University Health

Anticoagulation Guideline for Hospitalized Adult and Pediatric COVID-19 Patients

ADULT BACKGROUND

- Severe COVID-19 disease is associated with features of disseminated intravascular coagulation (DIC) and hypercoagulable states which can manifest as venous thromboembolism (VTE) and/or microthrombosis.[1,2]
- Centers for Disease Control and Prevention (CDC) estimates approximately 90% of hospitalized COVID-19 patients have underlying disease states such as obesity, hypertension, chronic lung disease, diabetes, and heart disease, which may increase the risk of thrombosis.[3]
- Critically ill patients with COVID-19 have been reported to have a VTE incidence rate around 30% which is significantly higher than non-COVID-19 critically ill populations.[4,5]
- Elevated D-dimer in the setting of severe COVID19 pneumonia is associated with worse outcomes. Some studies have found D-dimer above certain thresholds to have a high positive predictive value for VTE events and suggest these thresholds may be useful in determining when ultrasound screening and empiric full dose anticoagulation is indicated. However, the threshold associated with the highest risk is unknown. Additionally, studies correlating d-dimer based treatment with improvement in outcomes are lacking, and randomized controlled trials have shown similar outcomes regardless of D-dimer stratefication.[4,6-10]
- Randomized controlled trials have evaluated empiric therapeutic-dose anticoagulation in hospitalized COVID-19 patients without a diagnosed indication. In critically ill patients, empiric therapeutic-dose anticoagulation did not improve the primary outcome of days without organ support, and also increased major bleeding.[9] Alternatively, in the non-critically ill population, empiric therapeutic-dose anticoagulation showed superiority over prophylactic-dose in increasing survival to hospital discharge and reduced need for organ support, with major bleeding occurring in 1.9% and 0.9% of patients in each group respectively.[10] Similar benefits were demonstrated in an additional trial pending publication.[11]
- Hospitalized COVID-19 patients with a diagnosis necessitating therapeutic anticoagulation should be treated with treatment dose unfractionated or low molecular weight heparin instead of direct oral anticoagulants (DOACs) and warfarin which are less desirable due to illness-related hepatic dysfunction, reduced appetite and poor oral intake which may affect absorption or affect response to warfarin, and the possibility of rapid deterioration.[12,13,14]
- Post-discharge thromboprophylaxis has not shown to improve outcomes in COVID-19 patients and should not routinely be prescribed. Carefully selected patients at continued high risk for VTE and low risk for bleeding may be considered, however validated risk assessment scoring tools in this specific setting are not available.[14,15,16] Non-COVID-19 patient data suggests use of the modified IMPROVE VTE score coupled with the d-dimer to identify patients who may benefit from extended post-discharge thromboprophylaxis.[17]
- The algorithm below is intended to provide guidance for anticoagulation prophylaxis and treatment in COVID-19 patients and should not supersede clinical judgement. It may also be applied to “Persons Under Investigation” (PUIs) at the physician’s discretion and has been updated to include use in the pediatric population.

Adult Patients

COVID-19 (+) patients admitted to the hospital ***should*** receive anticoagulant prophylaxis unless contraindicated

Critically Ill DVT Prophylaxis

High suspicion/risk for thrombosis

- Superficial thrombosis in conjunction with evidence of high VTE risk
- Concern for new pulmonary embolism in a patient too unstable for diagnostic imaging

NO

High Dose Prophylaxis

Enoxaparin 0.5 mg/kg subcut BID (TBW)**

CrCl < 30 mL/min:
Enoxaparin 0.5 mg/kg subcut once daily**
< 50 kg: Heparin 5,000 units subcut every 8 hrs
≥ 50 kg: Heparin 7,500 units subcut every 8 hrs

All ICU patients should have four-extremity venous ultrasound every 7 days to evaluate the need for therapeutic anticoagulation

YES

Indication for therapeutic anticoagulation

(Including continuation of home therapy)

1st line - Enoxaparin 1 mg/kg subcut BID (TBW)
2nd line - Heparin 18 units/kg/hr IV (TBW) with standard boluses and titrations per protocol

DOACs and Warfarin
DO NOT USE for critically ill patients; may consider use in patients anticipating discharge

Non-Critically Ill DVT Prophylaxis

(Avoid DOACs for prophylaxis during hospitalization)

