Update on Anticoagulants in Childhood COVID-19 infection

Mehran Karimi MD

Shiraz, November 18,2021

Agenda

- Background
- Mechanisms of thrombosis
- Incidence of Thrombosis risk in hospitalized pediatric patients with COVID-19 infection
- Recommendations on anticoagulant thromboprophylaxis in childhood COVID-19 infection
- Choice of anticoagulant in children with COVID-19
- Clinical vignettes
- Discussion

Background

- The majority (95%) of children with acute infection have milder clinical course compared to adults
  - children are lees likely to develop severe disease than adults,
  - 6% of children have severe disease versus 26% of adults
- Pediatric patients remain at risk for thrombosis during hospitalization or MIS-C*
  - A postinfectious (inflammatory) complication which usually presents few weeks after COVID-19 infection.
- The data regarding prevalence and risk factors of thrombosis in children are scarce
- Anticoagulation therapy is associated with reduced mortality in hospitalized adult patients
  - But limited data are available showing safety and efficacy of anticoagulation in children with COVID-19

*Multisystem inflammatory syndrome in children

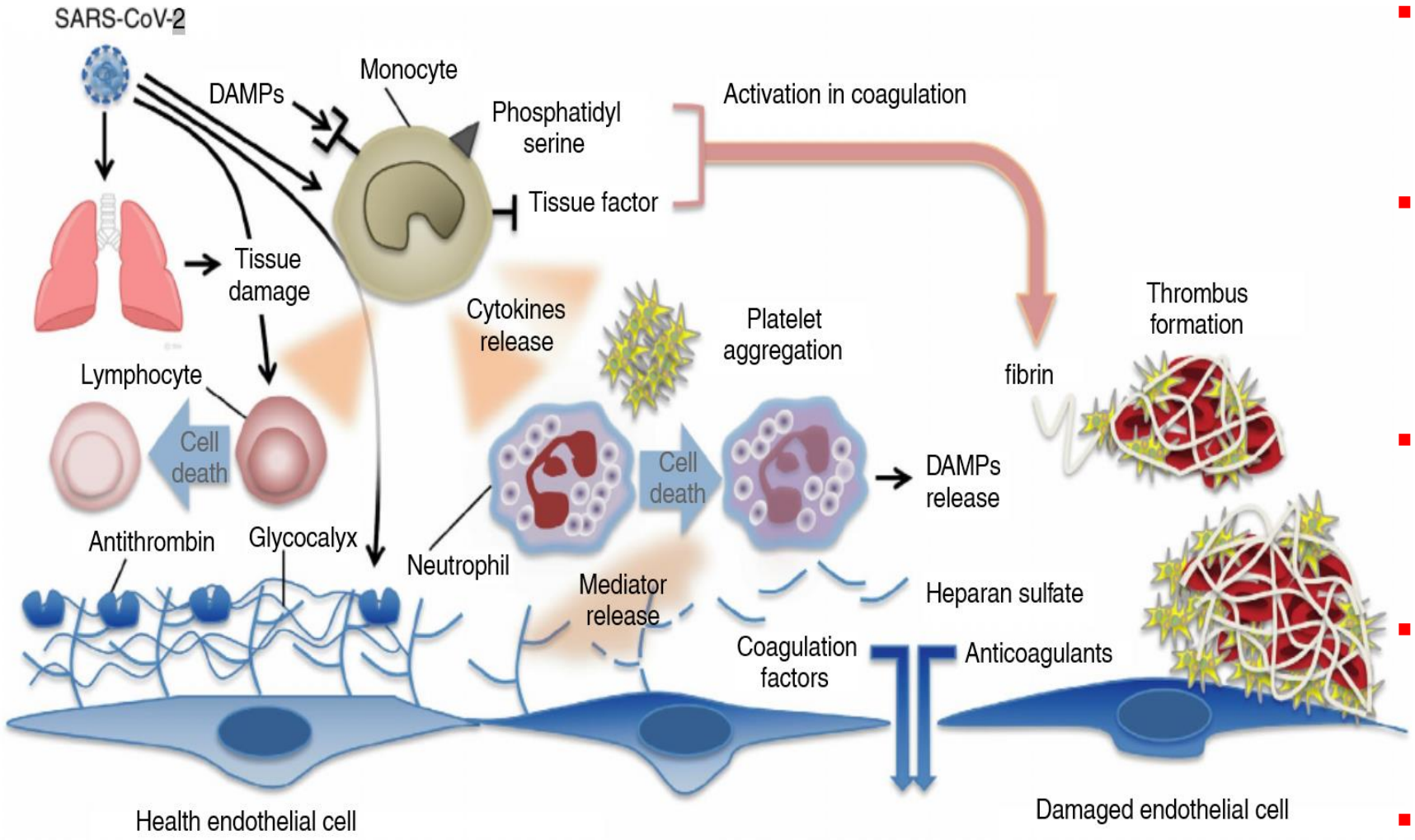
1.Karim M. et al. Acta Biomed 2020
2. Wang Y et al. Pediatr Inf Dis.J 2020
3.Tang N. et al. Journal Thromb Haemost. 2020
4. CDC COVID-19 Response Team. Unites States, 2020

Definition of severity COVID-19

- **Mild**
  - Patients present mild symptoms without radiographic features.
- **Moderate**
  - Patients present with fever, respiratory symptoms, and radiographic features.
- **Severe**
  - Patients meet one of three criteria: (a) dyspnea, RR greater than 30 times/min, (b) oxygen saturation less than 93% in ambient air, and (c) PaO2/FiO2 less than 300 mmHg.
- **Critical**
  - Patients meet one of three criteria: (a) respiratory failure, (b) septic shock, and (c) multiple organ failure.

National Health Commission of China. The guidelines for diagnosis and treatment of novel coronavirus (2019-nCoV) infected pneumonia (6th ed, in Chinese) issued by the National Health Commission of China. http://www.gov.cn/zhengce/ zhengce/2020-02/19/content 5480948.htm2020. Accessed February, 2020.

