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REVIEW ARTICLE

Coagulopathy and thromboembolism in children with COVID-19 — pathophysiology, thrombotic risk, clinical manifestations, and management

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Abstract

Coronavirus disease 2019 (COVID-19) is an infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Since the beginning of the pandemic, it has been generally accepted that children infected with SARS-CoV-2 either stay asymptomatic or present benign symptoms. Yet SARS-CoV-2 is widely known to cause serious consequences in children and adolescents. Complications may develop during infection, several weeks afterwards, or in the course of multisystem inflammatory syndrome in children (MIS-C). MIS-C manifests with fever, gastrointestinal, cardiovascular and/or neurological symptoms. Moreover, thromboembolism is a relatively common complication of COVID-19 and MIS-C. The purpose of this work was to review current reports on thromboembolic complications among children who underwent SARS-CoV-2 infection. Among the published cases of MIS-C, thromboembolic incidents ranged from 1.4% to 6.5%, taking the form of a brain infarct, deep vein thrombosis, pulmonary embolism, or splenic infarct. Several mechanisms leading to thrombosis in COVID-19 in children are considered. The development of acute infection in the lungs results in local clot formation in the pulmonary microcirculation, leading to perfusion disturbances. ADAMTS13 activity is also mildly reduced in patients infected with SARS-CoV-2, increasing the risk of microthrombosis. COVID-19-associated coagulopathy is characterized by elevated D-dimers and fibrinogen levels. Significantly increased D-dimers probably represent activation of coagulation caused by viremia and cytokine storm, as well as possible organ dysfunction. The treatment of thromboembolism in children includes low and high molecular weight heparins and acetylsalicylic acid. Pediatricians should be aware of the possible multiple complications associated with COVID-19 in children, including thromboembolic incidents.

Key words: COVID-19, MIS-C, children, coagulopathy, thromboembolism

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Introduction

Coronavirus disease 2019 (COVID-19) is an infectious disease caused by the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). The first cases of the disease were reported in Wuhan, China, in December 2019. The disease spread rapidly to over 200 countries, becoming a global pandemic by early 2020. To date, there have been c.252 million confirmed cases of infection worldwide [1–4]. World Health Organization (WHO) data shows that

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infections among children accounted for c.8.5% of all reported cases worldwide. According to the latest studies, this number is likely to be an underestimate due to the low percentage of tests performed in children [5].

COVID-19 infection in children usually has a mild clinical manifestation comprising cough, fever, sore throat and/or nasal discharge, or is in fact asymptomatic [5]. Exceptions include children with comorbidities, neonates, and preterm infants who have an increased risk of severe COVID-19 [6]. Although the infection is asymptomatic or mild in the pediatric population, some patients develop complications. The term 'pediatric inflammatory multi-organ syndrome temporally associated with SARS-CoV-2' (PIMS-TS) has been coined. PIMS-TS is a systemic inflammatory disease characterized by acute onset and it primarily affects children. The Center of Disease Control and Prevention (CDC) and the WHO have proposed the name 'multisystem inflammatory syndrome in children' (MIS-C) for this disease [7]. The disease occurs within 2–4 weeks of infection or contact with an infected person [8] and is characterized by laboratory markers of inflammation and prothrombotic state [9]. PIMS-TS/MIS-C manifests through fever, gastrointestinal symptoms and/or cardiovascular symptoms. Respiratory symptoms and even septic shock may also occur. PIMS more frequently affects boys than girls, with a median age of 8 years [10]. The main target of SARS-CoV-2 is the respiratory system, while extrapulmonary manifestations include a broad spectrum of cutaneous (IgA-associated vasculitis), neurological, endocrine, cardiovascular (myocarditis) and acute renal failure complications [5, 11, 12]. Cardiogenic shock, electrocardiographic (ECG) changes, left ventricular dysfunction, and coronary artery dilatation have been reported among patients with PIMS-TS [12]. In blood morphology, the most common abnormalities are leukopenia, lymphopenia, neutropenia and thrombocytosis. In contrast, hospitalized patients have had leukocytosis, neutrophilia and thrombocytosis [13]. No coincidence has been shown between hematological symptoms and disease severity in the pediatric population [14].

