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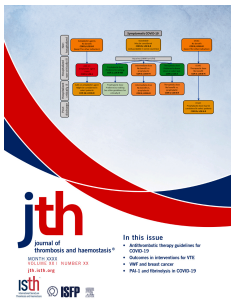

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Thrombotic Complications in Children with COVID-19 and MIS-C

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Abstract

Coronavirus disease 2019 (COVID-19) associated coagulopathy is multifactorial and involves inflammation driven hypercoagulability, endothelial dysfunction, platelet activation and impaired fibrinolysis. Hospitalized adults with COVID-19 are at an increased risk of both venous thrombo-embolism (VTE) and ischemic stroke, resulting in adverse outcomes including mortality. While children with COVID-19 follow a less severe course, both arterial and venous thrombosis have been reported in hospitalized children with COVID-19. Additionally, some children develop a post-infectious, hyper-inflammatory illness termed Multisystem Inflammatory Syndrome of Childhood (MIS-C), which is also associated with hypercoagulability and thrombosis. Several randomized trials have evaluated the safety and efficacy of antithrombotic therapy in adults with COVID-19, though similar pediatric data are lacking. In this narrative review we discuss the postulated pathophysiology of COVID-19 coagulopathy, and summarize principal findings of the recently completed adult trials of antithrombotic therapy. We provide an up-to-date summary of pediatric studies investigating the rate of VTE and ischemic stroke in COVID-19 and MIS-C, in addition to reviewing the findings of the single, non-randomized pediatric trial investigating the safety of prophylactic anticoagulation. Lastly, we outline the adult and pediatric consensus guidelines on the use of antithrombotic therapy in this cohort. A detailed discussion of the practical implementation and current limitations of published data will hopefully address knowledge deficits surrounding the use of antithrombotic therapy in children with COVID-19, and generate hypotheses for future research.

Keywords: COVID-19, MIS-C, thrombosis, pediatrics

Introduction

In December 2019, several cases of atypical pneumonia resulting in severe respiratory distress were reported in Wuhan, capital city of the Hubei province in China (1). The offending pathogen was identified to be a novel single-stranded beta-coronavirus that was named severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) (2). While initially thought to be a zoonotic transmission event, it soon became apparent that SARS-CoV-2 was extremely efficient at person-to-person transmission across continents, prompting the World Health Organization to declare this novel coronavirus disease (COVID-19) a global pandemic (3, 4). Since its initial description, COVID-19 has affected more than 600 million people worldwide, with over 6 million reported deaths (https://coronavirus.jhu.edu/map.html; accessed 01/30/2023). While viral pneumonia is the cardinal presentation of COVID-19, early in the pandemic its proclivity to cause a thrombotic coagulopathy became apparent. Initial reports described marked elevation in d-dimer and fibrinogen, mild thrombocytopenia and mild prolongation of the prothrombin time (PT) and activated partial thromboplastin time (APTT) in a significant proportion of hospitalized patients (4-7). This “COVID-19 coagulopathy” was associated with adverse outcomes in hospitalized patients including thromboembolism, stroke and death (4, 7, 8). Meta-analyses of adult observational studies estimate the incidence of venous thromboembolism (VTE) to be 7-8% in patients admitted to the medical wards with COVID-19, and 24-28% in patients admitted to the intensive care unit (ICU), often occurring despite prophylactic anticoagulation (9, 10). An additional 1-5% of hospitalized adults experience an arterial thromboembolic event including ischemic stroke (11, 12).

COVID-19 associated morbidity and mortally were initially thought to have disproportionately affected older adults. Data collated by the American Academy of Pediatrics (AAP) and Children’s Hospital Association estimated that children account for approximately 18% of all reported COVID-19 cases in the US (https://www.aap.org/en/pages/2019-novel-coronavirus-covid-19-infections; accessed 02/05/2023); while accounting for only 3% of all COVID-19 related hospitalizations, and 0.2% of COVID-19 related deaths (https://covid.cdc.gov/covid-data-tracker/#pediatric-data; accessed 02/13/2023). However, among the hospitalized children, 21-40% were admitted to the ICU, 6-9% have required invasive mechanical ventilation and up to 3% have died (13-16). Children with chronic co-morbid conditions including diabetes, obesity, congenital cardiac disease, chronic respiratory and neurological disorders and immunocompromised status are more likely to require hospitalization and develop severe disease (13, 17, 18).

Additionally, children are also at risk of developing Multisystem Inflammatory Syndrome of Childhood (MIS-C), a delayed hyper-inflammatory syndrome characterized by fever, multi-organ involvement, laboratory evidence of inflammation and a temporal association with SARS-CoV-2 exposure (19). Early studies estimated that 1 in 3,000-4,000 children with COVID-19 develop MIS-C (20, 21). As of January 2023, >9000 cases of MIS-C have been diagnosed in the US with 76 (1%) reported deaths (https://covid.cdc.gov/covid-data-tracker/#pediatric-data; accessed 02/13/2023). Children with MIS-C typically present with fever and gastro-intestinal symptoms including nausea, vomiting and abdominal pain. Cardiovascular involvement including shock, myocarditis, coronary artery aneurysms and decreased left ventricular ejection fraction have been reported in >80% of patients. Seventy-five to 80% of patients with MIS-C are admitted to the ICU, 40-60% require vasoactive support and 10-20% require invasive mechanical ventilation (22-25). Of note, recent studies have suggested that MIS-C is less common, and less severe with the Omicron variant of COVID-19 (26, 27).