Mechanisms of coagulation activation in COVID-19



- Both virus and damage-associated molecular patterns (DAMPs) from injured host tissue can activate monocytes.
- Activated monocytes release inflammatory cytokines and chemokines that stimulate neutrophils, lymphocytes, platelets, and vascular endothelial cells.
- Monocytes and other cells express tissue factor and phosphatidylserine on their surfaces and initiate coagulation.
- Healthy endothelial cells maintain their anti-thrombogenicity by expressing glycocalyx and its binding protein antithrombin.
- Damaged endothelial cells change their properties to procoagulant following disruption of the glycocalyx and loss of anticoagulant

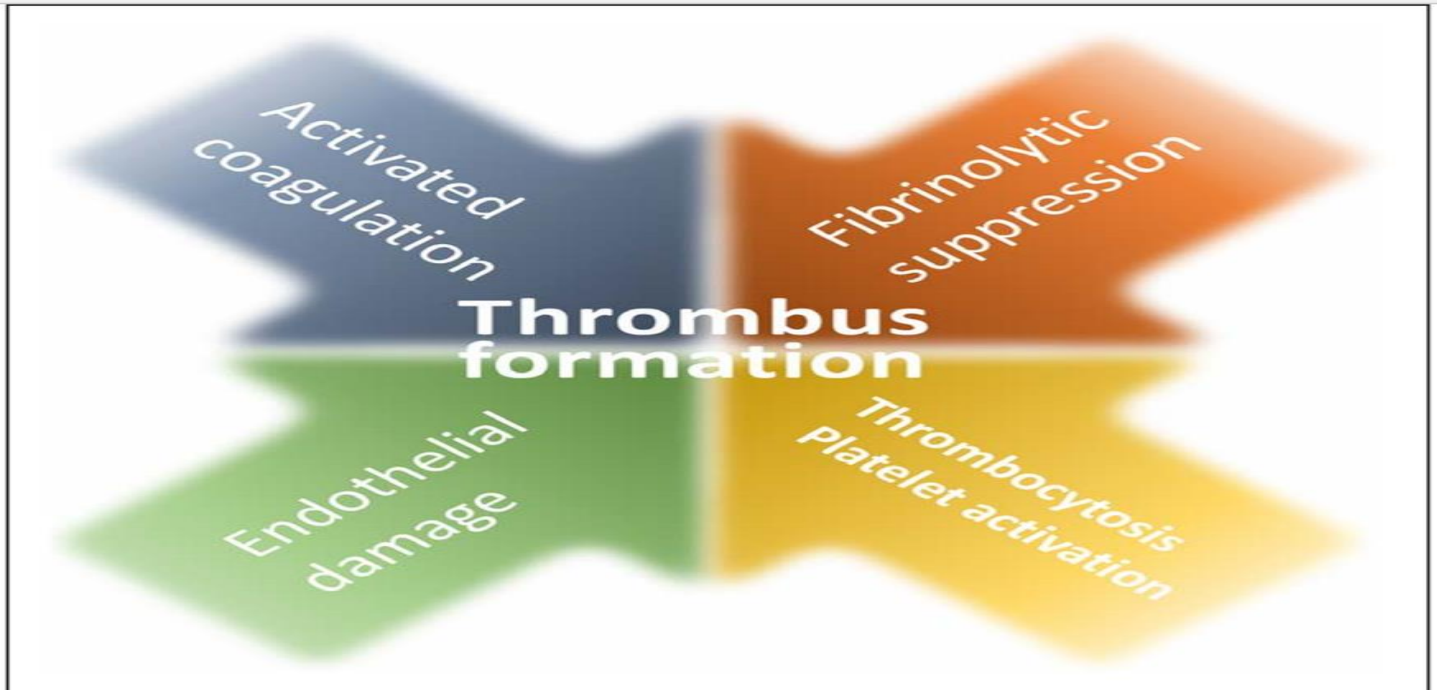
Iba T.Et al. J Thromb Haemost. 2020;00:1–7

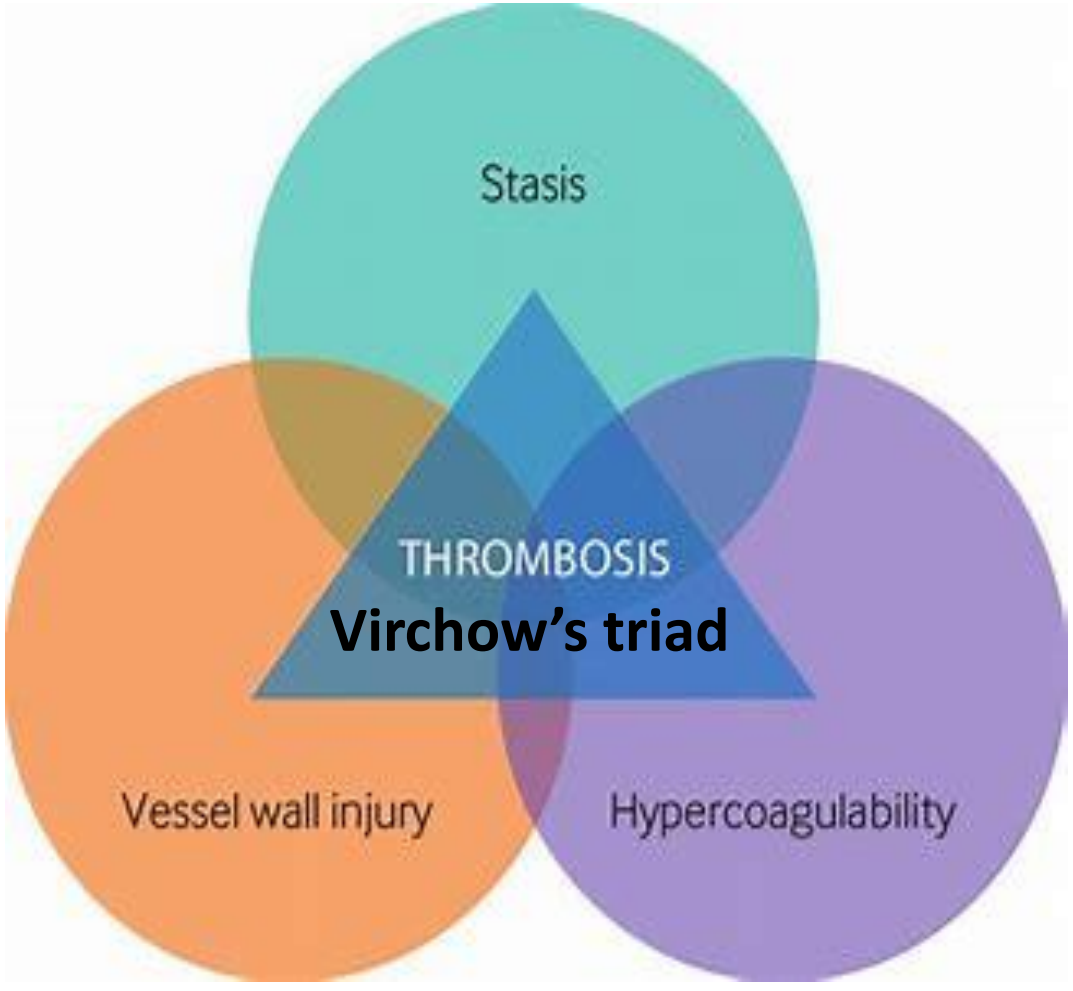
Summary of mechanisms of thrombosis in COVID-19

