or 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. For extended out of hospital prophylaxis, dosing should revert to "standard prophylaxis". Enoxaparin is the preferred agent for extended prophylaxis for patients recovering from COVID-19 disease. If the patient cannot self-inject, and extended prophylaxis is required: please seek advice from the haemostasis and thrombosis team regarding using a prophylactic dose of a DOAC (pharmacist or doctor). Please note that the product licenses for the direct oral anticoagulants do not cover administration for prophylaxis in this situation.

Diagnosis and Management of Venous Thromboembolism

Diagnosis and Management of VTE	
Diagnosis	D-dimer is unlikely to be helpful in hospitalised patients with COVID-19 (D-dimer likely to be elevated due to COVID-19)
	Consider PE if sudden unexplained respiratory deterioration or unexplained new cardiovascular instability e.g. hypotension
	Confirm PE by CTPA asap unless the patient is too unstable (see below)
	Cardiac echo may be useful in very unstable patients but cannot rule out a PE
	Use ultrasound for DVT diagnosis. Discuss suspected isolated iliac vein thrombosis with radiology
Treatment	Give a therapeutic dose of LMWH asap and within one hour if VTE is suspected whilst awaiting imaging, unless contraindicated
Dosing LMWH*	Calculate Cockcroft-Gault creatinine clearance (ml/min)**
Initial dose	
Cr Clearance > 30ml/min	Enoxaparin 1.5mg/kg s/c
Cr Clearance < 30ml/min	Enoxaparin 1mg/kg s/c ***
Subsequent doses	
Cr Clearance > 30ml/min	Enoxaparin 1mg/kg s/c bd from 18-24 hours after 1st dose
Cr clearance < 30ml/min	Enoxaparin 1mg/kg s/c od from 24 hours after 1st dose***
Seek advice from haematology	If poor clinical response to anticoagulation consider measuring LMWH antiXa and seek advice
	If **Clauss fibrinogen is < 1g/l or platelets < 50: withhold LMWH** and seek advice
	If heparin induced thrombocytopenia is suspected: carry out 4Ts score and seek advice

***dosing recommended here is higher than standard LTHT treatment guidance but is within spc for enoxaparin. This is a change from the usual practice of using tinzaparin as there are more licensed dosing options with enoxaparin.**

**creatinine clearance calculator is available in the Intranet: http://www.leedsformulary.nhs.uk/chaptersSubDetails.asp?FormularySectionID=99&SubSectionRef=99.02&SubSectionID=A100&drugmatch=4988#4988

*** consider seeking advice from clinical haematology or a pharmacist in anticoagulation and thrombosis. **Also note: patients on continuous renal replacement therapy (for example CVVH) should be dosed as per creatinine clearance > 30ml/min with monitoring of antiXa levels (aiming for a 4- hour peak of 0.5-1 unit/ml)**.

Note:
For patients who have been treated on clinical grounds for high suspicion of PE, consider the balance of risks of performing a CTPA and CTV if they are sufficiently stable within a week of first suspicion versus empirical therapeutic anticoagulation which then should continue for 3 months. Venous ultrasound should only be requested if there is a symptomatic leg and CTV is not possible. Logistics should be discussed with radiology.
Therapeutic anticoagulation should also be considered if there are concerns regarding repeated clotting of critical extracorporeal circuits (for example filters used in CVVH) or essential central lines despite adequate thromboprophylaxis. Continuous infusion of unfractionated heparin may also be considered for management of recurrent clotting of CVVH filters, bearing in mind that more heparin resistance may be seen with UFH.
Line related venous thrombosis should be treated as DVT as above.

For patients who have had a new VTE event during their hospital stay with COVID-19 disease, a switch to a DOAC may be considered 24-28 hours before discharge if they have made a full recovery. See DOAC guidance on Leeds Health Pathways. Choose a dose suitable for renal function. Dosing changes may be required after discharge for rivaroxaban and apixaban. When switching to rivaroxaban or apixaban , the initial full dose should be used for 3 weeks (for rivaroxaban) or 1 week (for apixaban) as per the spc before stepping down to maintenance dose (even if a few days of LMWH have been administered). If the patient is not suitable for a DOAC, reduce to standard treatment dose enoxaparin (1.5mg/kg od, or 1 mg/kg od for Cr clearance < 30ml/min) for patients who are able to self-inject.
Duration of anticoagulation is 3 months for patients with hospital associated VTE in the context of COVID 19 disease unless there is continued significant immobility after 3 months or concern regarding multiple on-going risk factors, when a longer duration should be considered. This should be highlighted on the EDAN sent to the GP at discharge. Please refer patients who have been treated for PE (proven or highly suspected) to the respiratory PE clinic for review within 3 months following hospital discharge.

Management of 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.

