



Thrombotic events in critically ill children with coronavirus disease 2019 or multisystem inflammatory syndrome in children

Aleksandra S. Dain, Leslie Raffini, and Hilary Whitworth

Purpose of review

To provide an update regarding what is known about thrombotic events and thromboprophylaxis in critically ill children with SARS-CoV-2 infection.

Recent findings

Pediatric patients with SARS-CoV-2 generally have mild illness; however, intensive care is required in about 20–30% of hospitalized children with COVID-19 and an even higher proportion in those with MIS-C. Increased rates of thrombosis have been observed in adults hospitalized with COVID-19, and clinical trials have attempted to optimize thromboprophylaxis. There is significant variability in the estimated incidence of thrombosis in pediatric patients (0–27%) because of variation in patient populations and study design. Multiple studies demonstrate an increased rate of thrombosis compared with baseline in hospitalized pediatric patients. Few studies have evaluated risk factors for thrombosis, but critical illness, older age, and other known thrombosis risk factors appear to increase the risk. Thromboprophylaxis strategies are inconsistent, with little evidence of efficacy but few reports of major bleeding.

Summary

Critically ill children with SARS-CoV-2-related illnesses are at increased risk of thrombosis. Thromboprophylaxis should be considered in select patients with COVID-19 or MIS-C, though the optimal strategy is not yet known. More data is required to guide practice to prevent thrombosis in this population.

Keywords

COVID-19, MIS-C, pediatrics, thromboprophylaxis, thrombosis

INTRODUCTION

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) continues to spread worldwide, causing the ongoing coronavirus-19 (COVID-19) pandemic. Early in the pandemic, it became evident that adults hospitalized with COVID-19 had increased rates of thrombosis leading to worse outcomes [1[■],2]. Although most children infected with SARS-CoV-2 have mild symptoms, some experience severe illness and death [3,4,5[■],6[■]]. Children are also uniquely at risk for the postinfectious multisystem inflammatory syndrome in children (MIS-C). MIS-C is defined by multiorgan involvement, laboratory markers of inflammation, fever, severe illness, and evidence of a recent SARS-CoV-2 infection [7]. As the pandemic evolved, reports describing increased rates of venous and arterial thrombotic events in children with COVID-19 and MIS-C emerged. Children hospitalized with COVID-19 or MIS-C often

have other known risk factors for thrombosis including critical illness, central venous catheters (CVCs), or prothrombotic comorbidities, further increasing their risk for thrombotic events. In this review, we discuss the current understanding of thrombosis in children with SARS-CoV-2-associated illnesses, focused on critically ill children and adolescents. Wherever relevant, we also discuss adult studies. This is an evolving area of research and clinical practice, and we anticipate emerging data may lead to additional insights and recommendations.

Children's Hospital of Philadelphia, Philadelphia, Pennsylvania, USA

Correspondence to Hilary Whitworth, Children's Hospital of Philadelphia, Colket Translational Research Building, 3501 Civic Center Blvd, Philadelphia, PA 19104, USA. Tel: +1 215 873 5155; e-mail: whitworthh@chop.edu

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KEY POINTS

- SARS-CoV-2-associated illness (COVID-19 and MIS-C) is associated with an increased risk of thrombosis in children and adolescents, even when compared with other hospitalized or critically ill children.
- The rate of thrombotic events appears particularly high in adolescents and those with other thrombosis risk factors, including critical illness.
- More research is needed to determine ideal thromboprophylaxis strategies in pediatric patients with COVID-19 or MIS-C.

SEVERITY OF SEVERE ACUTE RESPIRATORY SYNDROME CORONAVIRUS-2 INFECTION IN CHILDREN

As of 27 January 2022, the American Academy of Pediatrics and the Children's Hospital Association estimate 11 411 047 children have been infected with SARS-CoV-2, representing 18.6% of all cases [8[■]]. Children with prior comorbidities are more likely to develop severe disease and have a higher risk of death from COVID-19 [6[■],9[■]]. In one cross sectional study of 713 children hospitalized with acute COVID-19 (July through August 2021), 29.5% were admitted to the ICU, and 1.5% died [9[■]]. A majority had at least one underlying medical condition, the most common being obesity, asthma or reactive airway disease, and feeding tube dependence [9[■]]. Children with underlying medical problems and adolescents were admitted to the ICU at higher rates than younger children and those without comorbidities [9[■]]. Two large database studies reported similar ICU admission rates of 21–29.6% in children hospitalized primarily with COVID-19 [5[■],10]. Children hospitalized with MIS-C have an even higher ICU admission rate (58.2–73.8%) [11[■],12].