- **Endothelial damage**
- **Platelet activation**

→
- Increased ultra-large multimer of VWF and VWF Ag
- Increased Factor VIII and soluble P selectin,

- **Activate coagulation cascade**
- **Decrease Fibrinolytic activation (**disruption of the glycocalyx and loss of anticoagulant proteins including AT and thrombomodulin that causes



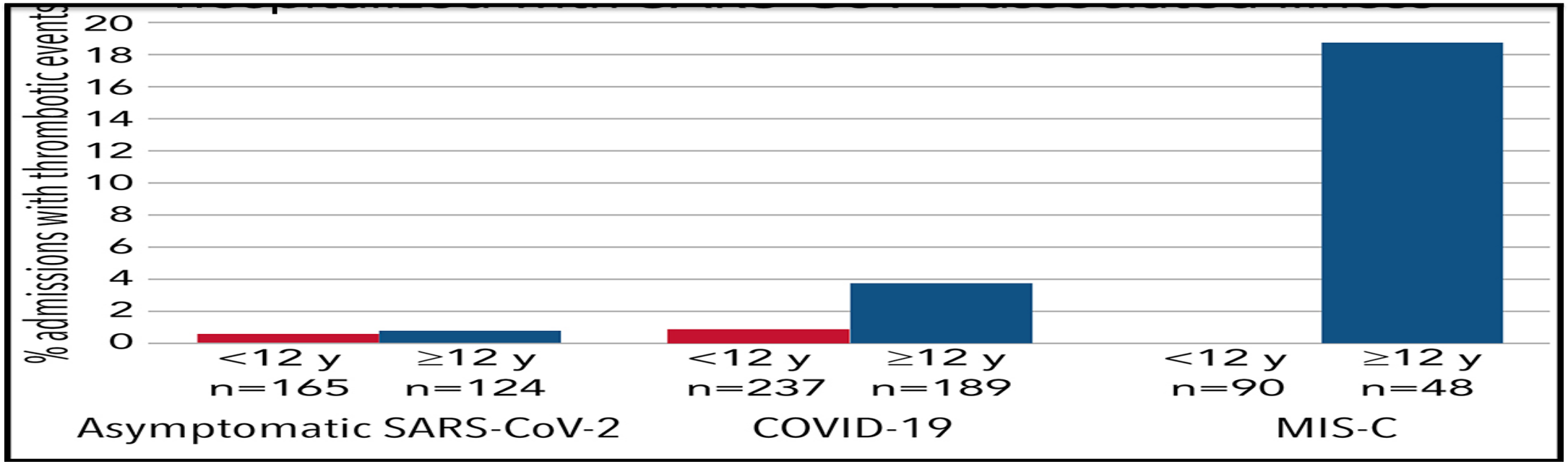


Incidence and type of thrombosis in COVID-19

- Studies show that about 25% to 70% of critically ill patients have confirmed venous thromboembolism or pulmonary embolism
- A recent study reported that the rate of symptomatic VTE was 7% (3/45) among patients 13 to <21 years of age and 1.3% (1/75) in children 5 to <13 years old
- Types of thrombosis:
  - Venous thromboembolism (VTE)
  - Pulmonary emboli (PE)
  - Microvascular thrombosis in lung and Kidney
  - Macrovascular thrombosis
    - ❖ Ischemic stroke
    - ❖ Myocadiac Infarction
    - ❖ Clotting of extracorporeal circuit
    - ❖ Mesenterial ischemia
    - ❖ Acute leg ischemia

1. F.A. Klok, et al. Thrombosis Research 191 (2020) 145–147
2. Thachil J, et al. JTH. 2020;18(5):1023-6.
3. Feldstein LR et al. N Engl J Med. 2020;383(4):334-346

Rate of thrombosis in children and adolescents hospitalized with COVID-19 or MIS-C



- Multicenter retrospective cohort study of 853 admissions (COVID-19# 426; MIS-C#138; and asymptomatic COVID-19#289)
  - 20 patients with thrombotic events including 1 stroke (MIS-C had the highest incidence)
- Cancer, central venous catheter, older age (≥12 years), and MIS-C are risk factors for thrombosis
- Two-third of pediatric patients developed thrombotic complications despite prophylactic anticoagulation
- Hospital mortality was 2.3% (13 of 564), but it was 28% (5 of 18) in children and adolescents with MIS-C or COVID-19 who developed thrombosis.