As the clinical spectrum of COVID-19 and MIS-C evolves in children, pediatricians, cardiologists and pediatric hematologists have encountered an increased rate of venous and arterial thromboembolism in hospitalized children, typically in the setting of additional risk factors for thrombosis. Pediatric hematologists across tertiary and quaternary care centers have also been called upon to develop COVID-19 and MIS-C specific thromboprophylaxis guidelines, often in the absence of robust clinical data. In this review, we discuss the pathophysiology of thromboembolism in COVID-19, critically analyze the pediatric literature and summarize published consensus guidelines. Given that pediatric guidelines are extrapolated from adult literature, we will also highlight key randomized trials conducted in adults.

Pathophysiology of Thrombosis in COVID-19

The pathogenesis of COVID-19 coagulopathy is multifactorial and includes, (i) endothelial cell injury and activation, (ii) inflammation, (iii) platelet activation and (iv) alteration in coagulation factors, altogether resulting in “thrombo-inflammation”. Infection with SARS-CoV-2 causes endothelial cell injury, although it remains unclear whether this is related to direct viral infection or the ensuing inflammatory process, partly because angiotensin-converting enzyme 2 (ACE2), the primary receptor for SARS-CoV-2, is expressed at much higher levels in epithelial cells of airways compared to endothelial cells (28). SARS-CoV-2 infection of epithelial cells and alveolar macrophages results in cytokine release and activation of interleukins, interferons, and tissue

necrosis factor (29). These intense inflammatory signals damage the protective barrier of endothelial cells and cause loss of antithrombotic protective factors, with exposure and leakage of tissue factor, fibrinogen, von Willebrand antigen and plasminogen activator inhibitor 1 (PAI-1) (30). These pro-thrombotic changes that occur in response to endothelial injury and inflammation promote platelet activation and fibrin formation and are further enhanced by complement activation (28, 31).

The coagulopathy observed in patients with severe COVID-19 is consistent with diffuse activation of coagulation, but in a pattern that differs from classic disseminated intravascular coagulation (DIC). Although d-dimers can be markedly elevated in both conditions, in COVID-19 the prothrombin time (PT) and activated partial thromboplastin time (aPTT) are only slightly prolonged, fibrinogen is elevated, and platelet counts are typically normal or modestly decreased (30). Elevated levels of factor VIII and von Willebrand (VW) antigen further contribute to the COVID-19 coagulopathy; while plasma concentrations of ADAMTS-13, the metalloprotease that cleaves large VW multimers into smaller multimers, are decreased (32). The large, uncleaved VW multimers are known to be pro-thrombotic, as observed in patients with very low levels of ADAMTS-13 who develop thrombotic thrombocytopenic purpura. Many of these laboratory findings (elevated d-dimer, fibrinogen and von Willebrand antigen, and decreased platelet count) have been associated with disease severity in patients with COVID-19 (30).

Hyper-reactive platelets, as demonstrated by increased platelet surface levels of P-selectin, also contribute to the pro-thrombotic milieu in patients with COVID-19 (32). Several studies have reported platelet rich thrombi in multiple organs in autopsy studies (33, 34). Platelet activation leads to release of cytokines and chemokines that further contribute to the activation of immune cells (32). Platelet leukocyte aggregates may induce the formation of neutrophil extra-cellular traps (NETs), which also contribute to thrombosis. When neutrophils die, they degranulate and release extracellular webs of chromatin forming a pro-thrombotic scaffold. NETs may also be formed in direct response to viral interactions (33). Several studies have suggested that NETs play an important role in small and large vessel thrombosis in COVID-19 and correlate with disease severity (32, 33). NETs can also trigger direct cytotoxic effects on endothelial cells.

While most studies elucidating these findings have been conducted in adults, small studies in children with severe COVID-19 and MIS-C demonstrate evidence of complement-mediated thrombotic microangiopathy (TMA) including elevated soluble C5b9 along with thrombocytopenia and microangiopathic hemolytic anemia (35). Studies in children with MIS-C demonstrate excessive cytokine production and vascular-endothelial dysfunction (36). Evidence of hypercoagulability on thromboelastography (TEG) in pediatric patients with MIS-C has also been described (37, 38). In addition to the pro-thrombotic alterations highlighted above, patients hospitalized with COVID-19 often have multiple additional risk factors for thrombosis, including venous stasis, obesity, cancer, central venous catheters, and in rare cases, extracorporeal membrane oxygenation (ECMO). Nonetheless, the unique thrombo-inflammatory state observed in adults with severe COVID-19 can be profound, and a better understanding of these pathways may lead to novel therapeutic approaches to reduce thrombotic events.

Randomized controlled Trials of Thromboprophylaxis in Adults with COVID-19

In response to the high rate of VTE noted in adults with COVID-19, several well designed, randomized clinical trials studying the safety and efficacy of antithrombotic therapy were completed (39). In symptomatic, but clinically stable outpatients, three placebo controlled, randomized trials (ACTIV-4B, ETHIC and OVID) showed no benefit of antiplatelet, prophylactic or therapeutic dose anticoagulant therapy on the rates of early hospitalization, thromboembolism and mortality (40-42).

