

LETTER TO THE EDITOR

COVID-19 anticoagulation recommendations in children

To the Editor:

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, is often associated with hypercoagulability and disseminated intravascular coagulation (DIC). This hypercoagulability is manifested as progressive lung and kidney disease, pulmonary emboli (PE), venous thrombotic events (VTE), recurrent line obstruction, and stroke in adults. Major hematology organizations, including the American Society of Hematology,¹ International Society of Thrombosis Haemostasis (ISTH),² Anticoagulation Network,³ and the British Society of Hematology Haemostasis and Thrombosis Task Force⁴ have published recommendations for anticoagulation of hospitalized symptomatic adults with COVID-19.

Pediatric antiviral and antiinflammatory medication management recommendations have been published in response⁵; however, guidelines regarding the thrombotic evaluation and anticoagulation management of hospitalized children with COVID-19 remain lacking. We reviewed the published literature about hospitalized adults with COVID-19 and, based upon published literature about thrombosis during childhood, developed preliminary recommendations for the hemostatic evaluation, imaging, risk assessment for thrombosis, and anticoagulation for children hospitalized with COVID-19.

A local assembly of pediatric intensivists and hematologists developed pediatric recommendations for children hospitalized due to SARS-CoV-2 infection following review of anticoagulation recommendations for adults with COVID-19 by the aforementioned prominent organizations in conjunction with relevant literature via PubMed. An institutional multidisciplinary Scientific Advisory Committee then performed the secondary review of the recommendations. The recommendations developed by our group are shown in Table 1.

The literature consistently reports a diversity of abnormal hemostatic laboratory results in SARS-CoV-2-infected adults. Most often, fibrinogen and D-dimer are elevated and correlated with acute inflammatory markers such as C-reactive protein. Prothrombin time prolongation is often seen.^{3,6} Unlike typical DIC, patients often exhibit a platelet count that is only mildly decreased, a partial thromboplastin time that is normal-to-mildly prolonged, and no signs of microangiopathy. Typical DIC can also be seen in adults and graded per the ISTH scoring system.^{7,8} The presence and severity of DIC in adults is suggested to have strong prognostic value.⁹ Rising D-dimer over time, reflecting increasing coagulation and fibrinolysis, is also associated with a worse mortality in adults.¹⁰

We recommend trending the DIC score⁷ with attention to the D-dimer in hospitalized children with COVID-19. If the DIC score or D-dimer rise and clinical status deteriorate, evaluation of new onset

thrombosis and possible intensification of antithrombotic treatment may be considered, with the caveat that it is unknown whether changes in either the DIC score or D-dimer have the same level of prognostication in children as seen in adults.

Whether or not SARS-CoV-19 infection confers a unique risk for thrombosis during critical illness in children is unknown, but reports in adults suggest a prothrombotic phenotype.^{9,11} Many additional risk factors predisposing to thrombosis are likely to be present for the child admitted with COVID-19. Therefore, a pediatric risk assessment and consideration of prophylactic anticoagulation should be performed at baseline and daily.

The recommendations for pharmacologic prophylaxis and indications for therapeutic anticoagulation are shown in Table 1. The majority of children who experience a hospital-acquired thrombotic event have greater than one risk factor for thrombosis. In the absence of a validated pediatric hospitalized VTE risk-prediction tool, our local institutional assessment is that pharmacologic prophylactic anticoagulation may be considered for children with the following risk factors¹²⁻¹⁵: (a) strong personal or family history of VTE, or (b) an indwelling central venous line and two or more additional risk factors, or (c) four or more risk factors.¹⁶ The decision to administer prophylactic anticoagulation must be balanced with the child's bleeding risk.

Although obtaining vascular imaging is ideal in the management of PE, VTE, and worsening respiratory disease or multiorgan failure thought to be due to thrombosis, consideration of SARS-CoV-2 infection control must be made in context of risk of transport for such studies. Confirmation of VTE by imaging may not be needed prior to treatment with anticoagulation if clinical suspicion is high. The risk of employee exposure and patient instability should be balanced against the immediate need for the study.