Thromboembolic disease is a relatively common complication of MIS-C. Up to a third of reported cases were brain infarcts. Other cases included intracardiac and radial artery thrombosis, deep vein thrombosis of the upper and lower extremities, pulmonary embolism, and splenic infarcts [15–17]. Congenital thrombophilia should also be considered in the differential diagnosis of thromboembolic complications. Factor V Leiden deficiency and prothrombin gene 20210A mutation increase the risk of early and recurrent thrombosis by 2–5 times on the basis of congenital thrombophilia, and there is a higher risk of thromboembolic complications [18, 19].

The purpose of this article is to summarize current knowledge regarding COVID-19 and MIS-C in children and to consolidate reports on thromboembolic complications among pediatric patients who have experienced a COVID-19 infection.

Material and methods

We searched the PUBMED library using the following search terms: "thromboembolic complications in children with COVID-19"; "thrombosis in children associated with COVID-19"; "thrombosis and MIS-C"; "hematological manifestation of COVID-19 in children"; and "thromboembolism in pediatric care units". The Pubmed database search excluded books and documents, and focused instead on reviews, systematic reviews and clinical trials. Publications in languages other than English were not included, apart from two articles in Polish concerning a child with PIMS-TS as well as congenital thrombophilia and venous thromboembolism. Data from the WHO website was used in compiling information on COVID-19 in children and MIS-C in children.

Clinical manifestations

In most analyzed studies, children infected with SARS-CoV-2 present mild or no symptoms, with the percentage of asymptomatic children reaching up to 35% [5, 20, 21]. The real prevalence of asymptomatic cases is likely to be higher, as children without symptoms are much more rarely screened than those with symptoms [22]. In contrast, serological findings show that nearly half of positive tested children did not report any symptoms [5, 23].

The most common symptoms of coronavirus disease in children are: acute respiratory infection with cough, rhinorrhea and sore throat; fever; headache; gastroenteritis; fatigue; myalgia; tachycardia; and tachypnea [20, 21, 24, 25]. Those patients with chronic diseases, such as asthma, obesity, diabetes or cancer, and infants (age <1 year) may be at increased risk of severe illness due to SARS-CoV-2 infection [26]. Neurological symptoms, including acute disseminated encephalomyelitis, acute transverse myelitis [27, 28], as well as respiratory failure, myocarditis, shock, acute renal failure and multiple organ failure, may occur in children who develop severe COVID-19 [29–31].

PIMS-TS is an acute and potentially dangerous inflammatory syndrome, in the course of which a variety of complications can develop. According to the data, it can be concluded that this syndrome is observed in approximately 1/1,000 children infected with SARS-CoV-2 [32]. Appropriate and well-timed treatment allows most patients to recover fully within a few days. There are currently several definitions of PIMS-TS in different countries. Despite these differences, all of them include six criteria [33]:

- **age:** 0–18;
- **fever:** no defined threshold value, but usually body temperature above 38.5°C persisting for at least three days;
- **high inflammatory markers:** elevated C-reactive protein (CRP), procalcitonin (PCT), erythrocyte sedimentation

rate (ESR), fibrinogen, lactate dehydrogenase (LDH), D-dimers, ferritin; no defined threshold values;

- **multi-organ damage:** symptoms affecting two or more organs or organ systems;
- **exclusion of other causes:** infectious and toxic causes, including sepsis, toxic shock syndrome, acute viral disease; acute appendicitis and peritonitis; proliferative diseases; inflammatory bowel disease;
- **association with COVID-19:** at least one of the following present (current or past): positive reverse transcription polymerase chain reaction assay (RT-PCR) for SARS-CoV-2; positive antigen test for SARS-CoV-2; positive antibodies to SARS-CoV-2; documented significant exposure to COVID-19 in the past 4–8 days.

To diagnose PIMS-TS, criteria 1–5 should be met. Criterion 6 is not obligatory. With a clinical picture strongly indicative of PIMS-TS, especially in a patient in a deteriorating or severe condition, this diagnosis should be considered even when criterion 6 is not fulfilled [33].