In patients admitted to the medical wards and intensive care unit (ICU), trials have typically compared the efficacy of prophylactic versus intermediate and therapeutic dose anticoagulation. Given a clear common goal, three international clinical trial platforms, namely ACTIV-4, REMAP-CAP and ATTACC harmonized their study protocols and outcomes to rapidly achieve results (43, 44). Anticoagulant drugs/regimens used in these trials were variable, though LMWH was most commonly prescribed. The primary outcome of this integrated multiplatform trial was organ support-free days, which was evaluated on an ordinal scale that combined in-hospital death and the number of days free of respiratory and cardiovascular support. In patients admitted to medical wards, those randomized to therapeutic-dose anticoagulation were more likely to survive without cardiovascular or respiratory support [aOR: 1.27 (95% CI: 1.03-1.58)] compared to those randomized to standard prophylaxis (43). Nineteen (1.6%) thrombotic events were reported in patients receiving therapeutic anticoagulation compared to 31 (3%) in those receiving standard prophylaxis. Major bleeding was noted in 1.9% of patients receiving

therapeutic anticoagulation versus 0.9% of patients receiving standard prophylaxis. In the RAPID trial, 465 moderately-ill patients were randomized to therapeutic versus prophylactic anticoagulation (45). The primary study outcome: a composite of death, mechanical ventilation or ICU admission was similar in both arms [16.2 vs. 21.9% (p=0.12)]. Rates of VTE [0.9 vs. 2.5% (p=0.19)] and major bleeding [0.9 vs. 1.7% P=0.69)] were also similar. However, mortality was significantly lower in patients receiving therapeutic-dose anticoagulation compared to those receiving standard prophylaxis (1.8 vs. 7.6%; p=0.006). In the ACTION trial, which primarily included moderately ill patients, rates of VTE [4 vs. 6% (p=0.19)] and death [11 vs 8% (p=0.13)] were similar in patients receiving therapeutic versus prophylactic-dose anticoagulation (46). The HEP-COVID trial randomized patients with COVID-19 (both moderate and critically ill patients), and a plasma d-dimer >4x upper limit of normal to therapeutic versus prophylactic heparin (47). Two hundred and fifty three patients were included in the analysis, of whom 170 (67%) were admitted to the medical wards. The primary outcome, a composite of death, venous and arterial thrombo-embolism was significantly lower in patients randomized to therapeutic dose heparin (28.7 vs 41.9%; p=0.03), though this effect was lost when only evaluating critically ill patients. Taken together, these data indicate a potential (though marginal) benefit of therapeutic-dose anticoagulation on survival in moderately ill patients with COVID-19.

This potential benefit of therapeutic-dose anticoagulation was lost when investigating critically ill patients. The multiplatform (ACTIV-4, REMAP-CAP, and ATTACC) trial also investigated 1098 critically ill patients (44). Therapeutic-dose anticoagulation was not associated with a greater possibility of survival to hospital discharge [aOR: 0.83 (95%CI: 0.67-1.03)], or a greater number of days free of respiratory or cardiovascular organ support [aOR: 0.84 (95%CI: 0.64-1.11)]. There were numerically fewer thrombotic events in patients receiving therapeutic anticoagulation (7.2%) compared to those receiving standard prophylaxis (11.1%), while major bleeding events were similar in both arms (3.8% versus 2.3%). The INSPIRATION trial compared intermediate dose LMWH to standard thromboprophylaxis in critically ill patients (48). The primary study outcome was a composite of – (i) venous and arterial thromboembolism, (ii) need for extracorporeal membrane oxygenation, and (iii) mortality within 30 days. The primary efficacy outcome occurred in 45.7% of patients receiving intermediate dose LMWH, compared to 44.1% patients receiving standard prophylaxis (p=0.7). The rates of VTE (3.3 vs 3.5%; p=0.87) and major bleeding (2.5 vs 1.4%; p=0.33) were also similar in both arms.

The rate of symptomatic VTE post-discharge in adults with COVID-19 has ranged from 1 - 2.5% (49, 50). The MICHELLE trial randomized 320 high-risk patients to prophylactic rivaroxaban for 35 days after discharge, versus standard of care (51). The primary efficacy outcome, a composite of thromboembolism and cardiovascular death occurred in 3% of patients randomized to rivaroxaban, compared to 9% of patients randomized to standard of care (p=0.0293). There were no major bleeds in either study arm.

Clinical Guidelines on Thromboprophylaxis (Adult)

Based on the data obtained from these well-designed clinical trials, several medical societies have published evidence based, clinical guidelines on thromboprophylaxis in adults with COVID-19. Table 1 provides an overview of the most recent consensus guidelines.

Cerebrovascular Manifestations of COVID-19

COVID-19 can involve both the peripheral and the central nervous system (CNS) (52, 53). Peripheral involvement includes dysosmia, dysgeusia, Guillain-Barre syndrome, and myositis. In the CNS, cerebrovascular complications have proved to be myriad; ischemic and hemorrhagic stroke as well as sinus/cortical venous thrombosis have complemented encephalitis, encephalopathy, acute disseminated encephalomyelitis and meningitis (54). Ischemic stroke has been described in 0.9-4.6% of hospitalized adults with COVID-19 (12). Patients with COVID-19 and stroke tend to be older, have severe COVID-19 symptoms, and additional cardiovascular risk factors including hypertension and diabetes (55). Stroke in adult patients with COVID-19 is associated with increased mortality (56).