SEVERE ACUTE RESPIRATORY SYNDROME CORONAVIRUS-2-INDUCED COAGULOPATHY

The primary inciting factor for hypercoagulability in SARS-CoV-2 infection is thought to be direct and indirect endothelial damage by viral infection and systematic inflammation, leading to activation of tissue factor pathways, platelets, and multiple cytokines [13[■],14]. Elevated D-dimer is the most common laboratory abnormality, though its prognostic ability is unclear in pediatric thrombotic events [13[■],15[■],16,17[■]]. Prolonged prothrombin time, elevated fibrinogen, and thrombocytopenia are also

markers of SARS-CoV-2 coagulopathy [15[■],18[■],19]. Consumptive coagulopathy and disseminated intravascular coagulation may be seen in critically ill patients and may increase bleeding risk [18[■]].

Ongoing research in MIS-C has also demonstrated alterations in the inflammatory cascade and hemostasis [11[■],20]. Little is known about the cause of thrombosis in MIS-C, though the mechanism is thought to be similar to that in acute COVID-19 [13[■]].

THROMBOTIC COMPLICATIONS AND THROMBOPROPHYLAXIS IN ADULTS WITH CORONAVIRUS DISEASE 2019

The estimated prevalence of thrombosis in hospitalized adults with COVID-19 has varied widely because of changes in clinical guidelines and variation in study design. A Cochrane review reports a weighted mean incidence of venous thromboembolism (VTE) in hospitalized adults of 7.4% with a range of 0–46.2% in the included studies [1[■]]. This incidence is higher for critically ill adults with COVID-19 [21]. Furthermore, adult patients who develop thrombotic events have a worse prognosis [2]. A similar pooled incidence of VTE was found even when studies were categorized by thromboprophylaxis strategy, indicating that thrombotic events occur despite thromboprophylaxis [21]. These data drove the development of multiple clinical trials evaluating the utility and dose intensity of thromboprophylaxis in adults with COVID-19.

Three international, adaptive, randomized clinical trials (REMAP-CAP, ACTIV-4a, and ATTAC) were coordinated in a multiplatform design to evaluate therapeutic dose unfractionated or low-molecular-weight heparin (LMWH), compared with standard care (prophylactic or intermediate dose) in hospitalized adults [22[■]]. Several anticoagulant regimens were allowed in these trials with dosing that varied with morbid obesity or abnormal renal function. In general, for enoxaparin, the most common LMWH in children, therapeutic dosing was 1 mg/kg twice daily or 1.5 mg/kg daily, prophylactic dosing was 40 mg daily, and intermediate dosing was 0.5 mg/kg twice daily [22[■]]. In the subset of critically ill adults, there was no benefit in primary outcome (median organ support-free days) in patients receiving therapeutic anticoagulation [22[■]]. Fewer patients receiving therapeutic dose had major thrombotic events compared with those receiving usual care (6.4 versus 10.4%); however, the combined outcome of major thrombotic events and death was similar [22[■]]. Major bleeding was higher in the therapeutic arm (3.8 versus 2.3%), though this difference was not statistically significant [22[■]]. Similarly, there was no

benefit of intermediate dose compared with prophylactic dose enoxaparin in the randomized controlled INSPIRATION trial that included 562 critically ill adults [23[■]].

In contrast to the lack of benefit of therapeutic (compared with standard) intensity anticoagulation in critically ill adults with COVID-19, results from several trials suggest that there is a potential benefit in hospitalized, non-ICU patients [24–26].

The 2021 American Society of Hematology guidelines suggest prophylactic over intermediate intensity anticoagulation for thromboprophylaxis in critically ill patients with COVID-19 (conditional recommendation 1A) [27[■]]. The 2022 National Institutes of Health guidelines strongly recommend prophylactic dose heparin thromboprophylaxis in critically ill adults (strong recommendation, level AI) and recommend against intermediate or therapeutic dose anticoagulation for this indication (moderate recommendation, level BI) [28[■]]. Elevated D-dimer has been associated with disease severity and thrombosis but it is a nonspecific marker. Current adult guidelines do not alter thromboprophylaxis strategies in critically ill patients based on D-dimer levels [27[■],28[■]].