The course of PIMS-TS may be similar to other autoinflammatory diseases, such as complete, incomplete and atypical Kawasaki disease, toxic shock syndrome, sepsis or juvenile idiopathic arthritis with systemic onset [34]. There is no individual laboratory test or clinical sign pathognomonic for PIMS-TS. The most common symptom of the disease and the primary diagnostic criterion is fever [7]. Cardiovascular symptoms occur in approximately 85% of patients and can have a variety of manifestations including coronary artery dilatation or aneurysms, myocarditis, moderate decreased left ventricular ejection fraction, pericardial effusion, mitral regurgitation, hypotension and shock [7, 12, 35, 36]. Approximately 50% of patients manifest respiratory symptoms, including upper respiratory tract symptoms, dyspnea and radiological changes [10, 37, 38]. Symptoms also affect the gastrointestinal tract (abdominal pain, vomiting, diarrhea) [10, 39, 40], skin and mucous membranes (erythema multiforme, urticaria, conjunctivitis) [41–43], neurological system (headaches, meningism) [44, 45], urinary system (acute kidney injury) [46, 47], with possible lymphadenopathy [7, 48]. Children with PIMS-TS can also develop thrombotic complications such as cerebral infarcts, arterial clots, upper and lower extremity deep vein thrombosis, pulmonary embolism and splenic infarcts [15, 49, 50]. In blood morphology, lymphopenia, leucocytosis, neutrophilia and thrombocytopenia are common. Markers of myocardial damage such as troponins and brain natriuretic peptide (BNP) are also frequently elevated [17, 37, 38].

Referring to thromboembolic complications, congenital thrombophilia may contribute to the prothrombotic effect of COVID-19, whereas the effect of hereditary thrombophilia on the course of infection has not yet been studied. There are also some reports of patients with Leiden mutation undergoing pulmonary embolism as a result of hypercoagulability [51]. Case analysis showed that higher D-dimers could be observed in hereditarily burdened patients, which may lead to the conclusion that the mutation positively correlates with infection [18].

The full spectrum of coronavirus disease and PIMS-TS is unknown and is still being completed. The long-term effects of COVID-19 should be observed in patients who underwent COVID-19 infection directly, but also in patients who were *in utero* during maternal infection [52].

COVID-19-associated coagulopathy and thromboembolic complications

Ever since the beginning of the COVID-19 pandemic, it has been obvious that children infected with SARS-CoV-2 have a lower risk of hospitalization as well as life-threatening complications compared to adult patients [53]. However, the virus is widely known to cause much more serious consequences in children and adolescents, including thromboembolic complications [54]. Several studies have described an increased rate of thrombosis with coronavirus infection in both adults and children [55, 56]. Among the published cases of young patients suffering from complications in the course of MIS-C, the rate of thromboembolic incidents ranged from 1.4% to 6.5% [57]. In 2020, a multicenter observational study including 186 patients with MIS-C was conducted at child health centers in the United States. It was found that 3.3% of the screened children developed deep vein thrombosis or pulmonary embolism and most were aged over 12 years. Thromboembolism appeared despite thromboprophylaxis [58].

SARS-CoV-2 seems not to have a self-sustained procoagulant effect. The coagulopathy is probably a result of a profound COVID-19 inflammatory response and endothelial activation, particularly in the pulmonary circulation where the infection develops [59]. SARS-CoV-2, due to its affinity for angiotensin-converting enzyme 2 and receptors in the vascular endothelium, causes acute injury and activates a local and subsequently systemic inflammatory response [60]. The development of acute infection in the lung results in local clot formation in the pulmonary microcirculation, leading to hypoxemia and perfusion disturbances. The formation of thrombi in small and medium-sized pulmonary arteries can spread to other organs, involving multi-organ injury and micro- and macrovascular thrombosis [61, 62].