Despite evidence for CNS involvement in COVID-19, documentation of direct viral involvement in the nervous system has proven challenging. Of 304 patients whose cerebral spinal fluid (CSF) was studied for SARS-CoV2, only 17 (6%) were positive. Furthermore, of 58 patients whose CSF was tested for SARS-CoV-2 antibodies, only 7 (12%) proved positive for intrathecal production of viral antibodies (57). Since both viral presence and antibody synthesis appear to be infrequent in CNS, it is unlikely that central neurologic symptoms of COVID-19 result from direct invasion of CNS (58-61). Instead, inflammation, intravascular coagulation and vascular endothelial dysfunction figure prominently in ischemic stroke occurrence among patients with COVID-19 (62, 63). Comparison of patients with stroke and COVID-19 versus those with stroke without COVID 19, demonstrate that both cytokines and molecules associated with endothelial activation were elevated in those with COVID-19 (64). Evidence of endothelial cell dysfunction is

reflected in elevation of endothelial biomarkers such as thrombomodulin, von Willebrand Factor antigen, and PAI1 (65). Furthermore, endothelial dysfunction or inflammation is indicated by the not uncommon occurrence of focal cerebral arteriopathy or cerebral arteritis in children with COVID 19 or MIS-C (66).

Venous Thromboembolism and Arterial Ischemic Stroke in Children

While historically considered rare, VTE is being increasingly recognized in children. National database studies conducted over two decades ago estimated the annual incidence of pediatric VTE to be 0.07-0.14/10,000 children (67, 68). These studies established a bimodal age distribution of VTE in children with peaks occurring in infancy and the adolescent years. They also documented that >95% of pediatric thrombotic events are provoked, typically occurring in the setting of risk factors like central venous lines, cancer, congenital heart disease, chronic renal disease and inflammation. The last two decades have noted a dramatic, 130 - 200% increase in the rate of VTE amongst hospitalized children (69, 70). Improved survival of critically ill children, increased use of central venous lines, and rising prevalence of adolescent obesity are hypothesized to be responsible for this increase. Long term consequences of pediatric VTE include post-thrombotic syndrome, loss of central venous access and chronic thrombo-embolic pulmonary hypertension.

Pediatric stroke is broadly classified as ischemic or hemorrhagic, with ischemic strokes occurring secondary to an arterial ischemic event or cerebral sinus venous thrombosis (CSVT). The estimated incidence of arterial ischemic stroke (AIS) in children is 0.1-0.4/10,000/year (71-73), and also exhibits a bimodal age distribution (74). In contrast to the dramatic rise in incidence of pediatric VTE, rates of childhood stroke in the US have remained relatively stable (75). Risk factors for childhood AIS are distinct from those in older adults, with arteriopathy, thrombophilia and cardiac disease being recognized as the most common co-morbid conditions (73). Case-fatality following childhood AIS is estimated to range from 3-7% (76-78), with persistent neurological deficits noted in 60-70% of survivors (73, 79).

Venous Thromboembolism in Hospitalized Children with COVID-19/MIS-C

One of the first studies to investigate VTE in hospitalized children with COVID-19 was conducted in the Bronx, New York. Mitchell and colleagues reported 27 consecutive patients admitted to Montefiore Children's Hospital in March 2020 with symptomatic COVID-19 (80). Sixteen (59%) patients had severe or critical illness, and 14 (52%) required increased

ventilatory support (defined as requiring ≥ 5L oxygen via nasal cannula [NC], high-flow NC, non-rebreather mask, or intubation). VTE was identified in 7 (26%) patients – 3 with DVT, and 4 with PE. Increased ventilatory support was the only risk factor associated with VTE diagnosis (p=0.0006). Of note, 4/7 (57%) patients with confirmed VTE were on prophylactic anticoagulation prior to the VTE diagnosis. None of the subsequent single-center observational studies (Table 2) have reported such a high rate of VTE with COVID-19 or MIS-C, with some reporting zero VTE cases (13, 14, 22, 37, 81-91). This variability, may in part be explained by specific cohorts investigated (e.g. critically ill patients versus those with asymptomatic SARS-CoV-2 infection), variation in thromboprophylaxis regimens, study setting (e.g. community hospital versus referral center) and study definitions used.

Two multi-center investigations that have reported granular data on the clinical presentation, thromboprophylaxis regimens used, risk factors and outcomes of thrombosis warrant further discussion. Whitworth and colleagues performed a retrospective cohort study across 7 tertiary and quaternary care children's hospitals in the United States (US) (83). Consecutive children (<21 years of age) admitted with COVID-19 and MIS-C between March 2020 – August 2020 were included. 814 unique patients underwent 853 admissions. Of them, 426 (50%) were admitted for COVID-19, 138 (16%) for MIS-C and 289 (34%) with asymptomatic SARS-CoV-2 infection. Rate of thrombo-embolism was 6.5% in patients with MIS-C, 2.1% in COVID-19 and 0.7% in those with asymptomatic SARS-CoV-2 infection. The highest rate of thrombo-embolism was noted in adolescents with MIS-C (19%). All-cause mortality was 2.3% (13/564) for the entire cohort, but 28% (5/18) for those with a history of thrombo-embolism. On multi-variable logistic regression analysis, adolescent age (OR: 16.8), central venous catheter (CVC; OR: 7.2), MIS-C diagnosis (OR: 6.4), cancer (OR: 6.3) and a d-dimer >5 x upper limit of normal (ULN; OR: 21.2) were identified as independent risk-factors for thrombo-embolism. With regards to thromboprophylaxis, anticoagulation use was reported in 30% of COVID-19 admissions, and 58% of MIS-C admissions. Low molecular weight heparin (LMWH) was the most commonly used anticoagulant (~90%). Notably, 71% (10/14) of hospital acquired thrombo-embolic events occurred despite the use of prophylactic anticoagulation. Major and clinically relevant non-major (CRNM) bleeding (92) was reported in 17 patients, with only one (6%) bleed reported in a patient receiving prophylactic anticoagulation.

