BTS Guidance on Venous Thromboembolic Disease in patients with COVID-19

Background

This document is aimed at respiratory and general medical physicians. It summarises published data regarding the risks of VTE in patients with COVID-19, and discusses clinical issues regarding prevention, diagnosis and management of VTE.

COVID-19 infection is associated with inflammation, DIC, hypoxaemia and immobility which may all predispose to the development of thromboembolic complications.[1-4] Abnormalities in coagulation appear to be common and are associated with poorer outcomes. Guan *et al* observed elevated D-dimers in 46% of patients in a series of 1099 patients.[1] In a study of 183 patients with COVID-19 pneumonia, Tang *et al* observed longer PT (median 15.5s versus 13.6s), APTT (median 44.8s versus 41.2s) and higher D-Dimers (median 2,120mcg/L versus 610mcg/L) in non-survivors compared with survivors.[5] They also noted that 71% of non-survivors developed DIC during their admission (defined by a DIC score of ≥5) as compared with 0.6% of survivors. In a subsequent paper, Tang *et al* also studied 449 patients with severe COVID-19 and observed median D-dimer levels of 2,120mcg/L in non-survivors and 610mcg/L in survivors while Huang *et al* reported median levels of 2,400mcg/L in 13 patients who required critical care management, and 500mcg/L in 28 patients who did not.[6, 7] It must be acknowledged, however, that D-Dimers are a non-specific acute phase reactant which may be elevated in pneumonias and other causes of sepsis.

Risk of VTE

Emerging data and clinical experience suggest an increased prevalence of venous thromboembolic events in COVID-19, especially in patients with more severe disease. Cui *et al* demonstrated lower leg DVTs in 25% of 81 patients in ICU; of note, no patients had received VTE prophylaxis and no CTPAs were performed.[7] In their study,the sensitivity, specificity, negative predictive value and positive predictive value for a diagnosis of DVT were 85%, 89%, 95% and 71% using a D-dimer threshold of 1,500mcg/L and 70%, 97%, 91% and 88% using a threshold of 3,000mcg/L. Klok *et al* identified thrombosis in 31% of 184 Dutch ICU patients (25 PE, 3 DVT and 3 ischaemic strokes).[8, 9] They observed that increasing age and coagulopathy (defined as an elevation in prothrombin time by >3s or activated partial thromboplastin time by >5s) were independent predictors of outcomes (D-dimer levels were not reported in this study). All patients had received VTE prophylaxis (a minority at doses higher than the usual prophylactic dose). Limited post-mortem data together with clinical experience also suggests a possible role of small vessel microthrombi in patients with severe COVID-19 infection.[10]

Diagnosis of PE

Given the apparent increased incidence of VTE in COVID-19, clinicians should suspect VTE if sudden worsening of hypoxaemia, blood pressure or tachycardia occurs, or if clinical signs suggestive of DVT develop. As VTE appear to be especially common in patients requiring critical care management, there should be a particularly high index of suspicion for VTE and a low threshold for

investigating/treating for VTE in this patient group. Diagnosing VTE may be more complex in patients with COVID-19 due to several factors:

- Clinical state making movement to the radiology department difficult (e.g. a CPAP-dependent patient with high oxygen requirements);
- Local radiology protocols regarding radiological investigations in patients with known COVID-19;
- Overrun radiological services due to very high numbers of hospitalised COVID-19 patients.

Therefore, although every effort should be made to radiologically confirm suspected PE (using CTPA or, if signs of DVT are present, compression ultrasonography), in some cases a presumptive diagnosis of PE may be made (often informed by D-Dimer levels) and therapeutic anticoagulation commenced. As right ventricular dysfunction is also common in moderate to severe ARDS, trans-thoracic echocardiography has limited utility in indirectly diagnosing acute PE, although more severe RV dysfunction may raise the suspicion of pulmonary embolic disease.[11] A bleeding risk score (e.g. VTE-BLEED) may be useful in identifying patients at low risk of bleeding in whom anticoagulation without imaging may be safe and patients at higher risk of bleeding in whom imaging is more essential.[12]

Risk assessment and anticoagulation dosing

In the study of Tang *et al* involving 449 patients with severe COVID-19, only 22% received heparin (at standard prophylactic dose in the majority).[6] Although a difference in survival of patients within the overall group who did or did not receive heparin was not observed, survival was superior in patients receiving (prophylactic dose) heparin who had a Sepsis-Induced Coagulopathy (SIC) score ≥4 [13] and/or D-Dimers >3,000mcg/L. Although the vast majority of medically sick patients in the UK receive standard dose thromboprophylaxis, given the apparent high incidence of VTE in critically ill COVID-19 patients who have received prophylactic anticoagulation, it seems reasonable to consider higher doses of LMWH in a proportion of patients.[9] It must be borne in mind that there is no evidence that increasing the dose of LMWH thromboprophylaxis improves clinical outcomes, or reduces the risk of VTE. Should such strategies be employed, care must be taken to consider patients' bleeding risks. One suggested approach for risk stratification within the UK uses D-Dimer thresholds of <1,000mcg/L, 1-3,000mcg/L and >3,000mcg/L to identify patients who should receive standard-dose, intermediate-dose and treatment-dose anticoagulation. However, in the absence of definitive published data to guide the optimal approach to identifying patients at increased risk of VTE who may benefit from intermediate or full-dose LMWH, it is not possible to advocate any particular approach and it is suggested that local protocols for risk stratification in COVID-19 patients are developed. Risk stratification may be based on factors such as:

- Location of patient's care (e.g. critical care)
- Disease severity (e.g. need for CPAP, PaO2/FiO2 ≤40 kPA (300 mmHg), SIC score ≥4 (appendix))[13]
- D-dimer thresholds, as in the above example.

Clinical trials of the use of higher intensity LMWH thromboprophyaxis in patients with COVID-19 are sorely needed to better guide risk stratification and clinical management.

Possible approach to LMWH dosing:

Пиздец важно!!!

Standard Risk Patient:	Standard prophylactic dose LMWH (e.g. for a 70kg patient with CrCl>30mL/min: dalteparin 5,000 units od, enoxaparin 40mg od)
High Risk Patient:	Intermediate dose LMWH (e.g. for a 70kg patient with CrCl>30mL/min: dalteparin 5,000 units bd, enoxaparin 40mg bd)
Proven or suspected acute VTE:	Therapeutic dose LMWH (bd dosing may be preferred in critical care patients who may require invasive procedures or if bleeding risk felt to be elevated). Duration of treatment would generally be 3 months due to the strong provoking factor.

Other practical issues

Close collaboration with local haematologists is essential in formulating local policies and in managing severely ill patients. Local policies for the use of LMWH in patients with thrombocytopaenia should be followed but prophylactic doses can be used when platelets are >30 x10^9/L.[14] Minor prolongations of PT and APTT (up to 5 seconds) are common in COVID-19 and are not contraindications to thromboprophylaxis.[15] Switching patients with severe COVID-19 who are receiving vitamin-K antagonists to therapeutic LMWH during their admission should be considered. In patients receiving DOACs prior to admission, awareness of interactions with anti-viral therapies which may be considered in selected COVID-19 patients and of the need to take rivaroxaban with food is also important and switching to LMWH may therefore also be necessary.

Extended thromboprophylaxis on discharge can be considered if the patient is considered at high risk of VTE (eg past history VTE, cancer, significantly reduced mobility, critical care admission) and the risk of VTE is felt to outweigh the risk of bleeding. The nature and duration of thromboprophylaxis in patients recovering from COVID-19 pneumonia is not clear but a standard prophylactic dose of LMWH or DOAC for 4 weeks may be a reasonable approach.

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Appendix

1. Sepsis-Induced Coagulopathy (SIC) score[13]

Category	Parameter	0 point	1 point	2 point
Prothrombin time	PT-INR	≤1.2	>1.2	>1.4
Coagulation	Platelet Count ($x10^9$/L)	≥150	<150	<100
Total SOFA	SOFA four items	0	1	≥2

The total Sequential Organ Failure Assessment (SOFA) is the sum of the four items (respiratory SOFA, cardiovascular SOFA, hepatic SOFA and renal SOFA)

2. Respiratory, Cardiovascular, Hepatic and Renal SOFA[16]

A. Respiratory

PaO_2/FiO_2 [kPA (mmHg)]	≥53.3 (400)	<53.3 (400)	<40 (300)	<26.7 (200) and mechanically ventilated	<13.3 (100) and mechanically ventilated
SOFA Score	0	+1	+2	+3	+4

B. Cardiovascular

Mean arterial pressure* OR administration of vasopressors required	**SOFA score**
MAP ≥ 70 mmHg	0
MAP < 70 mmHg	+1
dopamine ≤ 5 µg/kg/min or dobutamine (any dose)	+2
dopamine > 5 µg/kg/min OR epinephrine ≤ 0.1 µg/kg/min OR norepinephrine ≤ 0.1 µg/kg/min	+3
dopamine > 15 µg/kg/min OR epinephrine > 0.1 µg/kg/min OR norepinephrine > 0.1 µg/kg/min	+4

***if not available, MAP = DBP + 1/3(SBP-DBP)**

C. Hepatic

Bilirubin (mg/dl) [µmol/L]	< 1.2 [< 20]	1.2–1.9 [20-32]	2.0–5.9 [33-101]	6.0–11.9 [102-204]	> 12.0 [> 204]
SOFA Score	0	+1	+2	+3	+4

D. Renal

Creatinine (mg/dl) [µmol/L]	< 1.2 [< 110]	1.2–1.9 [110-170]	2.0–3.4 [171-299]	3.5–4.9 [300-440]	> 5.0 [> 440]
SOFA Score	0	+1	+2	+3	+4

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