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

This guidance does not override the individual responsibility of health professionals to make appropriate decision according to the circumstances of the individual patient in consultation with the patient and /or carer. Health care professionals must be prepared to justify any deviation from this guidance.

Introduction

This document outlines the guidelines for the laboratory testing and thromboprophylaxis of COVID-19 patients aged 16 years and over.

This guideline is for use by the following staff groups :

All healthcare professionals who undertake the prescription, preparation and administration of thromboprophylaxis for adult patients.

Lead Clinician(s)

Dr S Shafeek — Consultant Haematologist

Approved by Thrombosis Committee on:

Ratified by Medicines Safety Committee on:

Review Date:
This is the most current document and is to be used until a revised version is available:

Key Amendments made to this Document:

Date	Key Amendments	By:

Thromboprophylaxis Recommendations

Background

Venous Thrombo-Embolism (VTE) is commonly associated with acute infectious / inflammatory disorders as a result of both immobility through illness and changes in vascular biology and haemostasis promoting thrombosis. Increasingly it is felt that thrombosis is playing an important role in the pathology and clinical course of COVID-19 infection.

The pathology of thrombosis is both widespread thrombosis and microthrombosis. Such complicating thrombotic events may be significantly contributing to a poorer outcome in such individuals. Prevention of thrombosis and microthrombosis in COVID-19 may have significant benefit for patient health and use of scarce health resources.

When treating COVID-19 patients, early VTE risk factor identification and thromboprophylaxis is essential, as well as high vigilance and prompt treatment of all VTE complications (such as pulmonary embolus).

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 aged 16 and over. Enoxaparin (LMWH) anticoagulation is 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. Please note that some recommendations within this guidance sit outside the licensed use of enoxaparin.

Summary

1. Venous Thrombo-Embolism (VTE) is a recognised complication of COVID-19 infection.
2. The use of prophylactic LMWH in patients with coagulopathy may improve survival.
3. More intensive (intermediate dose) LMWH anticoagulation is proposed whilst awaiting formal trials of VTE prophylaxis strategies.

Thromboprophylaxis Flowchart for all COVID-19 patients (suspected and confirmed)

1. Risk assess all patients in the usual manner (on admission and as clinical condition changes)
    - Thrombotic risk for COVID-19 patients is usually high regardless of mobility – but multiple risks may change the management strategy
    - Assess bleeding risk against usual criteria (accepting that lower platelet counts are tolerated)

THROMBOTIC RISK	BLEEDING RISK / EXCLUSIONS
• Mobility reduced for ≥ 3 days • Active Cancer • Previous VTE disease • Dehydration • Metabolic / endocrine pathologies • Known thrombophilia	• Any contraindication to LMWH* • Evidence of active bleeding including from lungs/respiratory tract or gastrointestinal tract • Platelet count <30 x10^9/L • Recent stroke in preceding 4 weeks

*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.

2. If the patient is already on full oral anticoagulation, maintain this during admission. Consider switching to therapeutic LMWH, especially if invasive procedures anticipated.

3. If no strict contraindications, give VTE prophylaxis according to the table beneath for a minimum of 7 days. High risk patients defined as:
    - Critical care patients
    - Acute Respiratory CPAP cohort - patients with suspected or proven COVID-19 transferred to ARU due to a high O2 requirement (FiO2 ≥ 0.4). This includes patients in whom CPAP is being used as a bridge to ICU, or as a ceiling of care.
    - These doses may be continued if selected for standard thromboprophylaxis within the REMAP-CAP trial.

4. On discharge all patients should be risk assessed and if considered at high risk of VTE (e.g. significantly reduced mobility, past history of VTE, cancer or critical care admission) consideration should be made for extended VTE prophylaxis (either or both mechanical and pharmacological)

5. Enoxaparin (Inhixa) 40mg OD is the preferred choice for extended thromboprophylaxis. For patients (or a household member) who are unable to administer the injection, Rivaroxaban 10mg OD or Apixaban 2.5mg BD may be used as an alternative. Please note that this is off label use of DOACs for this indication. Suggested duration of prophylaxis is seven days from discharge but may be extended e.g. up to 14 days if clinical condition warrants. Patients must be counselled on the bleeding risk and how to seek medical advice should this occur. Currently no data exists to support these dosage recommendations and therefore this guidance may change as evidence emerges.