Minor bleeding: Use local measures and monitor clinical progress and Covid Coagulopathy parameters. Topical tranexamic acid may be used (but not oral or IV)

Major Bleeding and Covid Coagulopathy

Seek clinical haematology advice if continued bleeding despite the measures noted below or if there is on-going evidence of a severe coagulopathy: Clauss fibrinogen < 1g/l, PT or APTT ratios > 1.5, platelets < 50, despite administration of recommended products or if patient is on therapeutic anticoagulation

- Activate the major haemorrhage protocol. Ensure that all staff attending the clinical site are aware of the Covid status of the patient and have appropriate PPE
- Send a Covid coagulopathy screen (Haematology/Blood Sciences) and group and save (Blood Transfusion) to the labs urgently *.
- Red cell transfusion as clinically indicated
- Give FFP 12-15ml/kg as soon as possible.
- Give fibrinogen concentrate up front if current fibrinogen < 1g/l or if < 1.5g/l and bleeding continuing despite FFP (or empirically if no current fibrinogen available and baseline **Clauss** fibrinogen < 4.5g/l and estimated blood loss is > 1-1.5 x patient's blood volume). Do not give empirically to patients with high baseline Clauss fibrinogen levels. The product of choice is Riastap 3-4g for an adult of average body weight, given at a rate of 10g/10minutes**.
- Give one adult dose of platelets if baseline platelets < 50. Seek haematology advice re giving a further adult dose of platelets empirically if continued major bleeding in a thrombocytopenic patient despite all of the above measures or blood loss exceeds 1-1.5 x patient's blood volume.
- **Avoid use of tranexamic acid in COVID coagulopathy**
- Avoid the use of TEG/ROTEM unless risk assessment has shown no risk of aerosolisation of blood or TEG/ROTEM will be performed in a safety hood.
- Avoid use of Novoseven.
- For patients who are on treatment doses of anticoagulation, seek urgent haematology advice re anticoagulant reversal.

* ALL samples must be hand delivered IMMEDIATELY and DIRECTLY to labs including Haematology samples (Blood Sciences lab, blood group samples to Blood bank). The member of staff co-ordinating on site should telephone the Blood Sciences lab (as well as the Blood Transfusion lab) to inform them of urgent samples and request a phone call with results. Repeat FBC and coagulation screen and Clauss fibrinogen after the products as indicated have been administered and if bleeding is on-going.

**Infuse by inverting the bottle with the reconstituted product via an IV infusion set and a pump rather than trying to draw up the solution into a syringe

Ensure bleeding has stopped for 24 hours before restarting any anticoagulation. Start with prophylactic doses and seek haematology advice re escalation if appropriate.

Appendix

Tips for Management of Patients Requiring Hospital Admission for COVID-19 Disease who are Already Therapeutically Anticoagulated

Management should be individualised and the holistic needs of the patient should be taken into account. The bullet points below provide broad guidance.

- The general aim should be to continue to keep the patient therapeutically anticoagulated unless contraindicated (e.g. in the presence of clinical bleeding or in the presence of a significant risk of bleeding because of the development of overt DIC with a Clauss fibrinogen < 1g/l or a platelet count < 50 (see above). The choice of agent requires careful consideration.

- In general, for many patients requiring in patient management, on-going warfarin therapy is best avoided, especially in patients who are severely ill. Consider stopping warfarin and switching to therapeutic low molecular weight heparin. See above under management of VTE for dosing guidance for LMWH. LMWH should not be commenced whilst the INR is still in the therapeutic range. For some groups of patients, for example those with a mechanical heart valves who are clinically stable, it may be preferable to continue with warfarin. **Please seek advice from a consultant in haemostasis and thrombosis regarding management of patients who are admitted with COVID-19 disease who are on warfarin.**
- For patients on DOAC treatment who have milder illness and whose renal function is well preserved, DOAC treatment may be continued. Note that some DOACs lead to variable prolongation of the prothrombin time (+/- the APTT) and this should be taken into account in interpreting the COVID coagulopathy screen.
- For patients who are deteriorating and who are appropriate for escalation to Level 2 or 3 care, it is generally advisable to switch a DOAC to low molecular weight heparin, taking account of the clearance of the current anticoagulant medicine, the patient's renal function, body weight, and coagulation parameters. Please seek advice on switching from a haemostasis and thrombosis consultant.
- For patients who are deteriorating and who are not for escalation to level 2 or Level 3 care, there should be consideration of the balance of risks of continuing or stopping established anticoagulation, or substituting LMWH prophylaxis only, based upon the holistic needs of the patient.
- For patients who have recovered and who are being prepared for hospital discharge, please consider suitability for a DOAC or LMWH rather than warfarin as per guidance already circulated: http://nww.lhp.leedsth.nhs.uk/common/guidelines/other_versions/FINAL%20Guidance%20on%20safe%20switching%20of%20warfarin%20to%20DOAC%20COVID-19%20Mar%202020.pdf

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