Whitworth H. et al. Blood 2021

ASH Guidelines on Use of Anticoagulation in Patients with COVID-19

Critically Ill Patients - Recommendation 1A and 1B

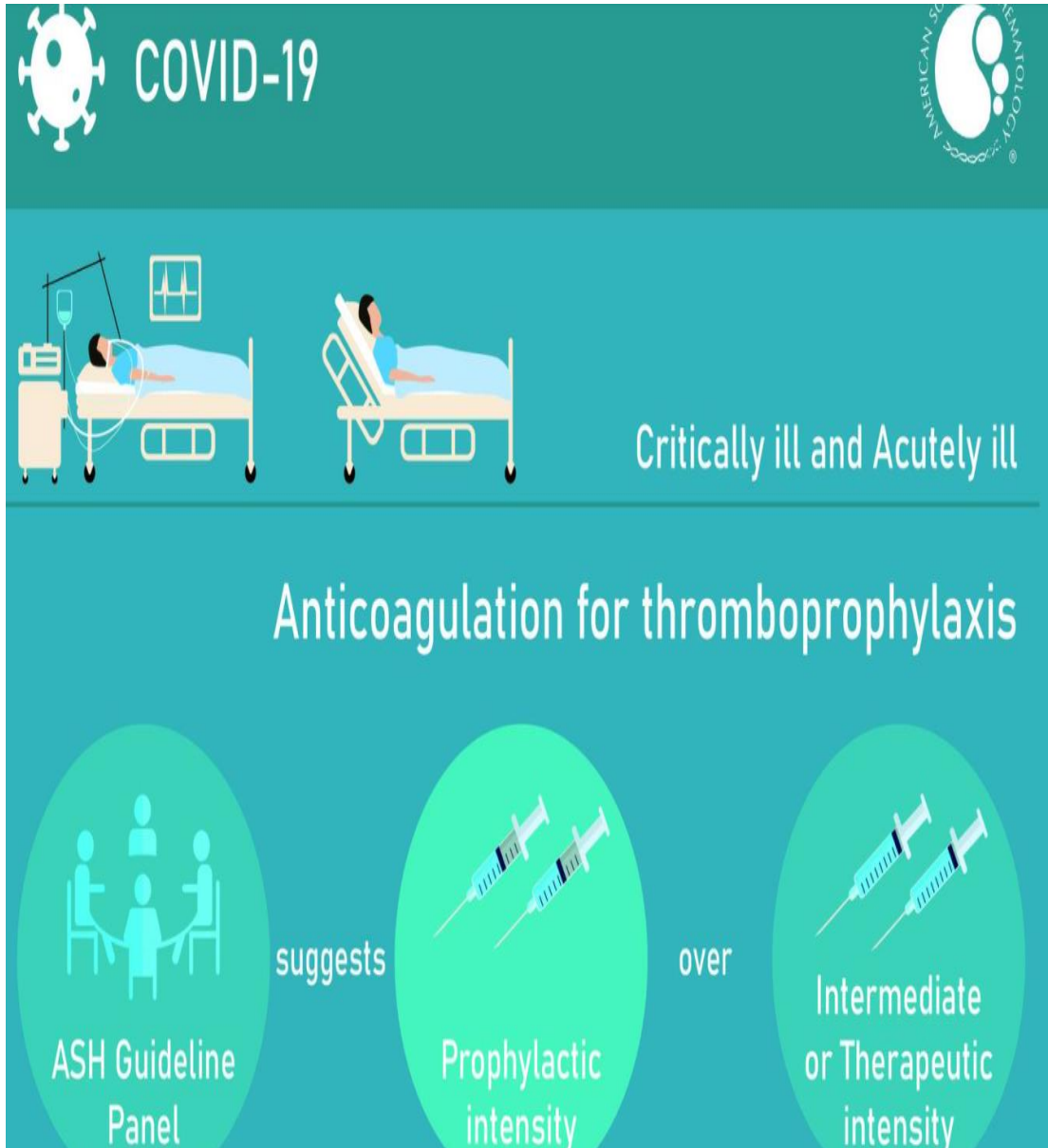
Recommendation 1 was split into two recommendations (1A and 1B) on April 7, 2021 with the emergence of new evidence: The ASH guideline panel suggests using prophylactic-intensityver intermediate-intensity or therapeutic-intensity anticoagulation for patients with coronavirus disease 2019 (COVID-19)–related critical illness who do not have suspected or confirmed venous thromboembolism (VTE) (conditional recommendation based on very low certainty in the evidence about effects ⊕◯◯◯)

Recomendation 1A

The American Society of Hematology (ASH) guideline panel *suggests* using prophylactic-intensity over intermediate-intensity anticoagulation for patients with coronavirus disease 2019 (COVID-19)–related critical illness who do not have suspected or confirmed venous thromboembolism (VTE) (conditional recommendation based on low certainty in the evidence about effects ⊕◯◯◯) .

Recommendation 1B

Therapeutic-intensity vs. prophylactic-intensity anticoagulation is forthcoming.



Anticoagulation therapy in children and young adults hospitalized with severe COVID-19

- Retrospective cohort analysis of 27 patients (age 2 months to 21 years) admitted to the hospital for symptomatic COVID-19 in New York
- Four (15%) patients died of COVID-19 complications
  - They were 2 months, 11, 14, and 18 years old, and all had comorbidities, which were cardiac defect, cancer, genetic syndrome, and trisomy 21, respectively
- VTE was identified in 7 (26%) patients
  - Three (11%)patients developed DVT and 4 (15%) developed PE (one had bilateral PE)
  - 4 patients were on prophylaxis and 3 patients on therapeutic dosing of anticoagulation
    - ❖Delayed start of anticoagulation was not identified as the cause for breakthrough VTE
  - A requirement for increased ventilatory support was a risk factor for VTE,
    - ❖7 of 14 (50%) patients in the High Ventilatory Support group developing VTE as compared with none of 13 patients in the Low Ventilatory Support group

Mitchell W. et al. Pedatr Blood Cancer 2021

Recommendations: for anticoagulants in pediatric patients with COVID-19

- Obesity and sickle cell disease were the most prevalent comorbid conditions
  - Sickle cell disease was not associated with an increased risk of thrombosis
- The LMWH was dosed at 0.75 mg/kg b.i.d. for neonates up to two months, and 0.5 mg/kg b.i.d. for over two months, with titration of anti-Xa level to 0.2-0.4 ng/mL
  - No patients developed VTE on LMWH prophylaxis titrated to anti-Xa level
- One patient presented with PE ten days post discharge, leading us to recommend prophylactic anticoagulation for two weeks post discharge.
- This study showed that children and young adults with symptomatic COVID-19 were at risk for VTE despite prophylactic anticoagulation
  - Treat patients requiring high ventilatory support [> 5 L nasal cannula(NC)] or D-dimer levels ≥ 5 µg/mL with full-dose anticoagulation (LMWH), titrated to an anti-Xa level of 0.6-1.1 ng/mL,