WEIGHT	**<50 kg**	**50-99 kg**	**100-150kg**	**>150kg**
ENOXAPARIN DOSE GIVEN SC	**40mg ONCE DAILY** (Consider 20 mg once daily – consultant discussion)	**40mg ONCE DAILY** (standard risk) **40mg TWICE DAILY** (high risk)	**40mg TWICE DAILY** (all inpatient settings)	**60mg TWICE DAILY** (all inpatient settings)
RENAL IMPAIRMENT:	If eGFR 15-30mls/min, reduce dose by 50% If eGFR <15ml/minute use unfractionated heparin 5000 units BD for patients weighing <50kg and TDS for patients weighing ≥50kg **RRT on critical care - use therapeutic heparin infusion**			

Critical Care patients

In addition to enoxaparin prophylaxis all patients should receive:

- Arterial line flush with heparinised saline (500units heparin in 500ml sodium chloride 0.9%) NB increase wasted blood to 5ml when sampling to avoid contamination with heparin
- Graduated compression stockings (GCS) unless contraindicated until mobilising.

For immobile patients on ITU with contraindications to LMWH, consider Intermittent Pneumatic Compression (flotrons®) instead of GCS.

For patients on RRT, use continuous IV unfractionated heparin (UFH infusion) as per Trust guidelines. Aim for APTTR 2.0 to 2.5

- If the filter is removed and the intention is that the patient may require filtration at a later time point, consider continuing the UFH infusion or bridging with prophylactic LMWH.
- If the filter is discontinued as it is no longer required, revert to thromboprophylaxis.
- If filter thrombosis occurs despite APTTR 2-2.5 or >1650units UFH/hour required to achieve target APTTR, discuss with a consultant haematologist.

On discharge from ITU or ARU CPAP cohort to other wards, thromboprophylaxis should revert to standard doses as above.

Coagulation Screening Recommendations

Summary

1. Coagulopathy is a recognised complication of COVID-19 infection
2. Abnormal laboratory coagulation results are predictive of mortality
3. The use of prophylactic LMWH in patients despite coagulopathy may improve survival

Recommendations[1-5]:

1. Full coagulation screening in COVID-19 infected inpatients should be done on admission and then repeated if admitted to critical care; it should ideally include the following (see appendix A)
    - FBC
    - PT (INR) and APTT
    - Fibrinogen
    - D dimer

2. Prophylactic LMWH (adjusted for weight and renal function – see above) should be given to all patients with COVID-19 (confirmed and suspected) unless there is a clear contraindication, active bleeding, a platelet count <30 x 10^9/L or fibrinogen <0.5 g/L
    - *A prolonged INR or APTT is not in itself a contraindication to LMWH*
    - For immobile patients on ITU with contraindications to LMWH, consider IPC (flotrons)

3. Do not give plasma products or platelets based on abnormal coagulation tests unless there is active bleeding.

4. D-Dimer is used for risk assessment purposes for the COVID-19 DIC score and should not be used in isolation as an indication for a CT-PA request or for therapeutic dose LMWH.

Appendix A

DIC Score for COVID-19

Laboratory test	Result	POINTS
Platelet count	50-100	1
	<50	2
D Dimer	1000-3000	1
	>3000	2
Fibrinogen	<1.0 g/l	1
Prolongation of INR	1.5-1.7	1
	>1.7	2

Tang et al. J Thromb Haemost. 2020;00:1–4:

- 71% of those who died had a DIC score of 5 or more compared with 0.6% of survivors

Appendix B: Evidence for thromboprophylaxis

BSH guidelines on management of DIC [6] recommend that in critically ill, non-bleeding patients with DIC, prophylaxis for venous thromboembolism with prophylactic doses of heparin or low molecular weight heparin is recommended (Grade A, Level IB).
Standard thromboprophylaxis offers at best a relative risk reduction for VTE of ~65% with an optimal risk benefit profile. However, the severe prothrombotic state induced by COVID-19 seems to require more intensive thromboprophylaxis / anticoagulation, and an intermediate dosing schemes between prophylaxis and therapeutic has therefore been proposed (3). Potential benefits of the intermediate dose of LMWH consist of superior efficacy as compared to the standard dose of LMWH. The potential for harm consists of an increased risk of bleeding.

