COVID-19, thromboprophylaxis and anticoagulation of ICU patients: shared clinical experience

A rapid dissemination summary report of a facilitated 'Knowledge Sharing Session' between clinicians with considerable collective experience of the management of COVID-19 infected patients across England.

The session was hosted on 22 April 2020, 10:30 to 11:30, by the Intensive Care Society (ICS), and 30 invited clinicians from acute and emergency care, intensive care, nursing, pharmacy, radiology, respiratory medicine, and thrombosis and haemostasis.

This paper is not a clinical guideline. It summarises the knowledge, practice and experience discussed at the session and these may change in this rapidly developing situation. It also highlights emerging unanswered questions where data sharing and research may help to inform clinical practice.

1. Patho-physiology of thrombosis in COVID-19

Two processes of thrombus formation were proposed & described:

1) Spontaneous

- Venous thromboembolic (VTE) disease: spontaneous clot in deep veins, or embolus from them to pulmonary circulation. Systemic arterial clot appears less common, although stroke is reported.
- Hyper inflammation of the lungs i.e. acute lung injury causing distal microvascular damage, thrombus in situ and impaired perfusion – which may be independent of observed VTE. On CTPA, subsegmental poor perfusion is sometimes reported without visible embolism

2) Triggered

- Clot around, for instance, catheters placed for renal replacement therapy

Elevation of D-dimers

- D-dimers are usually massively elevated in a subset of patients ('>20,000', '6-10 times upper limit'). Some report this pattern in most ICU patients.
- D-dimer elevation seems to correlate with increased VTE risk and with mortality, as reported in the published literature, and may reflect D-dimer production by damaged lung cells as a direct response to the hyper inflammation. D-dimer is not helpful in these patients as a marker for the presence of VTE. *(see note in Section 4 re: patients with lower D-dimers)*
- Evidence from China (1) reported a DIC-type coagulopathy; this did not fulfill ISTH criteria for DIC and has only been seen in patients dying with multiorgan failure. In one ECMO unit, PT & ISTH DIC score are often normal.

2. Reported prevalence of VTE and thrombosis-in-situ

- Higher than expected incidence of thrombosis (line thromboses; saddle emboli on CTPA; smaller vessel thrombosis on Dual Energy CT in absence of visible clot) are widely observed in practice and in the literature (2) although with some variation in extent:
  - ≈30% of CTPAs performed showing proximal or subsegmental occlusion (reported by several centres)
  - 10% of ICU patients with PE or DVT (audit data in one centre, n=70)
  - 29% ECMO patients with PE when scanned immediately after cannulation cf 10% pre-COVID-19 (one centre, n=30)
  - DVTs appear less common – present in ≈10% of those scanned
  - Ischaemic stroke with haemorrhagic transformation in young patients have also been observed
- Many centres have lowered thresholds for scanning and are now finding PEs in the absence of usual clinical indicators, e.g. ≤50% of scans of patients receiving pre-ICU CPAP revealed proximal artery and saddle emboli
- A small number of cases of bleeding e.g. subarachnoid haemorrhage were reported associated with ECMO use where higher rates of bleeding are expected

3. Thromboprophylaxis for ICU patients

- Many centres are moving to using 'intermediate' doses of low molecular weight heparin (LMWH) as thromboprophylaxis (e.g. increasing from OD to BD or weight-based dosing bands; consideration should be given to breadth of weight-based dosing bands in respect of linearity of dosing). Some units are using full therapeutic dose LMWH although there is no evidence to support this. Other units are using unfractionated heparin (UFH), but this should be used with caution due to the increased risks of bleeding (6%).
  - Approximately half doses of LMWH as per local regimen are recommended in renal failure (pragmatic definition creatine clearance <30ml/min) alongside monitoring closely for signs of accumulation - the UK thrombosis and haemostasis community now uses LMWH in preference to UFH in renal failure and have wide experience of this (talk to your local Thromboprophylaxis committee).
  - For monitoring UFH, **anti-factor Xa levels** were recommended over aPTT (may be shortened by elevated fibrinogen and factor VIII levels); peak anti-factor Xa levels are advised if bruising or other signs of bleeding.
- Most units are anticoagulating all ICU patients on renal replacement therapy using full heparinization (UFH) in addition to citrate filtration; one reported using argatroban