Mitchell W. et al. Pedatr Blood Cancer 2021

Consensus-based recommendations on the use of anticoagulant thromboprophylaxis in children hospitalized for COVID-19

- Twenty surveys were sent, and there were 18 respondents (response rate, 90%), consisting of 11 pediatric hematologists and seven pediatric intensivists

Scenario	D-dimer >5 times upper limit of normal values	Non-COVID-19 clinical risk factors for hospital-associated-VTE	Anticoagulant thromboprophylaxis suggested
Hospitalized for COVID-19–related illness (includes MIS-C)	Yes	N/A	Yes
	No	One or more[a]	Yes
		None	**No**
Hospitalized with asymptomatic SARS-CoV-2 infection	N/A	Multiple (≥3)	Yes
		Few or none	**No**

[a] While there was consensus among experts surveyed for the stated recommendations, specific risk factors endorsed by survey respondents varied

Goldenberg NA. et al. J Thromb Haemost. 2020

Clinical recommendations based on expert opinion

- Thromboprophylaxis in children hospitalized with COVID-19–related illness (including MIS-C) if
  - Superimposed clinical risk factors for hospital-associated VTE or
  - Markedly elevated plasma D-dimer levels (≥5 times the ULN) (**strong consensus**)
  - Hospitalized asymptomatic COVID-19 with ≥3 clinical risk factors for hospital-associated VTE
- Low-dose LMWH subcutaneously twice daily if clinically stable without severe renal impairment
- The use of low-dose anticoagulant thromboprophylaxis is not believed to confer a high risk of clinically significant bleeding in MIS-C patients who are receiving aspirin at doses ≤5 mg/kg/d (**strong consensus**)
- Not be routinely prescribed in hospitalized/outpatient asymptomatic children and in the absence of an indwelling central venous catheter or multiple clinical risk factors for VTE (**strong consensus**)
- Post-discharge thromboprophylaxis in children with markedly elevated plasma D-dimer levels at hospital discharge/ superimposed clinical risk factors for VTE with a planned

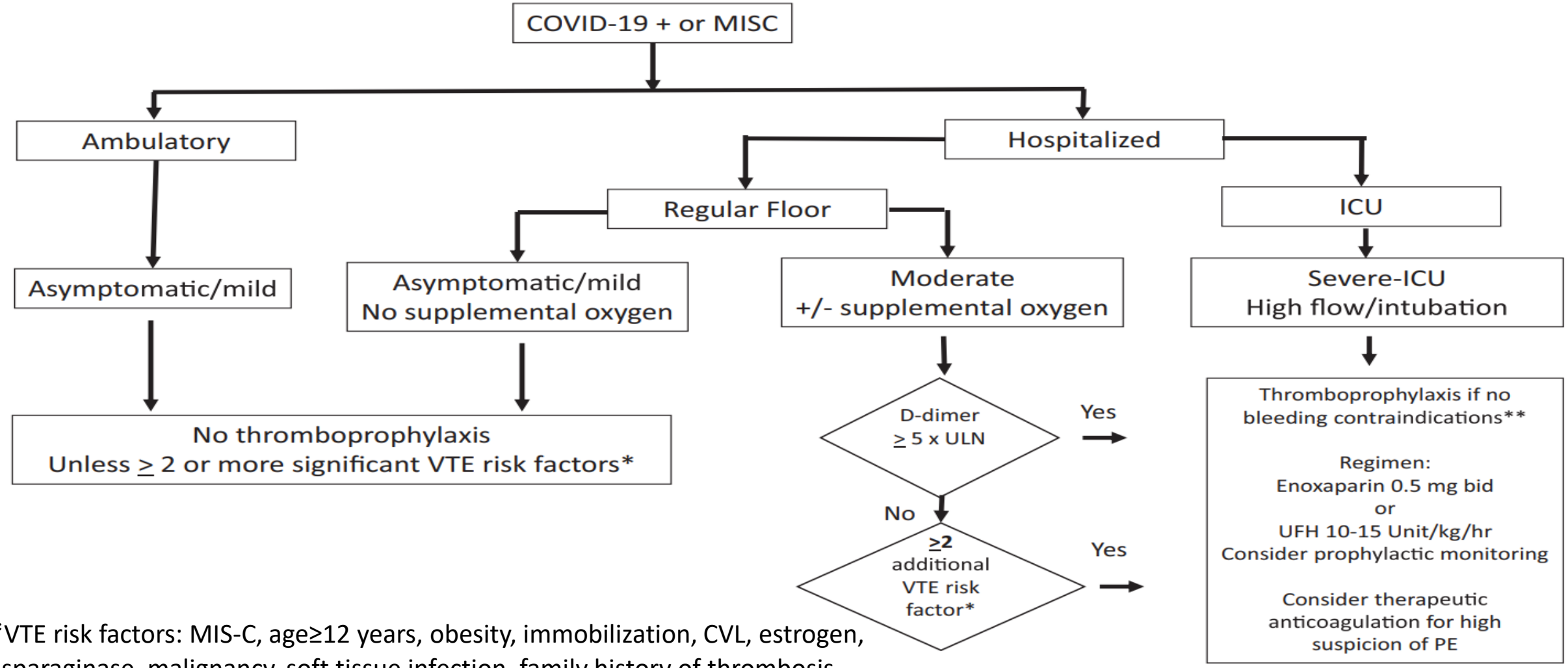
Goldenberg NA. et al. J Thromb Haemost. 2020