ISTH guidelines (4) recommend that prophylactic LMWH can be administered to patients with COVID-19 down to a platelet count of 25. Patients with a higher D dimer/DIC score (appendix A) may have the most to gain. These guidelines note that bleeding is rare in the setting of COVID-19. If bleeding does develop, similar principles to septic coagulopathy with respect to blood transfusions may be followed
ISTH guidance (5) recommends that mechanical thromboprophylaxis should be used alone if platelets <30,000 or bleeding.
The traditional platelet threshold for use of prophylactic LMWH in the UK is 75 x 10^9/l for general medical and surgical patients so a recommendation of 30 x 10^9/l represents a specific change in practice for COVID-19 patients.

References

1. 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

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3. 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.

4. 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

5. https://thrombosisuk.org/covid-19-thrombosis.php

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7. 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

8. Venous thromboembolism in over 16s: reducing the risk of hospital-acquired deep vein thrombosis or pulmonary embolism. NICE guideline (NG89) Published March 2018

9. Condliffe R, Bunclark K, Hurdman J, Kiely D, MacLean R, Price L, Valerio C, Wort J. BTS Guidance on Venous Thromboembolic Disease in patients with COVID-19. V1.0 20 April 2020 [accessed 30.4.2020] Available from: https://brit-thoracic.org.uk

MONITORING TOOL

This should include realistic goals, timeframes and measurable outcomes.

Key control:	Checks to be carried out to confirm compliance with the policy:	How often the check will be carried out:	Responsible for carrying out the check:	Results of check reported to: *(Responsible for also ensuring actions are developed to address any areas of non-compliance)*	Frequency of reporting:
WHAT?	**HOW?**	**WHEN?**	**WHO?**	**WHERE?**	**WHEN?**
All patients must be have their thromboembolic risk assessed on admission	Oasis data collection	Every admission	Ward clerks	Deviations from guideline recommendations may be reported via DATIX.	Each time a reportable issue arises
All patients should be prescribed thromboprophylaxis in accordance with the risk assessment and this guideline.	Review of prescribing	Every Prescription	Senior medical staff Clinical Pharmacists	Deviations from guideline recommendations may be reported via DATIX	Each time a reportable issue arises

CONTRIBUTION LIST

Key individuals involved in developing the document

Name	Designation
Dr Shafeek	Consultant Haematologist
Keith Hinton	Clinical Team Lead Pharmacist, Surgery & Critical Care

Circulated to the following individuals for comments

Name	Designation
Oliver Chapman	Consultant Haematologist
Nick Pemberton	Consultant Haematologist
Thomas Skibbe	Consultant Haematologist
Tracey Chan	Consultant Haematologist
Sangam Hebbali	Consultant Haematologist
Juliet Mills	Consultant Haematologist
Andy Burtenshaw	Clinical Director Critical Care
Nick Cowley	Consultant Critical Care
Bethan Barker	Consultant Respiratory Medicine
Jamie Johnson	Consultant Respiratory Medicine
Rachael Montgomery	Deputy Chief Pharmacist

Circulated to the following CD's/Heads of dept for comments from their directorates / departments

Name	Directorate / Department
Andy Burtenshaw	Clinical Director Critical Care

Circulated to the chair of the following committee's / groups for comments

Name	Committee / group
Mike Hallissey	Chair Trust Thrombosis Committee
	Medicines Safety Committee

Supporting Document 1 - Equality Impact Assessment Tool

To be completed by the key document author and included as an appendix to key document when submitted to the appropriate committee for consideration and approval.