4. Investigation and management of Venous Thromboembolism

- Clinical parameters considered by individual trusts to trigger VTE imaging - or anti-coagulation in the absence of imaging - included:
  - For ward patients (pre-ICU): a step change in ventilation with no explanation on chest x-ray for this, and a step change in D-dimers (as these are lower on wards)
  - For ICU patients: look for hypercoaguable states with thrice weekly bloods (troponin, BNP, d-dimer) & step-changes in oxygen requirements to consider who needs a scan
  - For ICU patients: if possible (dual energy) scan everyone at the time of intubation
  - For very unwell patients (RESP score 1 or 2) who are not candidates for ECMO: consider anticoagulation if not contraindicated, or nitric oxide where available, where they appear to have a large shunt fraction
  - In all, ECG or echocardiographic changes consistent with PE/clot should increase suspicion

Imaging of COVID-19 patients within individual trusts

- During the current phase of the pandemic, many centres may have *increased* capacity for scanning due to reduction in usual workload. When normal workload resumes access may vary with the complexity of infection control requirements when handling COVID-19 and non-COVID-19 patients.
- One centre has adopted a standard imaging protocol for ICU patients to maximise efficiency (see Appendix) – where items can be omitted if not required.
- Another adopted early CTPAs (on hospital admission) and has not reported increased PEs on initial scan or on ICU although the reasons for this are not clear (was it too early? Was there false reassurance from initial scan?)
- Compression ultrasound of leg veins were considered less useful as they are often negative

Anticoagulation in the absence of radiological confirmation

- There was some support for low thresholds for anticoagulation where radiological confirmation is not possible, given the high thrombotic burden and potential long-term sequelae of lung damage
- Haematologists highlighted confirmation of diagnosis is helpful to define the duration for therapy to mitigate future risk
- Imaging in patients already on therapeutic doses (eg for renal replacement therapy) but with clinical features consistent with new VTE should be pursued – to identify refractory VTE which requires escalation of treatment.

Emerging questions for consideration

- *Is there a role for specific platelet inhibitors? Thrombi seen on post-mortem are typically mixed ie fibrin and platelet present, but the risks of bleeding would increase with anti-platelets so we need trials to assess their net effects.*
- *How effective is anticoagulation is in preventing thrombus formation in situ in those cases where this is driven by hyperinflammatory response? What is the role of anti-inflammatory agents?*
- *How long should anticoagulation continue on discharge from ICU and from hospital?*

Upcoming Research

Trials are under development for ICU patients and other inpatients. There will be a new arm of REMAP-CAP (see below) to look at full dose LMWH/UFH and also there are plans to compare prophylactic versus full dose of LMWH in ward patients.

Prevalence studies: NHSX is pooling data across 30-50 trusts (images, bloods, scans & Covid swab results) over 3 years which can be used to inform this work.

REMAP-CAP: a platform trial for severely ill patients with COVID-19

REMAP-CAP www.remapcap.org is an international adaptive platform trial that was specifically designed to be employed in a pandemic to evaluate multiple interventions simultaneously in critically ill patients. Interventions presently consist of antivirals, steroids and immunomodulatory agents with additional interventions also being considered. In the UK the trial is being led by ICS Director of Research Professor Anthony Gordon in conjunction with ICNARC. This study has received urgent public health badging by the Chief Medical Officer and is listed as one of the UK's prioritised platform trials.

The protocol design has now been published: https://www.atsjournals.org/doi/abs/10.1513/AnnalsATS.202003-192SD

If your ICU would like to sign up, please contact: ukremap-cap@icnarc.org

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Appendix

Sample protocols of care for COVID-19 patients in intensive care

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Appendix 1

King's Critical Care Units Clinical Guidance on Thromboprophylaxis in COVID patients admitted to ITU

Recent data has highlighted a number of coagulation changes in those with COVID-19, including prolonged PT, APTT, elevated fibrinogen, elevated d-dimer [Tang 2020a]. Of these changes D-dimer has been shown to be significantly elevated in patients [Tang 2020a] and be a marker of poor outcome [Zhou, 2020]. Additionally use of thromboprophylaxis in this cohort is associated with improved survival (of note, a minority of patients in the published cohort received thromboprophylaxis [Tang 2020b].