Non-COVID-19 clinical risk factors for hospital-associated VTE in children

- Central venous catheter
- Mechanical ventilation
- Prolonged length of stay (anticipated >3 days)
- Complete immobility (Braden Q Mobility Score = 1)
- Obesity (BMI >95th percentile)
- Active malignancy, nephrotic syndrome, cystic fibrosis exacerbation, sickle cell disease vaso-occlusive crisis, or flare of underlying inflammatory disease (lupus, juvenile idiopathic arthritis, inflammatory bowel disease)
- Congenital or acquired cardiac disease with venous stasis or impaired venous return,
- Previous history of VTE
- First-degree family history of VTE before age 40 years or unprovoked VTE
- Known thrombophilia (protein S, protein C, or antithrombin deficiency; factor V Leiden; factor II G20210A; persistent antiphospholipid antibodies)
- Pubertal, post-pubertal, or age >12 years
- Receiving estrogen-containing oral contraceptive pill
- Status-post splenectomy for underlying hemoglobinopathy

1.Mahajerin A. et al. Haematologica. 2015
2. Branchford BR. Et al. J Thromb Haemost. 2017

Framework for thromboprophylaxis assessment in children



*VTE risk factors: MIS-C, age≥12 years, obesity, immobilization, CVL, estrogen, asparaginase, malignancy, soft tissue infection, family history of thrombosis

**Bleeding contraindications: active bleeding, significant risk of bleeding, platelet count <20,000 mm3.

SHARATHKUMAR ET AL. Pediatr Blood Cancer. 2021.

Anticoagulation management algorithm for pediatric patients ≤ 18 years old with COVID-19: based on 4 clinical scenarios

Pediatric patients with COVID-19

Asymptomatic/ Mild , not necessary to hospitalize or hospitalize but no need supplemental oxygen

Moderate/ Severe-ICU, need hospitalization and supplemental oxygen/ or ≥2- 3 VTE risk factors/ or D-dimer ≥ 5 ULN

1

No thromboprophylaxis unless ≥ 2-3 VTE risk factors*, indwelling central venous catheter or D-dimer ≥ 5 ULN**

2

Start thromboprophylaxis if not contraindicated***:
Enoxaparin dose (monitor by Anti-Xa): 0.5 mg/kg SC bid or UFH 10-15 unit/kg/hour (monitor by PTT)

- CBC, Bun, Cr, PT/PTT, D-dimer, fibrinogen, AT3,
- **Target Anti-Xa (**4-hour post-dose**): 0.2-0.4** units/ml every other day

3

- Consider intensified thromboprophylaxis (Enoxaparin: 0.75 mg/kg SC BID) if:
  - Critical ill (patients meet one of three criteria: respiratory failure, septic shock, and multiple organ failure)/ or ICU admission with high ventilatory support****
  - Those with worsening clinical situation
- **Target Anti-Xa: 0.4-0.8** units/ml

4

- Consider therapeutic dose anticoagulation (Enoxaparin: 1 mg/kg SC BID) if:
  - Detect thrombosis on imaging
  - High suspicion of DVT/PE but imaging impractical
- **Target Anti-Xa: 0.6-1.1** units/ml

- On discharge:
  - 2-4 weeks prophylactic or therapeutic anticoagulation if risk factors/marked elevated D-dimer exist

Karimi Mehran. Amanati Ali and Bordbar Mohammad Reza

COVAC-TP study: Ongoing clinical trial to evaluate safety and efficacy of thromboprophylaxis in children with COVID-19 in USA

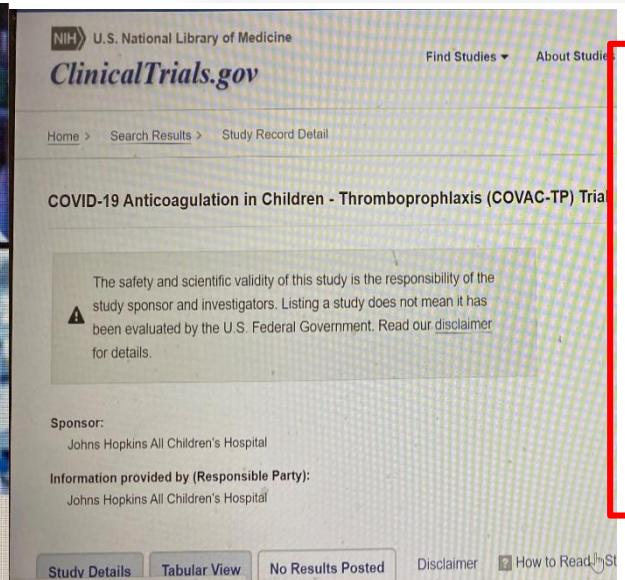
- Summary
- Details

COVID-19 Anticoagulation in Children – Thromboprophlaxis (COVAC-TP) Trial

STATUS	END DATE	PARTICIPANTS NEEDED	SPONSOR
Recruiting	Oct 15, 2022	38	Johns Hopkins All Children's Hospital

Updated on 25 July 2021

See if I



- A systematic review with metanalysis on thrombotic events in children and adolescent patients with COVID-19:
  - No difference in the incidence of thrombotic events between patients under prophylactic LMWH and without
  - Prophylactic doses of LMWH seem to be inefficient in preventing thrombotic events and therapeutic dose of UFH seem more efficient (unpublished data)

Choice of anticoagulant for VTE prophylaxis in pediatric patients with COVID-19

- LMWH or UFH is the anticoagulant choice in children with acute infection
- Stable patients with normal renal function, LMWH is used over UFH because:
  - Reliable pharmacokinetics and pharmacodynamic responses
  - Longer half life and anti-inflammatory and immunomodulatory properties
  - Potential antiviral property (it interacts with the spike S1 protein receptor binding domain)
- There is no consensus of monitoring anti-Xa for prophylaxis dosing
  - However, improved efficacy and safety with target dosing has been reported
- In case of higher risk of bleeds, UFH is preferred since it can be reversed by using antidote
- Direct oral anticoagulants (DOACs) is not yet approved by FDA for age of less than 18 years
- Low-dose aspirin is recommended for all children with MIS-C until the platelet count is normalized and coronary arteries show to be normal ≥4 weeks after the diagnosis of MIS-C
  - Thromboprophylaxis is given if cardiac EF is < 35% or significant coronary artery aneurysms