THROMBOTIC EVENTS IN CHILDREN WITH CORONAVIRUS DISEASE 2019 OR MULTISYSTEM INFLAMMATORY SYNDROME IN CHILDREN

Data on thrombotic complications in children with SARS-CoV-2-associated illnesses include case reports, case series, and multicenter cohort studies. These studies report variable rates of thrombosis, but overall, there is a much lower incidence of thrombosis in children compared with adults hospitalized with COVID-19. Interpretation of pediatric data on SARS-CoV-2 and thrombotic events has many limitations. Several studies have combined venous and arterial thrombosis as well as patients with COVID-19 and MIS-C, and many have not separately reported critically ill children. Furthermore, large studies evaluating children with COVID-19 or MIS-C may not have included thrombotic events as a specific outcome, or may have included only certain thrombotic events (stroke, VTE) with limited descriptions of the events [9[■],10,12]. Select case-series and cohort studies are summarized in Table 1.

In a United States, multicenter, retrospective cohort study of 814 consecutive pediatric patients hospitalized with SARS-CoV-2-associated illness from March through August 2020, the incidence of venous and arterial thrombotic events was 0.7% in patients with asymptomatic SARS-CoV-2, 2.1% in patients with COVID-19, and 6.5% in MIS-C

[17[■]]. In this cohort, 32% of children with COVID-19 and 62% of children with MIS-C required ICU admission [17[■]]. Most patients with thrombotic events (72%) were admitted to the ICU, compared with 38% of patients without thrombosis [17[■]]. The development of thrombotic events was associated with older age (≥ 12 years), the presence of a CVC, cancer, and MIS-C [17[■]]. The highest rate of thrombosis (19%, 9/48) was observed in patients with MIS-C who were at least 12 years of age [17[■]]. Of the 19 thrombotic events in patients with symptomatic COVID-19 or MIS-C, there were 11 deep vein thromboses (DVT), 3 pulmonary embolisms (PE), 3 intracardiac thromboses 1 acute ischemic stroke, and 1 cerebral sinovenous thrombosis [17[■]]. The mortality in patients with COVID-19 or MIS-C with thrombotic events in this cohort was 28% (5/18), which mirrors adult data that demonstrate thrombosis is associated with worse prognosis in COVID-19 [2,17[■]]. A multicenter study from Egypt reported lower extremity DVT in 5/394 (1.3%) of children with COVID-19 [29[■]]. Although the age of the patients with DVT was not reported, none were critically ill [29[■]]. Elevated D-dimer was associated with DVT in this cohort [29[■]].

The *Overcoming COVID-19 Network*, a large multicenter registry, observed DVT or pulmonary embolism in 11/539 (2%) patients with MIS-C and 8/577 (1%) patients with severe acute COVID-19 [11[■]]. Details about patients with DVT/PE were not reported, although four patients with MIS-C were previously published, and in that report, three of four thrombotic events occurred in patients at least 13 years of age [30[■]]. A subsequent report from this network reported 12 of 1695 (0.7%) ischemic or hemorrhagic strokes [31[■]]. Many of these patients had underlying risk factors for stroke [31[■]]. The cause of SARS-CoV-2-associated neurologic disease, including stroke, is unclear and likely multifactorial but neuroinflammation may play a role [31[■],32[■],33].

Mitchell *et al.* [34[■]] reported the highest rate of thrombotic complications (7/27, 26%) in a single center study of hospitalized pediatric patients with symptomatic COVID-19 in New York. There were three DVT and four PE, and three of seven patients were older than 12 years [34[■]]. A majority (59%) were critically ill, and increased ventilatory support was associated with thrombosis [34[■]]. Four (57%) of the seven patients with thrombotic events received prophylaxis prior to developing thrombosis [34[■]].

Notably, some studies report much lower thrombosis rates. Antoon *et al.* [5[■]] reports thrombotic complications in 0.4% (18/4063) of patients with either MIS-C or acute COVID-19 in a multicenter administrative database, and there were no thrombotic complications in three single-center,

Table 1. Thrombosis in select studies of hospitalized children with severe acute respiratory syndrome coronavirus-2-associated illnesses