There have been described three stages of COVID-19-associated coagulopathy: stage 1 with elevated D-dimers; stage 2 — where elevated D-dimers are accompanied by modestly prolonged prothrombin time/international normalized ratio (PT/INR) and activated partial thromboplastin time (APTT) and mild thrombocytopenia; and stage 3 — patient's critical condition and laboratory findings leading to the classic disseminated intravascular coagulation [59,

63]. Studies suggest that nearly half of children with MIS-C have elevated D-dimers and fibrinogen levels [54, 64, 65]. Significantly increased D-dimers during COVID-19 probably represent activation of coagulation caused by viremia and cytokine storm, as well as possible organ dysfunction, and this can be used as a prediction of the need for more aggressive medical care [59, 66]. On the other hand, it has been reported that c.5-42% of patients with COVID-19 demonstrate thrombocytopenia varying between 100–150 G/L [67]. In addition, the elevation of fibrinogen, as an acute phase protein, correlates with increase of interleukin-6 (IL-6) levels, and confirms the link of inflammation and hypercoagulability in SARS-CoV-2 infection [68]. Initially increased fibrinogen levels may decrease in a case of COVID-19 progression, as observed in many Chinese centers where a sudden reduction in fibrinogen levels <1.0 g/L was characteristic in patients shortly before death [69].

The term associated with activation of the coagulation system due to underlying inflammatory processes, including COVID-19 infection, is 'thromboinflammation' or 'immunothrombosis' [70]. Monocytes, activated by pathogens and damage-associated molecular patterns, stimulate neutrophils, lymphocytes and vascular endothelial cells, which express tissue factor and phosphatidylserine on their surfaces and can stimulate coagulation. Normal endothelial cells sustain their antithrombogenicity via the expression of glycocalyx and antithrombin, its binding protein. Acute vascular endothelial injury during COVID-19 changes the cellular properties to procoagulant as a result of glycocalyx disruption and loss of anticoagulant proteins [71]. This generates thrombosis induced by underlying inflammatory processes.

As a consequence of activation or damage, endothelial cells release Weibel-Palade bodies containing ultra-large molecular weight von Willebrand factor (vWF) multimers. These vWF multimers have the potential to bind to platelets and lead to microthrombosis if they are not trimmed by an disintegrin-like and metalloprotease (reprolysin type) with thrombospondin type 1 motif 13 (ADAMTS13) [72, 73]. The activity of ADAMTS13 is mildly reduced in patients infected with SARS-CoV-2 [74, 75], who also present higher levels of vWF together with increased coagulation factor VIII activity, what reflects the combined effect of enhanced release of Weibel-Palade bodies from endothelial cells and acute phase reactions [74, 76].

Children have c.20–30% lower concentrations of most coagulation factors in their hemostatic systems than do adults [77], which suggests that they will present with thrombotic complications less frequently and that their treatment outcomes will be better compared to adults. However, children and adolescents may develop a super-inflammatory response giving rise to host endothelial cell damage and subsequent coagulopathy with a significant risk of mortality [15, 61].

Prophylaxis and treatment

In the prevention of thromboembolic complications, rapid vessel occlusion plays a key role. Pharmacological methods such as anticoagulation or thrombolytic therapy are most commonly used. The choice of treatment takes into account: the location and extent of the thrombus; the degree of vessel occlusion; the child's age; the type of thrombotic agent and the recurrence of thrombosis; and the coexistence of thrombophilia or the persistence of elevated levels of D-dimers and factor VIII as indicators predicting a more severe course of the disease. In order to prevent possible hemorrhagic complications, treatment should be carried out under the control of basic coagulation parameters: PT, APTT, fibrinogen, D-dimers and platelet count. For unfractionated heparin, the saturating dose is usually 75 IU/kg, administered over 10 minutes. The maintenance dose depends on age and blood clotting test results. The initial dose is 28 IU/kg/h in children under 1 year and 20 IU/kg/h in older children [78].