More recently, Tehseen and colleagues reported data from an international, multicenter pediatric registry of COVID-19 (89). Nine hundred and fifteen children hospitalized with COVID-19 and MIS-C between February 2020 and March 2021 were included. Three hundred and eighty-five (42%) patients were diagnosed with COVID-19, 288 (31%) with MIS-C, and 249 (26%) with asymptomatic SARS-CoV-2 infection. Rate of thrombo-embolism was 1.7% in patients with MIS-C, 1.3% in patients with COVID-19 and 0.8% in patients with asymptomatic SARS-CoV-2 infection. For patients with symptomatic COVID-19, congenital heart disease (CHD), use of CVC and need for respiratory support were identified as risk factors for VTE; while in patients with MIS-C, obesity, need for respiratory support and cytokine storm were risk factors for thrombosis. One hundred and thirty-nine patients (15%) were placed on prophylactic anticoagulation, and LMWH remained the most commonly prescribed anticoagulant (~60%). All cause mortality for the entire cohort was 1.3%, and 8.3% for patients with a history of thrombosis. Nine (1%) patients developed severe hemorrhage, thought the association of hemorrhage with prophylactic anticoagulation was unclear.

Pediatric studies investigating the rate of thrombo-embolism with COVID-19 and MIS-C have several limitations (13, 14, 22, 37, 80-91). They are typically retrospective investigations, lack uniform inclusion criteria and often use different definitions for key outcome variables (e.g. hemorrhage). Large multicenter investigations and administrative database studies often lack granularity of data (13, 22). Conversely, smaller single-institution studies often combine data on patients with COVID-19 and MIS-C, and occasionally combine arterial and venous thrombotic events (93). These limitations notwithstanding, several conclusions can be drawn from the published pediatric data. Thrombo-embolism is reported in 0-3% of pediatric patients with COVID-19, and 0-6% of patients with MIS-C. This rate of thrombo-embolism is significantly lower than published adult data. Children with COVID-19 and MIS-C who develop thrombosis, often have the simultaneous presence of additional risk factors for thrombosis including critical illness, CHD, cancer, obesity and the need for central venous access. The rate of thrombosis in hospitalized children with asymptomatic SARS-CoV-2 infection at 0.7-0.8%, is similar to a VTE rate of 0.5-1% previously reported in the US (70, 94). Similar to adult data, children with COVID-19 and MIS-C who develop thrombosis, often do so despite being on prophylactic anticoagulation. Lastly, a diagnosis of VTE is associated with increased mortality, highlighting the need for well-designed pediatric trials investigating the appropriate dose of prophylaxis in this cohort.

Ischemic Stroke in Hospitalized Children with COVID-19

Occurrence of ischemic stroke in children with COVID-19 initially appeared in case reports. However, Beslow and colleagues who reported on behalf of the International Pediatric Stroke Study and the British Paediatric Neurology Association in 2021, presented survey data from 42 international pediatric centers that represented 971 children with COVID-19. Of these only 8 were found to have ischemic stroke (0.82%). Interestingly, of the 361 documented childhood stroke cases recorded during the study period, 1 of 108 (0.9%) with neonatal AIS, 0 of 33 with neonatal CSVT, 6 of 166 (3.6%) with childhood AIS, and 1 of 54 (1.9%) with childhood CSVT were found to be positive for SARS-CoV-2. Among all children studied, significant proportions of both neonates and children with stroke were not tested for SARS-CoV-2; only 30.5% of neonates and 60% of children older than 28 days to 18 years old with ischemic stroke were tested for SARS-CoV-2. Despite this, the aforementioned 8 cases represented 4.6% of children with ischemic stroke who were also tested for SARS-CoV-2 (95).

In a larger analysis of 1695 children with COVID-19 from the *Overcoming COVID-19* U.S. public health registry, 365 (22%) were found to have neurologic involvement. Of these, 12 (0.71%) had acute ischemic stroke (96). Finally, in a study published in 2022, once again for the International Pediatric Stroke Study, 48 international centers provided data on children hospitalized with COVID-19 and on incident AIS patients during the 6 month study period. In all, 7,231 children with COVID-19 were hospitalized. Simultaneously, 335 children presented with AIS, 23 of whom tested positive for SARS-CoV-2. Thus, 23 of 7,231 hospitalized children with COVID-19 (0.32%) also had AIS. Moreover, 23 of 335 children with AIS were hospitalized for COVID-19 leading to a 6.9% rate of COVID-19 among the children with AIS captured in this study. Of these, COVID-19 was judged to constitute the main risk factor for AIS in 6 (26.1%) patients. In 5 (21.7%) patients, stroke was due to large vessel obstruction. Six children (26%) had radiologic evidence of either cerebral arteritis or focal cerebral arteriopathy of childhood. Notably, inflammatory marker data were available in 22 of the 23 children; 17 had elevation of at least one such marker, including CRP, ferritin, ESR or procalcitonin (66). Table 4 provides an overview of these studies.