Please complete assessment form on next page;

NHS Worcestershire Acute Hospitals NHS Trust

Herefordshire & Worcestershire STP - Equality Impact Assessment (EIA) Form
Please read EIA guidelines when completing this form

Section 1 - Name of Organisation (please tick)

Herefordshire & Worcestershire STP		Herefordshire Council		Herefordshire CCG	
Worcestershire Acute Hospitals NHS Trust	✓	Worcestershire County Council		Worcestershire CCGs	
Worcestershire Health and Care NHS Trust		Wye Valley NHS Trust		Other (please state)	

Name of Lead for Activity	

Details of individuals completing this assessment	**Name**	**Job title**	**e-mail contact**
	Keith Hinton	Pharmacist	Keith.hinton1@nhs.net
Date assessment completed	29.04.2020		

Section 2

Activity being assessed (e.g. policy/procedure, document, service redesign, policy, strategy etc.)	**Title:** Guideline			
What is the aim, purpose and/or intended outcomes of this Activity?	Provide advice in managing thromboembolic risk in Covid-19 positive patients			
Who will be affected by the development & implementation of this activity?	❑ ✓ ❑	Service User Patient Carers Visitors	❑ ❑ ❑ ❑	Staff Communities Other _____
Is this:	❑ Review of an existing activity ✓ New activity			

	❑ Planning to withdraw or reduce a service, activity or presence?
What information and evidence have you reviewed to help inform this assessment? (Please name sources, eg demographic information for patients / services / staff groups affected, complaints etc.	
Summary of engagement or consultation undertaken (e.g. who and how have you engaged with, or why do you believe this is not required)	
Summary of relevant findings	

Section 3

Please consider the potential impact of this activity (during development & implementation) on each of the equality groups outlined below. **Please tick one or more impact box below for each Equality Group and explain your rationale**. Please note it is possible for the potential impact to be both positive and negative within the same equality group and this should be recorded. Remember to consider the impact on e.g. staff, public, patients, carers etc. in these equality groups.

Equality Group	Potential positive impact	Potential neutral impact	Potential negative impact	Please explain your reasons for any potential positive, neutral or negative impact identified
Age		✓		
Disability		✓		
Gender Reassignment		✓		
Marriage & Civil Partnerships		✓		
Pregnancy & Maternity		✓		
Race including Traveling Communities		✓		
Religion & Belief		✓		
Sex		✓		
Sexual Orientation		✓		
Other Vulnerable and Disadvantaged Groups (e.g. carers; care leavers; homeless;		✓		

Equality Group	Potential positive impact	Potential neutral impact	Potential negative impact	Please explain your reasons for any potential positive, neutral or negative impact identified
Social/Economic deprivation, travelling communities etc.)				
Health Inequalities (any preventable, unfair & unjust differences in health status between groups, populations or individuals that arise from the unequal distribution of social, environmental & economic conditions within societies)		✓		

Section 4

What actions will you take to mitigate any potential negative impacts?	Risk identified	Actions required to reduce / eliminate negative impact	Who will lead on the action?	Timeframe
		.		
How will you monitor these actions?				
When will you review this EIA? (e.g in a service redesign, this EIA should be revisited regularly throughout the design & implementation)				

Section 5 - Please read and agree to the following Equality Statement

1. Equality Statement

1.1. All public bodies have a statutory duty under the Equality Act 2010 to set out arrangements to assess and consult on how their policies and functions impact on the 9 protected characteristics: Age; Disability; Gender Reassignment; Marriage & Civil Partnership; Pregnancy & Maternity; Race; Religion & Belief; Sex; Sexual Orientation

1.2. Our Organisations will challenge discrimination, promote equality, respect human rights, and aims to design and implement services, policies and measures that meet the diverse needs of our service, and population, ensuring that none are placed at a disadvantage over others.

1.3. All staff are expected to deliver services and provide services and care in a manner which respects the individuality of service users, patients, carer's etc, and as such treat them and members of the workforce respectfully, paying due regard to the 9 protected characteristics.

Signature of person completing EIA	
Date signed	
Comments:	
Signature of person the Leader Person for this activity	
Date signed	
Comments:	

Supporting Document 2 – Financial Impact Assessment

To be completed by the key document author and attached to key document when submitted to the appropriate committee for consideration and approval.

	Title of document:	Yes/No
1.	Does the implementation of this document require any additional Capital resources	No
2.	Does the implementation of this document require additional revenue	No
3.	Does the implementation of this document require additional manpower	No
4.	Does the implementation of this document release any manpower costs through a change in practice	No
5.	Are there additional staff training costs associated with implementing this document which cannot be delivered through current training programmes or allocated training times for staff	No
	Other comments:	

If the response to any of the above is yes, please complete a business case and which is signed by your Finance Manager and Directorate Manager for consideration by the Accountable Director before progressing to the relevant committee for approval