Therapeutic anticoagulation is suggested for children receiving anticoagulation prior to admission and those who are receiving extracorporeal organ support. It may also be considered for children who experience recurrent thromboses of access devices, while balancing the concurrent risk of bleeding.

Systemic alteplase can be considered for massive pulmonary emboli over local thrombolysis, given the risk of exposure to vascular interventionalists. Catheter-directed alteplase and mechanical thrombolysis for hemodynamically unstable PE or limb-threatening deep vein thrombosis can still be considered, but with discussions and care coordinated between pediatric intensivists, hematologists, and interventionalists. Research into the use of systemic alteplase for progressive respiratory failure is ongoing.¹⁷

The literature describing SARS-CoV-2 infection causing severe illness and COVID-19 in children is limited, but growing. Based on

TABLE 1 Recommendations for evaluation, prevention, and treatment of pediatric COVID-19-related venous thrombotic events (VTE)

Clinical parameter	Pediatric recommendations	Other considerations
Laboratory evaluation and monitoring	<ul style="list-style-type: none"> We recommend obtaining a complete blood count (CBC) with platelet count, fibrinogen, prothrombin time, D-dimer on admission, and serially for monitoring 	<ul style="list-style-type: none"> Common findings: <ul style="list-style-type: none"> Elevated D-dimer Elevated fibrinogen Mildly decreased platelet count DIC Increases in D-dimer and DIC severity may indicate worsening disease process
Imaging	<ul style="list-style-type: none"> Baseline or surveillance imaging are not recommended in the absence of clinical symptoms of venous thromboembolism Imaging may not be needed prior to initiation of therapeutic anticoagulation if a thromboembolic event or pulmonary embolus is strongly suspected 	<ul style="list-style-type: none"> Type of imaging for diagnosis of VTE should consider hospital epidemiologic practices and risks of exposure during transport and while obtaining the study
Risk evaluation for thrombosis	<ul style="list-style-type: none"> We recommend that all pediatric patients admitted for management of SARS-CoV-2 infection be evaluated upon admission, and daily thereafter for thrombotic risk We recommend that all patients at risk for thrombosis with SARS-CoV-2 infection be initiated on mechanical and/or pharmacologic prophylaxis, if appropriate 	<ul style="list-style-type: none"> Risk factors for thrombosis to consider: <ul style="list-style-type: none"> Personal history of thrombophilia or VTE First-degree relative with VTE Presence of central venous line Postpubertal age Decreased mobility from baseline Burns Active malignancy Indications of venous stasis or cardiac low flow state Estrogen therapy Active systemic infection Flare of inflammatory disease Obesity Severe dehydration Recent surgery or trauma
Pharmacologic management	<ul style="list-style-type: none"> If pharmacologic prophylaxis is indicated, we recommend low-molecular weight heparin or unfractionated heparin over other agents given more extensive pediatric experience with heparin agents Therapeutic anticoagulation is recommended for patients receiving anticoagulation therapy prior to admission and for patients with highly suspected or demonstrated VTE 	<ul style="list-style-type: none"> We do not recommend use of direct oral anticoagulants due to limited data in children and adults with COVID-19
Thrombolytic therapy	<ul style="list-style-type: none"> Thrombolytic therapy can be considered for patients with a hemodynamically unstable pulmonary embolus or limb-threatening deep vein thrombosis Overall, we suggest that decision making for thrombolytic therapy be a coordinated approach involving the critical care team, hematologists, and interventionalists 	<ul style="list-style-type: none"> Systemic alteplase may be preferred over local mechanical thrombolysis given the risk of exposure with transfer and utilization of an interventional suite; however, contraindications to systemic alteplase must also be considered

current knowledge in adults and appreciation of the risk for thrombosis in children, we have developed preliminary recommendations for laboratory and imaging evaluation, assessment of thrombotic risk, and anticoagulation therapy. We recognize that as the pediatric experience with COVID-19 increases, additional information will be garnered and the recommendations will likely need modification. We present our local institutional recommendations, and further consideration of consensus recommendation by hematology societies at-large is welcomed and anticipated.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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