Thromboprophylaxis Trial in Children with COVID-19/MIS-C

In contrast to multiple randomized trials of antithrombotic therapy in adults with COVID-19, there has been only one prospective pediatric phase 2 clinical trial. The COVID-19 Anticoagulation in Children – Thromboprophylaxis (COVAC-TP) trial (clinicaltrials.gov: NCT043544155) was a

multicenter, open-label, non-randomized, single-arm study to evaluate the safety and efficacy of enoxaparin in children (<18 years of age) with COVID-19 and MIS-C (97). Thirty-eight participants (median age: 12.1 years) were enrolled on the trial, and received twice-daily enoxaparin titrated to achieve an anti-factor Xa activity of 0.2 – 0.49 IU/mL. The primary safety-endpoint was the rate of major and CRNM bleeding within 30-days of enrollment (92). The cumulative rate of hospital acquired VTE within 30-days of enrollment was defined as an exploratory efficacy outcome. Twenty participants had MIS-C and 18 had primary COVID-19. Patients with MIS-C were younger, had a lower BMI and higher d-dimer compared to patients with COVID-19. While no participant developed a major or CRNM bleed, two participants (5.3%) developed a CVL associated DVT within one week of enrollment.

Thromboprophylaxis Recommendations for Children with COVID-19 and MIS-C

The absence of prospective data confirming the efficacy of primary thromboprophylaxis in children with COVID-19 and MIS-C has prevented the development of evidence-based guidelines. Consensus guidelines based on expert opinion, adult data, and observational pediatric data have been proposed by the Pediatric/Neonatal subcommittee of the International Society on Thrombosis and Haemostasis (ISTH) (98), Anticoagulation Forum (62) and the American College of Rheumatology (for MIS-C only) (99) (Table 3).

The guidelines proposed by the ISTH and the Anticoagulation Forum are similar and suggest the use of LMWH, administered twice-a-day, and titrated to achieve an anti-factor Xa activity of 0.2 – 0.49 IU/mL in children with COVID-19/MIS-C who have additional risk factors for thrombosis such as CVL, cancer, immobilization sickle cell disease etc. Thromboprophylaxis is also recommended in patients with marked elevation of d-dimer (>5x ULN). Both guidelines also discourage the use of thromboprophylaxis in children with asymptomatic SARS-CoV-2 infection, unless they have multiple additional risk factors for VTE. The ISTH consensus guidelines suggest the use of thromboprophylaxis post-discharge for up to 30-days in patients with have persistent VTE risk factors, or those who have elevated d-dimers at the time of discharge. Of note, no pediatric study has established the safety and efficacy of post-discharge thromboprophylaxis in COVID-19/MIS-C. Additionally, in adults, the NIH Anticoagulation Forum guidelines discourage the use of post-discharge anticoagulant prophylaxis in adults with COVID-19 who don't have suspected or confirmed VTE, or other indications for anticoagulation (100, 101).

The American College of Rheumatology recommends the use of low dose aspirin (3-5 mg/kg/day; maximum 81 mg/day) in all patients with MIS-C, which should be continued until the platelet counts have normalized and after confirming normal coronary arteries ≥ 4-weeks after diagnosis (62). They recommend the use of therapeutic dose anticoagulation in addition to low-dose aspirin in patients with coronary artery aneurysm and a Z-score ≥10; and in patients with an ejection fraction <35%. In patients without cardiac involvement, the authors recommend an individualized approach to anticoagulant prophylaxis based on additional risk factors for thrombosis and patient's perceived bleeding risk.

At Boston Children's Hospital, all patients (irrespective of COVID-19 status) undergo risk assessment for VTE at the time of admission using a clinical decision support (CDS) tool. Pharmacological prophylaxis with LMWH is typically recommended for patients with multiple simultaneous risk factors for thrombosis, who achieve a cumulative score of ≥3 on the CDS tool, and don't have any contraindications to anticoagulation. Symptomatic COVID-19 is currently added to the CDS as an independent risk-factor for thrombosis (score of 1) (90). Pharmacological prophylaxis is additionally recommended for any patient with COVID-19 ≥18 years, critically ill patients and in patients with marked elevation in d-dimers on presentation (i.e. ≥5x ULN). Pharmacological prophylaxis in patients admitted to Boston Children's Hospital with MIS-C have been previously published (37, 102).

Management of VTE and AIS in Children with COVID-19 and MIS-C

Children with COVID-19 and VTE are typically treated with therapeutic anticoagulation for 6-weeks to 3-months (103, 104). Given its short half-life and complete reversibility with protamine sulfate, we recommend using unfractionated heparin in critically ill children with laboratory evidence of coagulopathy. Low molecular weight heparin, fondaparinux, vitamin K antagonists or direct oral anticoagulants may be used once patients are clinically stable and ready for discharge. Systemic and/or catheter-directed thrombolysis are typically reserved for patients with limb or life threatening venous thrombosis (104).