Recent observational data from COVID-19 infected patients admitted to ITU reports a high incidence of VTE (25-30%) [Cui 2020; Klok 2020]. Of note, in the cohort from the Netherlands all patients received thromboprophylaxis. There is additional suspicion of possible microangiopathy, contributing to respiratory deterioration despite routine thromboprophylaxis in UK (personal communication with multiple centres). Some centres are routinely using therapeutic anticoagulation due to these concerns and an apparent lack of bleeding phenotype (despite a lack of evidence to support this approach).

We therefore propose the use of intermediate dose thromboprophylaxis in all patients admitted to ITU (unless high bleeding risk eg, recent stroke/high risk surgery/major bleeding/platelets <50x10^9/l). Patients randomised to the upcoming TRIC study should follow management as per randomisation and trial protocol.

Recommendations

1. All patients admitted to ITU with COVID-19 should have a VTE risk assessment completed on EPR. All patients will be at high VTE risk, the presence of bleeding risk factors will influence the use of thromboprophylaxis.

Bleeding risk factors
• Active bleeding • Acquired bleeding disorders • Concurrent use of anticoagulants known to increase the risk of bleeding such as warfarin with INR > 2 or DOAC • Acute stroke† • Thrombocytopenia (platelet count<50x10^9/l, checked on admission)* • Uncontrolled systolic hypertension (≥ 230/120 mmHg or higher) • Untreated inherited bleeding disorders (such as haemophilia) • Trauma patients# • Neurosurgery, spinal surgery or eye surgery# • LP/epidural/ spinal anaesthesia within the previous 4 hrs or expected within the next 12 hrs • Other procedures with high bleeding risk #

† If acute stroke and SCDs contraindicated, consider anticoagulant prophylaxis daily in the MDT
*If platelets 30-50x10^9/l, consider standard dose anticoagulant prophylaxis in the absence of additional bleeding risk factors and monitor platelet count daily
Review the bleeding risk daily in the MDT and consider escalating to intermediate dose anticoagulant prophylaxis as soon as appropriate

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2. In the absence of bleeding risk factors, prescribe intermediate dose thromboprophylaxis (see Table below).

3. For patients with high VTE risk and high bleeding risk apply sequential compression devices (SCD) unless contraindicated (see below), with individual decision to add standard weight based thromboprophylaxis as per Trust guidelines

4. For patients on RRT, use continuous IVv unfractionated heparin (UFH infusion) as per Trust guidelines. Aim for APTR 2-2.5
    - If the filter is removed and the intention is to continue filtration at a later time point, continue UFH infusion.
    - If the filter is discontinued as it is no longer required, revert to thromboprophylaxis.
    - If filter thrombosis occurs despite APTR 2-2.5 or >1650units UFH/hour required to achieve target APTR, consultant decision to be made re switching to argatroban. Stop UFH infusion for 4 hours and take APTT prior to initiating argatroban (refer to link)

5. On ITU discharge to the ward, thromboprophylaxis should revert to standard doses as outlined in Trust guidelines

Intermediate dose thromboprophylaxis			
Weight	**eGFR >30ml/min**	**eGFR<30ml/min, not on RRT**	**On Continuous Renal Replacement Therpay**
<50kg	Enoxaparin 40mg SC od +/- SCD	UFH 5000 units SC bd +/- SCD	Systemic IV UFH infusion Aim for APTR 2-2.5 (refer to link)
50-100kg	Enoxaparin 40mg SC bd +/- SCD	UFH 5000 units SC tds +/- SCD	
101-150kg	Enoxaparin 60mg SC bd +/- SCD	UFH 10,000 units SC bd +/- SCD	
>150kg	Enoxaparin 80mg SC bd +/- SCD	UFH 12,500 units SC bd +/- SCD	

Contraindications to SCD (and AES)
• Lower limb ischaemia and suspected or proven peripheral vascular disease • Peripheral arterial bypass grafting or vein harvest for CABG • Peripheral neuropathy or other cause of sensory impairment • Recently diagnosed lower limb DVT **(do not use SCD if DVT within last 4 weeks)** • Allergy to material of manufacture • Severe leg oedema • Local condition in which compression may cause damage (ie fragile tissue paper skin, dermatitis, gangrene, recent skin graft • Unusual leg size or shape, or major limb deformity • Severe right sided cardiac failure

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Appendix 2: COVID-19 complex assessment decision tree for CT

The Royal Brompton & Harefield NHS Foundation Trust