Standard Dose Prophylaxis

BMI < 40: Enoxaparin 40 mg subcut once daily***
BMI ≥ 40: Enoxaparin 40 mg subcut BID
BMI ≥ 50: Enoxaparin 60 mg subcut BID
CrCl < 30 mL/min:
Enoxaparin 30 mg subcut once daily**
Heparin 5,000 units subcut every 8 hrs
≥ 100 kg: Heparin 7,500 units subcut every 8 hrs

OR

Initial Therapeutic Dose Prophylaxis Strategy

(see exclusions on page 3)

Enoxaparin 1 mg/kg subcut BID
CrCl < 30 mL/min:
Enoxaparin 1mg/kg subcut once daily
Heparin 18 units/kg/hr IV (TBW) with standard boluses and titrations per protocol

Post-Discharge Extended Thromboprophylaxis Not Routinely Recommended

Educate patients on the signs and symptoms of VTE and to seek urgent medical attention if symptoms develop. **(See page 3 for more information)**

**May consider checking LMW heparin assay 4 hrs after the 2nd dose to ensure target prophylaxis level (0.2-0.4) is achieved. High degree of inflammation may lead to a need for increased dosing.
***Patients presenting with trauma should continue to receive Enoxaparin 30 mg SUBCUT BID per standard practice.
DOACs = Direct oral anticoagulants (apixaban, rivaroxaban, dabigatran, edoxaban, betrixaban)
Subcut = subcutaneously

Initial Therapeutic Dose Prophylaxis Strategy

- Reserved for non-critically ill patients with moderate COVID-19 disease who DO NOT meet any of the following exclusion criteria.
- Exclusion Criteria: [9,10]
    - Oxygen support through highflow nasal cannula
    - Current use of dual antiplatelet therapy
    - Platelet count < 50,000, INR > 2.0, or Hemoglobin < 8 g/dL
    - History of heparin induced thrombocytopenia
    - Acute or subacute bacterial endocarditis
    - Active bleeding
    - Risk factors for bleeding including: intracranial surgery, stroke or GI bleed within 3 months; history of intracerebral arteriovenous malformation or bleeding; intracranial malignancy; thrombolysis within previous 7 days, major surgery within previous 14 days, uncontrolled hypertension (SBP > 200 mmHg, DBP > 120 mmHg), presence of an epidural or spinal catheter

Post-Discharge Extended Thromboprophylaxis

- May be considered in carefully selected patients at continued high risk of VTE and low bleed risk for **14 - 30 days**
- Non-COVID-19 patient data[17]: modified IMPROVE VTE score ≥ 4, or 2-3 plus elevated d-dimer; excluded patients with cancer, on dual antiplatelet therapy, active GI ulcer, bleeding in the previous 3 months, history of bronchiectasis/pulmonary cavitation
- Options include:
    - Rivaroxaban 10 mg PO once daily (avoid in severe hepatic or renal dysfunction) **OR** enoxaparin 40 mg subcut once daily
    - If CrCl < 30 mL/min: enoxaparin 30 mg subcut once daily **OR** heparin 5,000 units subcut every 8 hrs

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PEDIATRIC BACKGROUND

- Most of what is known regarding thrombotic potential with COVID-19 infection is extrapolated from the adult literature. Despite the duration of COVID-19 presence in the community, there is still little to be known about pediatric VTE risk and optimal prophylactic regimens. Prior to the spread of the delta variant, pediatric VTE prophylaxis consensus guidelines supported use of pharmacologic VTE prophylaxis in pediatric hospitalized patients with COVID-19 or multisystem inflammatory syndrome in children (MIS-C) diagnosis.[1]
- Children infected with COVID-19 have previously demonstrated heterogeneity in clinical severity.[2] However, a new delta variant strain has proven more infectious[3] and is now sending more children to the hospital to seek care given severity of symptoms (unpublished, based on regional reports).
- A phase II study looking at safety, dosing, and efficacy of using twice daily VTE prophylaxis in COVID-19 positive patients ages 0-18 yr has been completed without available publication at this time.[4] Published expert opinion endorsed by the International Society of Thrombosis and Hemostasis recommend the following[1]:

    - (Strong consensus; 83%) Suggest mechanical and pharmacologic VTE prophylaxis in hospitalized children with COVID-19 related illness or MIS-C who have:
        - Superimposed clinical risk factors (see table 1 below) **OR**

- D-dimer ≥ 5 times the upper limit of normal

  AND

- No contraindication to anticoagulation (see table 2 below)

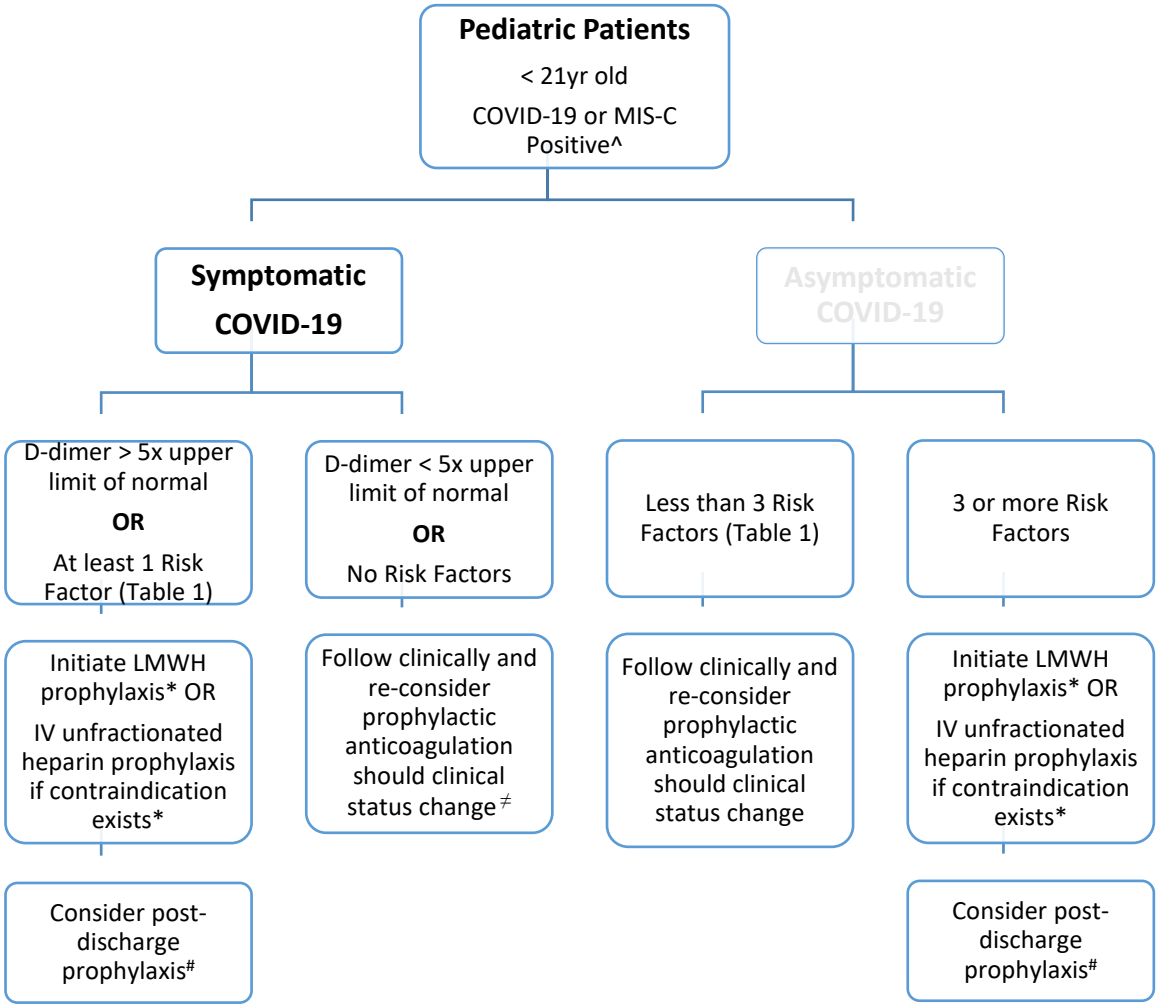
- (Weak consensus; 78%) Suggest low dose LMWH subcutaneously twice daily to achieve anti-Xa activity level of 0.2 to < 0.5 U/mL in patients who are otherwise clinically stable without severe renal impairment in the absence of contraindications.
  - For patients with contraindications, consider continuous unfractionated heparin IV with anti-Xa activity target of 0.1 – 0.35 U/mL
- (Strong consensus; 89%) Significant thrombocytopenia (count less than 20-50k), hypofibrinogenemia (< 100 mg/dL by Clauss), ISTH defined major bleeding, concomitant aspirin administration at doses > 5 mg/kg/day likely confer higher risk of bleeding with anticoagulation. However, in the absence of other bleeding risk factors, low dose anticoagulation prophylaxis is not thought to increase risk of significant bleeding in MIS-C patients receiving aspirin doses ≤ 5 mg/kg/day for cardiac issues or Kawasaki-like disease.
- (Weak consensus; 61%) Continuation of anticoagulation prophylaxis post-discharge should be considered in pediatric patients with COVID-19 illness or MIS-C who have very elevated d -dimer at discharge **AND** superimposed risk factors (see table below). Duration of prophylaxis post-discharge should be until the clinical risk factor resolves OR 30 days post-discharge (whichever occurs sooner). Guidelines suggest using LMWH prophylaxis dosing twice daily or therapeutic dosing once daily (anti-Xa activity 0.5-1.0 U/mL) in patients without contraindications or significant risk of bleeding.
- (Strong consensus; 89%) Suggest not routinely prescribing anticoagulation for VTE prophylaxis in hospitalized children with asymptomatic COVID-19 in the absence of central venous catheter OR multiple risk factors for hospital associated VTE (see table 1 below).