Author	COVID-19 (n)	MIS-C (n)	Critically ill (%)	Thrombosis [n (%)]		Anticoagulation [n (%)]		Location	Type of thrombotic event
				COVID-19	MIS-C	COVID-19	MIS-C		
Mitchell <i>et al.</i> [34 [■]]	27	0	59%	7 (26)	N/A	11 (41)	N/A	New York, NY, United States	Portal vein (1), U (1), PE (4), DVT (1)
Whitworth <i>et al.</i> [17 [■]]	426	138	39%	9 (2.1)	9 (6.5)	128 (30)	80 (58)	United States (multicenter)	DVT (11), PE (3), Intracardiac (3), AIS (1), CSVT (1)
Del Borrello <i>et al.</i> [36 [■]]	30	6	11%	0		4 (13)	2 (33)	Turin, Italy	N/A
Leeman <i>et al.</i> [15 [■]]	47	9	27%	0		16 (29)		Miami, FL, United States	N/A
Capone <i>et al.</i> [35 [■]]	0	33	79%	N/A	0		NR	New York, NY, United States	N/A
Feldstein <i>et al.</i> [11 [■]]	577	539	58%	8 (1)	11 (2)	162 (28)	337 (63)	United States (multicenter)	DVT or PE
Antoon <i>et al.</i> ^a [5 [■]]	3720	343 ^b	21%	18 (0.4)			NR	United States (multicenter)	NR
Saleh <i>et al.</i> [29 [■]]	394	4	26%	5 (1.3)			NR	Egypt (multicenter)	DVT
Beslow <i>et al.</i> ^c [32 [■]]		971	NR	8 (0.82)			NR	International (multicenter)	AIS (7), CSVT (1)

AIS, arterial ischemic stroke; COVID-19, coronavirus disease 19; CSVT, cerebral sinovenous thrombosis; DVT, deep vein thrombosis; U, internal jugular; MIS-C, multisystem inflammatory syndrome in children; N/A, not applicable; NR, not reported; PE, pulmonary embolism.

^aAdministrative database study.

^bIncluded patients with Kawasaki disease or MIS-C.

^cStudy only evaluated for ischemic stroke. Included any patient hospitalized with positive SARS-CoV-2 test and did not differentiate between MIS-C, acute COVID-19, or asymptomatic SARS-CoV-2 infection.

Represents a combination of COVID-19 and MIS-C.

smaller studies of 33–56 patients admitted with SARS-CoV-2-associated illnesses [15[■],35[■],36[■]].

Cases of cerebral infarcts as well as venous and cardiac thrombosis have been reported in children requiring extracorporeal membrane oxygenation (ECMO) for COVID-19 or MIS-C [31[■],37[■],38–40]. Adult studies have reported an increased risk of venous, arterial, and circuit thrombosis in patients requiring ECMO for COVID-19 [41,42]. No large studies have evaluated whether pediatric patients on ECMO with SARS-CoV-2-related illness are at increased risk of thrombosis.

The variable rates of thrombosis reported in children with COVID-19 and MIS-C (0–27%) are likely related to differences in study population (age, underlying medical condition, critical illness), and possibly because of variation in thromboprophylaxis strategies [5[■],11[■],15[■],17[■],29[■],34[■]–36[■]]. There are differences in how thrombosis was identified, including administrative data codes, imaging findings, or clinician reports. Despite the variation in studies, critically ill children, especially adolescents, with COVID-19 or MIS-C appear to have an increased incidence of thrombosis compared with

baseline VTE incidence in critically ill children (7.4 per 1000) [43].

THROMBOPROPHYLAXIS IN CHILDREN WITH CORONAVIRUS DISEASE 2019 AND MULTISYSTEM INFLAMMATORY SYNDROME IN CHILDREN

Similar to reports of thrombotic events occurring despite pharmacologic thromboprophylaxis in adult cohorts, many of the thrombotic events in the pediatric studies occurred despite thromboprophylaxis [17[■],34[■],44,45]. Early in the pandemic, pediatric hematology and critical care experts organized consensus guidelines for thromboprophylaxis in children hospitalized with COVID-19 or MIS-C, based largely on expert opinion and extrapolation of adult data [46[■]]. The guidelines suggest thromboprophylaxis with low-dose LMWH targeting an anti-Xa activity of 0.2 to less than 0.5 units/ml for children hospitalized with COVID-19 or MIS-C who have additional VTE risk factors (CVC, mechanical ventilation, obesity, malignancy, cardiac disease, etc.) or who have

D-dimer at least five times the upper limit of normal, unless there are contraindications to anticoagulation [46^{***}]. Anticoagulant prophylaxis was not recommended for children with asymptomatic SARS-CoV-2 infection who are hospitalized for other causes, unless there are other VTE risk factors present [46^{***}]. Importantly, these guidelines were developed prior to adult thromboprophylaxis trials and most of the pediatric studies looking at incidence and risk factors. Elevated D-dimer was associated with thrombotic events in some pediatric studies but its use as a predictor of thrombosis is limited because of the variation in timing and frequency of testing [17^{*},29^{*}]. Furthermore, adult thromboprophylaxis guidelines do not recommend dose titration in critically ill patients based on D-dimer levels [27^{**},28^{**}]. It is important to consider these limitations and new data when interpreting the pediatric guidelines.