An alternative to unfractionated heparin is subcutaneously administered low molecular weight heparins. The best studied low molecular weight heparin preparations for use in children are enoxaparin and reviparin. The usual initial dose of enoxaparin is 1 mg/kg every 12 hours, with subsequent doses adjusted according to anti-Xa activity. In the youngest children (<2 months) or those weighing less than 5 kg, the dose is 1.5 mg/kg every 12 hours [79]. For a first thromboembolic episode, heparins are used for 5–10 days, preferably under imaging control of lesions regression. Heparin treatment is prolonged in cases of pulmonary embolism and extensive deep vein thrombosis. In children with spontaneous thrombosis, treatment is continued for at least six months or until the risk factor has resolved. In this situation, low molecular weight heparins or oral anticoagulants are used (warfarin is recommended) [80]. According to the data, acetylsalicylic acid (ASA) used in low doses of 75–325 mg/day has anticoagulant and anti-inflammatory effects. A positive effect of ASA on thromboembolic events due to COVID-19 infection has been documented in studies [81]. All patients with the Kawasaki disease phenotype or with present coronary artery lesions should receive ASA at an initial dose of 30–50 mg/kg/day in four separate doses, reduced 48 h after resolution of fever to 3–5 mg/kg/day in a single dose [82]. Other patients who do not meet the criteria for a diagnosis of Kawasaki disease should receive ASA at an antiplatelet dose of 3–5 mg/kg for a minimum of six weeks (until coronary artery lesions are excluded by follow-up echocardiography) [34]. ASA treatment should be avoided in patients with active bleeding, a significant bleeding risk, and/or a platelet count ≤80 G/L [83].

It is worth noting that vaccination of children against COVID-19 is recommended and may prevent the disease

or prevent its severe course and, consequently, thromboembolic complications resulting from the presence of the virus in the body. COVID-19 vaccination in adolescents aged 12 years and older is effective and safe, and the benefits of vaccination far outweigh the risks [84]. Similar observations apply to vaccination in younger children (5–11 years). In adolescents aged 12 to 18, the mRNA vaccines Comirnaty (Pfizer&BioNTech) and Spikevax (Moderna) can currently be used, and in children aged 5–11 — a separate formulation of the vaccine Comirnaty, containing a lower dose of the active substance. The vaccine was authorized on the basis of the results of a clinical trial conducted in more than 2,000 children aged 5–11. The safety profile of the vaccine has been confirmed [85, 86]. Finally, mRNA vaccination effectively reduces the severity of COVID-19 infection and is considered safe for pregnant women as well as the fetus. Administration of two doses of the vaccine is associated with higher maternal and fetal antibody levels [89 87], which may protect the child at birth from infection.

Discussion

In this review, we have summarized reports on thromboembolic complications in children after COVID-19 or during MIS-C. Systematic reviews have helped us to gather knowledge regarding the possible pathomechanism of thromboembolism development in children. On the other hand, case reports and observational studies have been used to discuss clinical data, such as the type of complications, the risk of their development, the age groups of patients, and the effectiveness of thromboprophylaxis. The presented patients were aged between 9 months and 21 years, but were mostly older than 12 years. Based on the study by Hameed et al. [35], the rate of thromboembolic complications in the patient group was 8.6%, while in the study by Whitworth et al. [88] it was 2.5%. Complications affect both boys and girls. The most common thrombotic incidents among these patients were pulmonary thromboembolism, deep vein thrombosis of upper and lower extremities, acute ischemic stroke, and intracardiac thrombosis. It can be noted that complications occurred despite the use of thromboprophylaxis. In most patients, the complications were cured with good clinical results. Deaths occurred in critically ill patients and were often related to another comorbidity. The study by Zafanello et al. [9] reported one death among 19 patients. In contrast, in the study by Whitworth et al. [88], there were six deaths out of 20 patients. However, the higher mortality and more severe course of infection in this study may have been influenced by comorbidities of patients, such as cancer. The study also identified several factors associated with a significantly higher risk of thromboembolism: elevated D-dimers, age over 12, MIS-C, presence of a central venous catheter, obesity, and the previously mentioned active cancer.