1.Monagle P. et al.Blood Adv. 2018 2. SHARATHKUMAR ET AL. Pediatr Blood Cancer. 2021
3. Mitchell W. et al. Pedatr Blood Cancer 2021 4. Goldenberg NA. et al. J Thromb Haemost. 2020

How to approach thrombosis risk factors in children with COVID-19 infection and MIS-C

- **Severity assessment of COVID-19 infection:**
  - Hospitalization and Increased requirement for oxygen support (worse outcome including thrombosis: 7%)
  - ICU admission with high ventilatory support (≥ 5 L/min O2, high flow NC, mask or intubation): high VTE risk
  - Hospitalized without oxygen support with asymptomatic/mild symptoms
  - Hospitalized with oxygen support with asymptomatic/mild symptoms
  - Ambulatory asymptomatic/mild symptoms

- **Non-COVID-19 risk factors for hospital-associated VTE in children**

- **Laboratory parameters of CAC that are associated with increased risk of thrombosis and disease severity**
  - D-Dimers: predict disease severity and determine the intensity and duration of thromboprophylaxis
  - Elevated Fibrinogen
  - CBC and peripheral smear: Modest decrease in platelet
  - PTT and PT: Mild prolongation of PT (in case of prolongation of coagulation tests, LAC test is recommended)

- **Trend disease progression:**
  - CRP and serum ferritin

1. SHARATHKUMAR ET AL. Pediatr Blood Cancer. 2021.

How to approach anticoagulant therapy in childhood COVID-19: Case report#1

- A 16-year-old boy with B-thalassemia intermedia on hydroxyurea therapy presented with fever, cough and oxygen saturations of 85%.
- He underwent splenectomy when he was 13 years. The test was positive for COVID-19 by PCR.
  The Chest X-ray showed bilateral infiltration.
- Laboratory results: Hb: 9 gr/dl, WBC: 40,000/mm^3 and platelet count: 650,000/mm^3
  D-dimer was 6-times ULN, Bun: 18, Creatinine: 0.9

- What is the severity assessment of COVID-19 infection in this case? **Severe/critical**

- What is the VTE risk factor in this case?
  1-Underlying disease: Thalassemia intermedia and splenectomy
  2-Age: >12 years

- What laboratory markers are considered for thrombosis risk?
  1- High D-dimer≥ 5ULN
  2-High platelet count

- How do we manage B-thalassemia and COVID-19?
  1-Thromboprophylaxis: LMWH, 0.5 mg/kg/SC BID
  2- therapeutic anticoagulation: in cases with high suspicion of pulmonary emboli and inability to obtain adequate imaging
  3- Low dose aspirin < 5 mg/kg

How to approach anticoagulant therapy in childhood COVID-19: Case report#2

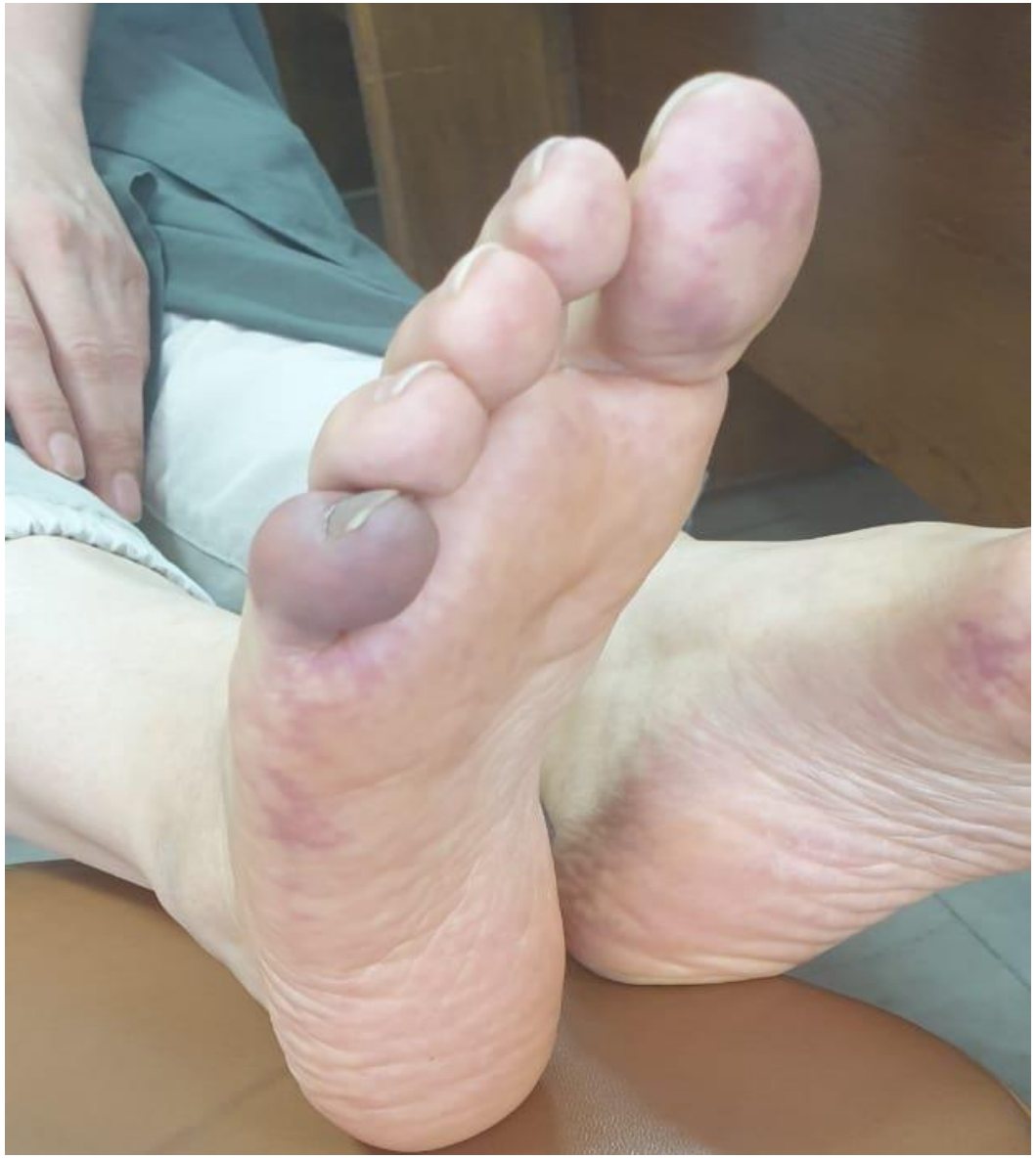
- A 14-year-old boy presents with acute lymphoblastic leukemia (ALL), is currently undergoing induction therapy through central line. He received Asparaginase 4 days ago and had COVID-19 exposure to his friend caused positive his PCR for COVID-19 . He is asymptomatic and his oxygen saturations are 95% on room air with normal chest X-ray.
- What is the severity assessment of COVID-19 infection in this case? **Asymptomatic**
- What is the VTE risk factor in this case?