Individual institutions have adjusted the pediatric recommendations based on the new epidemiologic data and adult thromboprophylaxis trials described above. The Children's Hospital of Philadelphia guidelines, which are publicly available, recommend enoxaparin every 12 hours, targeting an anti-Xa of 0.2–0.4 units/ml (in the absence of contraindications) in critically ill children with COVID-19 at least 12 years of age and those less than 12 years if the child requires intubation and/or a CVC [47]. For MIS-C, we recommend enoxaparin every 12h targeting an anti-Xa of 0.2–0.4 units/ml in patients at least 12 years and low-dose aspirin for those less than 12 years, after assessing for contraindications [48]. Of note, enoxaparin is not approved by the US Food and Drug Administration for use in children. As there are no pediatric-specific SARS-CoV-2 thromboprophylaxis trials focused on efficacy, this dosing strategy is based on expert opinion. Twice daily dosing is consistent with prophylactic intensity in children but would be considered intermediate intensity in adults, for whom prophylactic intensity is typically once daily dosing [27^{**},49]. For patients older than 18 years of age cared for in pediatric centers, it is reasonable to follow adult guidelines, which are based on high-quality, randomized controlled trial data [27^{**},28^{**}].

The COVID-19 Anticoagulation in Children – Thromboprophylaxis (COVAC-TP) trial is the only pediatric study evaluating the safety of thromboprophylaxis in children [50]. This study evaluated the safety of low dose LMWH targeting an anti-Xa level of 0.2–0.49 IU/mL in 38 children. There were no clinically relevant bleeding events. Efficacy was an exploratory outcome and two children (5.3%) developed VTE [50].

Antiplatelet therapy in multisystem inflammatory syndrome in children

Low-dose aspirin is recommended by the American College of Rheumatology for children with MIS-C until normalization of the platelet count and confirmed normal coronary arteries at least 4 weeks after diagnosis [51^{*}]. The addition of anticoagulation in select MIS-C patients with cardiac involvement is recommended and the authors suggest an individualized approach to anticoagulation in the absence of cardiac involvement, depending on additional patient risk factors for bleeding and thrombosis [51^{*}].

BLEEDING IN CHILDREN WITH CORONAVIRUS DISEASE 2019 AND MULTISYSTEM INFLAMMATORY SYNDROME IN CHILDREN

Data on bleeding in pediatrics is primarily restricted to case reports [31^{*},52–56]. One cohort study reports major bleeding in 1.6% of COVID-19 and 2.4% of MIS-C admissions; about half (4/9) occurred on anticoagulation [17^{*}]. Bleeding in adults is associated with therapeutic anticoagulation and is particularly increased in patients receiving ECMO [18^{*},21]. Major bleeding appears uncommon overall in pediatrics, despite the use of prophylactic anticoagulation in hospitalized patients as well as aspirin in MIS-C.

THROMBOSIS TREATMENT

Thrombotic events in pediatric patients with COVID-19 or MIS-C are considered provoked and treated as such, typically with therapeutic anticoagulation for 6 weeks to 3 months [57,58^{*}]. Critically ill patients are at higher risk for bleeding and, in line with adult guidelines, we recommend initial unfractionated heparin or LMWH over direct oral anti-coagulants [59].

CONCLUSION

Pediatric data are limited and vary significantly in their findings. However, there appears to be an increased rate of thrombotic complications in critically ill children with COVID-19 or MIS-C, even when compared with other critically ill children. Children with thrombotic complications may have worse outcomes but often have co-existing morbidities that likely contribute [17^{*}]. Thromboprophylaxis appears well tolerated in pediatrics and should be strongly considered in critically ill children with COVID-19 or MIS-C, many of whom have multiple

risk factors for thrombosis. Optimal intensity of anticoagulation in this population has not been determined. Carefully designed prospective studies focused on thrombotic and hemorrhagic complications in hospitalized children with SARS-CoV-2-related illness are needed to better inform current management strategies and improve outcomes.

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Conflicts of interest

There are no conflicts of interest.

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- of special interest
- ■ of outstanding interest

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