Title of Paper:

Recommendations for anticoagulation and thrombosis management of pediatric COVID-19 – a single center multidisciplinary consensus

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Word Count:

Abstract (68 words), Main Text (1200 words)

Tables, Figures, Supporting information:

1 table

Short Title:

Recommendations for anticoagulation and thrombosis in pediatric COVID-19

Keywords:

COVID-19, Pediatrics, Thrombosis, Hypercoagulation, Venous Thromboembolism, Anticoagulation

Abbreviations:

ASH	American Society of Hematology
AN	Anticoagulation Network
British	British Society of Haematology Haemostasis and Thrombosis Task Force
COVID-19	Coronavirus Disease 2019
DIC	Disseminated Intravascular Coagulation
ISTH	International Society of Thrombosis and Haemostasis
PE	Pulmonary Embolus
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
VTE	Venous Thromboembolism

Abstract

Coronavirus Disease 2019 (COVID-19) is associated with hypercoagulability and adult guidelines have been published regarding the evaluation and anticoagulation of adults infected with COVID-19. Pediatric resources on this topic are lacking. We developed preliminary recommendations for the thrombotic evaluation and anticoagulation treatment for children hospitalized with COVID-19 by reviewing the available literature and guidelines and adapting the information for the pediatric population through a multidisciplinary consensus driven approach.

Introduction

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. Anticoagulation is an important aspect of treatment for hospitalized SARS-CoV-2 infected adults. Although the optimal management of hospitalized adults infected by SARS-CoV-2 is in evolution, there are published consensus treatment recommendations for administration of antiviral and immunosuppressant medications and anticoagulation. Major hematology organizations, including the American Society of Hematology (ASH),[1] International Society of Thrombosis Haemostasis (ISTH),[2] Anticoagulation Network (AN),[3] and the British Society of Hematology Haemostasis and Thrombosis Task Force (British)[4] have published recommendations for anticoagulation of hospitalized symptomatic adults with SARS-CoV-2 infected adults with COVID-19.

To date, SARS-CoV-2 infection in children has generally been associated with less severe disease. Nonetheless, neonates and children with comorbid conditions such as congenital heart, lung and airway diseases, malnutrition, autoimmunity and malignancy remain at risk for more severe illness warranting hospitalization. As a result, pediatric antiviral and anti-inflammatory medication management recommendations have been published in response.[5]

Pediatric consensus recommendations regarding the evaluation of the hemostatic system, anticoagulation prophylaxis and treatment for hospitalized children with COVID-19 are lacking.

We reviewed the published literature about hospitalized ill adults infected with SARS-CoV-2 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.

Methods

A PubMed review of literature available in English for the searches "anticoagulation and coronavirus or covid", "anticoagulation and SARS-CoV-2," "children and coronavirus," "children and covid," "pediatrics and covid" and "pediatric and coronavirus" was performed. Anticoagulation recommendations for assessment and management of adults with COVID-19, developed by prominent organizations such as ASH,[1] ISTH,[2] AN[3] and British,[4] were reviewed in conjunction with relevant literature regarding anticoagulation in adults and children. Following the literature review, a group of pediatric intensivists and hematologists developed pediatric recommendations for children hospitalized due to SARS-CoV-2 infection. Then the institutional Scientific Advisory Committee comprised of pediatric hematologists, intensivists, rheumatologists, emergency medicine physicians, a pharmacist and a pulmonologist performed the secondary review of the recommendations.

Results

Literature review confirmed the absence of published pediatric-specific consensus recommendations. The recommendations developed by our group are shown on Table 1.

Discussion

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. A prolongation in prothrombin time (PT) is often seen.[3,6] Unlike typical DIC, patients often exhibit a platelet count that is only mildly decreased, a partial thromboplastin time (PTT) that is normal-to-mildly prolonged and no signs of microangiopathy (including RBC fragmentation).

However, typical DIC can also be seen in some adults and graded per the ISTH scoring system.[7,8] An analysis of coagulation parameters in 183 SARS-CoV-2 infected adults in Wuhan, China, demonstrated that 71.4% of non-survivors met ISTH diagnostic criteria for DIC compared to 0.6% of survivors, suggesting that the presence and severity of DIC has prognostic value.[9] Rising D-dimer over time, reflecting increasing coagulation and fibrinolysis, is also associated with a worse mortality in adults.[10]

The published guidelines for evaluating a hospitalized symptomatic adult with COVID-19 suggest sequential monitoring of platelet count, D-dimer, fibrinogen and PT to trend the DIC score. Since similar hemostatic changes can be seen in hospitalized children, we recommend trending the ISTH DIC score with particular attention to the D-dimer in conjunction with clinical status. If the DIC score or D-dimer rise and clinical status deteriorates, 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 prognostication in children as seen in adults.

The recommendations for pharmacologic prophylaxis and indications for therapeutic anticoagulation are shown in Table 1 and are extrapolated from review of the adult literature and established risk factors for thrombosis in hospitalized children.[11-14] 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 factors: 1) strong personal or family history of VTE or 2) an indwelling central venous line and 2 or more additional risk factors or 3) 4 or more risk factors.[15] The decision to administer prophylactic anticoagulation must be balanced with the child's bleeding risk.

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.[9,16] 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.

Low molecular weight heparin is a convenient first-line anticoagulant due to the ease of subcutaneous administration and a possible beneficial anti-inflammatory effect, however, unfractionated heparin can also be used for prophylaxis. Mechanical thromboprophylaxis with sequential compression devices should be considered whether or not chemical thromboprophylaxis is administered, while considering contraindications such as extremity fracture or deformity, restrictions due to patient size or burns/open wounds associated with extremity.[17]

Although obtaining vascular imagining 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 thrombosis of access devices, while balancing the concurrent risk of bleeding. Higher doses of unfractionated heparin are likely needed to achieve therapeutic levels, given the degree of inflammation (with associated increase in heparin-binding proteins) that can occur with SARS-CoV-2 infection.

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.[18]

The literature describing SARS-CoV-2 infection causing severe illness and COVID-19 in children is limited, but growing. Based on 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 report no competing interests

Acknowledgements

We would like to acknowledge the Children's Hospital Colorado Scientific Advisory Council, especially Todd Carpenter, Eva Grayck, Marion Sills, Juri Boguniewicz, and Pam Reiter for their assistance in review of the guidelines.

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