Table 1. Risk Factors for VTE in Pediatrics

Central venous catheter
Mechanical Ventilation
Prolonged length of stay: anticipated > 3 days
Complete immobility (Braden Q Mobility Score = 1)
Obesity (BMI > 95% for age percentile)
Active malignancy
Nephrotic syndrome
Cystic fibrosis exacerbation
Sickle cell disease vaso-occlusive crisis
General inflammatory disease flare (i.e., Lupus, JIA, Inflammatory bowel disease)
Congenital or acquired cardiac disease with venous stasis or impaired venous return
Prior history of VTE
First degree family history of VTE prior to 40 yr of age OR unprovoked VTE
Known thrombophilia (i.e., Protein S or protein C deficiency, ATIII deficiency, Factor V Leiden, Prothrombin II mutation, anti-phospholipid antibodies)
Pubertal, post-pubertal, or > 12 years of age
Receiving estrogen containing oral contraceptive pill
Status-post splenectomy for underlying hemoglobinopathy

Table 2. Contraindications for Anticoagulation in Pediatrics

Absolute:
Hemorrhage, evidence or high risk of
Relative:
Bleeding disorder, known tendency – consult Pedi Hematology
Platelet count unable to be sustained > 50,000mm^3 (contraindication depends on etiology)
Intracranial mass
Lumbar puncture or epidural catheter removal in prior 12 hours
Neurosurgical procedure
Pelvic fracture within past 48 hours
Uncontrolled hypertension



^Recommend screening for personal and family history of bleeding disorder in addition to screening coagulation labs prior to anticoagulation.

*Recommend prophylaxis if no contraindications exist (Table 2). LMWH thromboprophylaxis guidelines located at this link. Recommend q12hr dosing with goal anti-Xa activity of 0.2 to < 0.5 U/mL. Unfractionated heparin guidelines located at this link. Consider heparin infusion if there are contraindications to LMWH or severe renal impairment. Recommend continuous IV infusion with target anti-Xa activity 0.1 - 0.35U/mL.

≠Consider trending D-dimer daily

#Post discharge VTE prophylaxis should be considered in patients who have markedly elevated D-dimer at discharge and superimposed risk factors (Table 1). Duration of prophylaxis post-discharge should be until the clinical risk factor resolves OR 30 days post-discharge (whichever occurs sooner). Suggest using LMWH prophylaxis dosing twice daily (anti-Xa activity 0.2 to < 0.5U/mL) in patients without contraindications (Table 2) or significant risk of bleeding. Refer patients who are discharged on LMWH to follow-up in Hematology Clinic with Dr. Maida or the nurse practitioner within 1 week.

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