Optimal therapy for children with acute AIS and COVID-19 has not been determined. Thrombolytic treatment with tissue plasminogen activator (tPA) has been studied in children who present with acute stroke within 4.5 hours of symptom onset, and appears to be effective and safe in appropriately selected cases (105, 106). Adults with acute stroke and COVID-19 have been treated successfully within 4.5 hours of symptom onset with tPA. None experienced

post-treatment hemorrhage (107). While appropriately selected children are now treated with thrombectomy for acute stroke, this treatment remains in the early stages of study (108, 109). Currently, vascular inflammation on radiologic evaluation should raise concern about delivery of a catheter to an intracranial artery. Steroid therapy should be considered for children with COVID-19 or MIS-C and who have neuro-radiologic evidence for cerebral arteritis or focal cerebral arteriopathy (110, 111). Aspirin dosed at 81 mg/day has typically been used after arterial ischemic stroke in patients with cerebral arteritis/arteriopathy to promote intravascular flow through stenosed cerebral vessels. Finally, neuroprotective methods of treatment that target eunatremia, euglycemia, euthermia and maintenance hydration should be employed (106, 112).

Conclusion

Increased thrombosis in hospitalized patients with COVID-19 is thought to result from inflammation derived hypercoagulability and endothelial dysfunction. In response to the high rates of VTE and associated morbidity and mortality, several large randomized trials on antithrombotic therapy have led to evidence-based recommendations regarding the use of anticoagulation in adults with COVID-19.

Most children with COVID-19 follow a milder course with a lower risk of thrombotic complications. However, children with pre-existing medical conditions like cancer, congenital heart disease, diabetes and obesity are at an increased risk of severe infection and hospitalization. Interestingly, these co-morbid conditions are also independent risk factors for pediatric thrombosis. Additionally, a minority of children with COVID-19 develop a post-infectious, hyper-inflammatory syndrome termed MIS-C. Observational studies have reported an increased rate of both ischemic stroke and VTE in hospitalized children with COVID-19/MIS-C. Approximately, 0.3-0.8% of hospitalized children with COVID-19 have an ischemic stroke. While data on VTE rates are more heterogeneous, multi-center investigations estimate that 1.2-5% of children with COVID-19, and 1.4-6.5% of children with MIS-C develop VTE. The COVAC-TP trial has documented the safety of intermediate-dose LMWH in hospitalized children with COVID-19 and MIS-C, though the efficacy of this regimen is less clear. Six to 71% of reported thrombotic events in hospitalized children have occurred despite the use of pharmacological prophylaxis.

Additional investigations are therefore required to identify hospitalized children who warrant more aggressive thromboprophylaxis. Pediatric studies are also needed to investigate the role of post-discharge prophylaxis, and the role of prophylaxis in high-risk ambulatory patients (e.g. with high-risk thrombophilia). The impact of evolving sub-variants of SARS-CoV-2 on the thrombotic risk, and consequently on thromboprophylaxis recommendations also needs further clarification. Adequately powered, randomized clinical trials may not be feasible in children given the low incidence of VTE. Instead, prospective multicenter cohort studies, using existing networks such as the International Pediatric Thrombosis Network (IPTN) and International Pediatric Stroke Study (IPSS) may help achieve some of these goals.

Authorship Details

RK, MR and LR wrote the first draft of the manuscript. All authors critically reviewed the manuscript and approved the final version for consideration of publication.

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Table 1: Consensus-based antithrombotic guidelines for adults with COVID-19

Organization/Year	Ambulatory Patients	Medical Ward	Intensive Care Unit	Post-discharge
National Institute of Health; 2022*	Not recommended	- Standard dose thromboprophylaxis - Therapeutic intensity anticoagulation in patients with (i) elevated d-dimers, and (ii) low-flow oxygen requirement - LMWH and UFH preferred	Recommend standard-dose thromboprophylaxis	Not recommended
Anticoagulation Forum; 2022 (99)	Not recommended	Suggest therapeutic intensity UFH or LMWH for thromboprophylaxis	Recommend standard-dose thromboprophylaxis	Suggest rivaroxaban 10 mg QD x35 days in select patients
American Society of Hematology; 2021 – 2022 (38, 100, 113)	Not discussed	Suggest therapeutic intensity anticoagulation for thromboprophylaxis	Suggest standard dose thromboprophylaxis	Not recommended
American College of Chest Physicians; 2022 (101)	Not discussed	Recommend therapeutic dose anticoagulation with UFH or LMWH	Recommend standard-dose thromboprophylaxis	Not discussed

UFH: unfractionated heparin; LMWH: low molecular weight heparin; * https://www.covid19treatmentguidelines.nih.gov (accessed: 02/14/2023)

Table 2: Studies investigating venous thromboembolism in children with COVID-19 and MISC