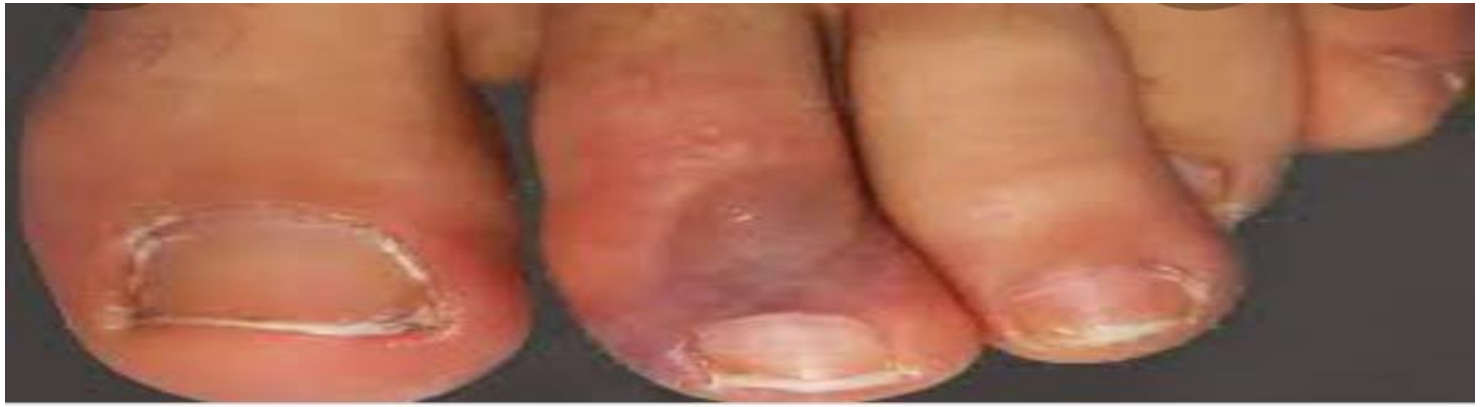
  1-Underlying disease (Active malignancy is a risk factor for thrombosis with COVID-19[1])
  2-Age: >12 years,
  3-Central line
  4-Asparaginase
- What laboratory markers are considered for thrombosis risk? **Not applicable**
- Is there a role for thromboprophylaxis in this ambulatory case with COVID-19?

  1-VTE events, some fatal, do occur in the outpatient setting[2]
  2- Viral shedding has been reported up to 2 months in those with immunosuppression with chemotherapy.
  3- This case has 4 VTE risk factor and thromboprophylaxis may be helpful but VTE risk is not well studied in this population.

1.Whitworth H. et al. Blood 2021
2.Overstad S. et al. Thromb Res. 2020

Acute leg ischemia following COVID-19 infection which is associated with markedly increased D-dimer





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Acute acro-ischemia in the child at the time of COVID-19.

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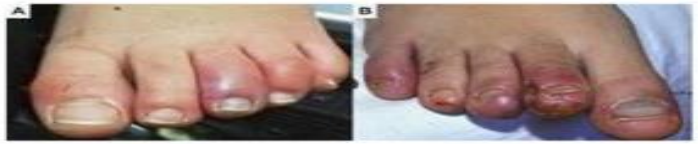

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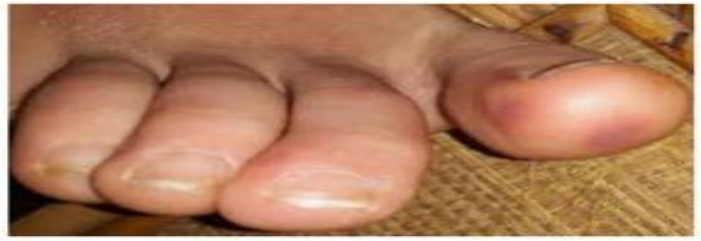

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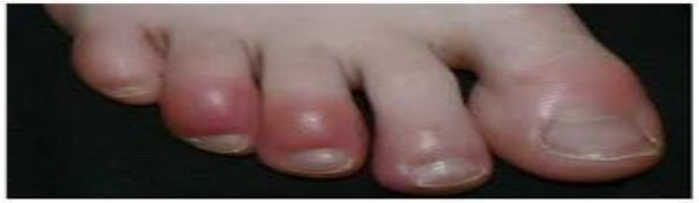

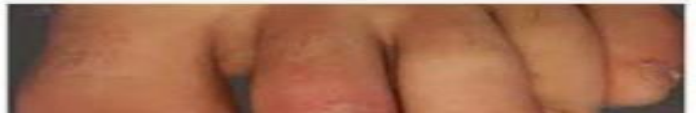

Discussion

- Thrombosis is major cause of morbidity and mortality with COVID-19 and is associated with coagulopathy
- The data about VTE risk in children with COVID-19 are limited and render clinical challenge about considering thromboprophylaxis
- Exposure to known risk factors for VTE and disease severity are key elements to make decision
- D-Dimers may be helpful in determining the intensity and duration of thromboprophylaxis.
- The pharmacological thromboprophylaxis in children with COVID-19 is generally limited to those with moderate to severe/critical hospitalized patients
- Expert opinion and personal experience to manage pediatric patients with COVID-19 are important while we have significant knowledge deficits in understanding COVID-19-associated coagulopathy (CAC) and thrombotic risk in children

Thank you for your listening

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