Author/Country	Study Design	Sample Size		Prophylactic anticoagulation‡		Rate of VTE		Predictors of VTE	Mortality in patients with VTE
		COVID-19	MIS-C	COVID-19 (%)	MIS-C (%)	COVID-19 (%)	MIS-C (%)		
Singe-Center Studies									
Mitchell et al. USA (80)	Retrospective cohort	27	N/A	11 (41)	N/A	7 (26)	N/A	Increased ventilatory support	1/7 (14) mortality
Del Borrello et al. Italy (86)	Prospective cohort	30	6	4 (13)	2 (33)	0		N/A	N/A
Leeman et al. USA (82)	Retrospective cohort	47	9	13 (23)		0		N/A	N/A
Ankola et al. USA (37)	Retrospective cohort	N/A	30	N/A	20 (67)	N/A	0	N/A	N/A
Cohen et al. USA† (85)	Retrospective cohort	543	N/A	N/A		14 (2.6)	N/A	Obesity	NR
Al-Ghafry et al. USA (84)	Retrospective cohort	40	N/A	N/A	20 (50)	N/A	0	N/A	N/A
Schmitz et al. USA (88)	Retrospective cohort	71	36	18 (25)	29 (81)	1 (0.6)	0	NR	NR
Karimi et al. Iran (81)	Retrospective cohort	150	34	20 (13)	13 (38)	0	2 (6)	NR	NR
Yan et al. USA (90)	Quality improvement	329	N/A	106 (28)	N/A	5 (1.5)	N/A	NR	NR
Multicenter Studies									
Aguilera-Alonso et al. Spain (114)	Prospective National Registry	321	47	24 (6.5)		4 (1.2%)	0	NR	0
Feldstein et al. USA (22)	Retrospective cohort	577	539	162 (28)	337 (63)	8 (1)	11 (2)	NR	NR
Whitworth et al. USA (83)	Retrospective cohort	426	138	128 (30)	80 (58)	9 (2)	9 (6.5)	Older age; cancer; CVC; MIS-C; d-dimer >5 ULN	5/18 (28) mortality
Antoon et al. USA (13)	Administrative database	3720	343	NR	NR	13 (0.3)		NR	NR
Fernandes et al. USA (14)	Retrospective/ Prospective cohort	212	69	57 (27)	41 (59)	11(5)	1 (1.4)	NR	NR
Saleh et al. Egypt (87)	Retrospective cohort	394	4	N/A		5 (1.3)		Elevated d-dimer	NR
Tehseen et al. Canada, Costa Rica, Iran (89)	Retrospective cohort	385	288	58 (15)	79 (27)	5 (1.3)	5 (1.7)	CHD, respiratory support, cancer, obesity, cytokine storm	1/10 (10) mortality
Zabeida et al. Canada (91)	Retrospective cohort	43	11	18/79 (23)*		0	0	N/A	N/A

‡ low molecular weight heparin, unfractionated heparin, direct oral anticoagulants and vitamin K antagonists; † detailed information only available for patients with pulmonary embolism; *79 patients included 25 patients with asymptomatic SARS-CoV-2 infection; VTE: venous thromboembolism; N/A: not applicable; NR: not reported

Table 3: Consensus-based antithrombotic guidelines for children with COVID-19 and MIS-C

	Ambulatory Patients	Hospitalized Patients	Post-Discharge
International Society on Thrombosis and Haemostasis (98)	No recommendations	Prophylactic LMWH Q12 hours (target anti-FXa: 0.2 – 0.49 U/mL) ***or*** UFH (target anti-FXa: 0.1 – 0.34 U/mL) suggested for: • Superimposed VTE risk factors ***or*** • D-dimer ≥ 5x ULN Prophylactic anticoagulation not recommended in patients with asymptomatic SARS-CoV-2, in the absence of additional VTE risk factors	Prophylactic LMWH Q12 hours ***or*** Q24 hours considered for up to 30-days post-discharge for: • Persistent VTE risk factors ***or*** • D-dimer ≥ 5x ULN
Anticoagulation Forum (99)		Prophylactic LMWH Q12 hours (target anti-FXa: 0.2 – 0.49 U/mL) suggested for: • Superimposed VTE risk factors ***or*** • Markedly elevated D-dimer Prophylactic anticoagulation not recommended in patients with asymptomatic SARS-CoV-2, in the absence of additional VTE risk factors	Thromboprophylaxis considered on a case-by-case basis for select patients with multiple ongoing risk factors
American College of Rheumatology (MIS-C only) (62)		Low dose aspirin (3-5 mg/kg/day; maximum 81 mg/day) Therapeutic dose anticoagulation (LMWH → VKA, DOAC): • CAA with z-score ≥10 ***or*** • Ejection fraction <35% ***or*** • Thromboembolism Prophylactic dose anticoagulation: • Individualized based on VTE risk factors	Aspirin therapy should be continued till: • Platelet count is normal ***and*** • Normal coronary arteries confirmed ≥4 weeks after diagnosis Therapeutic anticoagulation should be continued till: • Till CAA z-score ≥10 • Till ejection fraction ≥35% • Thromboembolism (~ 6 weeks - 3months)

LMWH: low molecular weight heparin; anti-FXa: anti-factor Xa; UFH: unfractionated heparin; VTE: venous thromboembolism; ULN: upper limit of normal; VKE: vitamin K antagonists; DOAC: direct oral anticoagulant; CAA: coronary artery aneurysm

Table 4: Studies investigating ischemic stroke in children with COVID-19

Author/Country	Study Design	Children with COVID-19	Children with COVID-19 and ischemic stroke (%)	Children with stroke or neuro deficit	Children with stroke or neuro deficit who tested positive for SARS-CoV-2 (%)
Beslow et al. International (95)	Retrospective database	971	8 (0.82)	361	8/175 (4.5)
LaRovere et al. USA (96)	Retrospective database	1.695	12 (0.71)	365	12/365 (3.3)
Beslow et al. International (66)	Retrospective database	7,231	23 (0.32)	335	23/335 (6.9)