COVID-19-associated coagulopathy is a unique spectrum of changes in coagulation parameters that occur in both children and adults. They result from the simultaneous action of multiple mechanisms, including endothelial activation in the pulmonary circulation [59]. COVID-19-associated coagulopathy (CAC) is characterized by elevated D-dimers and fibrinogen levels without marked changes in platelet count and prothrombin time. This correlates with multiple complications and severity of disease course [66]. Coagulopathy associated with COVID-19 may resemble other coagulopathies e.g. sepsis-induced coagulopathy (SIC) and disseminated intravascular coagulopathy (DIC) in its course, but there are some differences. Patients with CAC initially show elevated fibrinogen levels and increased D-dimers with little change in prothrombin time and platelet count, compared to acute bacterial sepsis [87]. D-dimers in COVID-19 infection are high or very high and usually several times above the upper limit of normal. In contrast, no increase in D-dimers is observed in SIC/DIC, which is due to fibrinolytic exclusion [66].

D-dimer level is a marker of disease severity and a predictor of adverse outcomes in children, as well as adults [3, 68]. According to previous studies, an elevation in D-dimers increases the risk of developing venous thromboembolism fivefold in children. Although D-dimers are not a marker specific for COVID-19 infection, they have been included in pediatric thrombosis risk assessment guidelines based on studies in the adult population [50]. In 2020, a single-center study in Italy observed a significant difference between D-dimers in COVID-19 and MIS-C. In MIS-C cases, D-dimer values increased as the patient's clinical condition worsened and were significantly higher than in COVID-19 cases [56]. Although children have a milder course of disease and a lower risk of thrombotic complications than adults, it must be remembered that they can develop pulmonary embolism, deep vein thrombosis, thrombotic macroangiopathy, and even ischemic stroke [50].

A very interesting but rare case seems to be acute ischemic stroke occurring in patients during coronavirus disease, even shortly after birth. Beslow et al. [89] conducted a survey of 42 centers with clinical data on hospital admissions for SARS-CoV-2. Of the 971 (0.82%) pediatric patients with SARS-CoV-2, eight had an ischemic stroke (including one infant). There were however only about 30% of neonates and 60% of children with strokes screened for SARS-CoV-2, which may suggest an underestimation of stroke incidence in this population. In seven of eight patients with SARS-CoV-2, additional risk factors for stroke were identified. Patients had an infection, conformed to MIS-C criteria, or had a positive serology. There are reports of a low percentage of possible COVID-19 intrauterine infections. A crucial factor in determining the onset of infection (*in utero*, intrapartum or postpartum) is the time of sample collection and contact with the infected mother [90]. In the future,

Table I. Summary of selected works on coronary disease 2019 (COVID-19)-associated thromboembolic complications in children

Reference	Publication type	Number of patients with thrombotic incidents (age/sex)	Relation to COVID-19/ /MIS-C	Spectrum of thromboembolic complications	Thromboprophylaxis	Treatment outcomes
Zafanello et al. [9]	Systematic review	19 (9 mo — 17 yr; 10 F, 9 M)	4 MIS-C, 10 PCR test positive, 1 SARS--CoV-2 antibody positive	Arterial thrombosis in lungs, digestive tract, heart, brain, eyes, kidneys or skin	UFH in 8 studies, ASA in 3 studies, hydroxychloroquine in 2, IVIg in 1 study, and tocilizumab (8 mg/ /kg) in a patient with sickle cell disease	6 patients full clinical improvement 6 patients needed rehabilitation 1 patient with MIS-C died suddenly after hospital admission
Kavthekar et al. [16]	Case report	1 (16 yr M)	MIS-C	Multiple intracardiac thrombi and pulmonary TE	No data	Deceased (cardiac arrest)
Ouarradi et al. [17]	Case report	1 (14 yr F)	PCR test negative, SARS-CoV-2 antibody positive	Bilateral pulmonary TE	UFH + discharged with warfarin and ASA	After 2 mo disappearance of thrombi
Hameed et al. [35]	Single--center observational study	35 (6–14 yr), 4 (<5 yr), F and M)	MIS-C, PCR test negative	2 splenic infarct 1 anterior and middle cerebral artery infarct	No data	No data
Appenzeller et al. [51]	Case report	1 (21 yr M)	PCR test positive, asymptomatic COVID-19	Lower extremity DVT	No thromboprophylaxis + + discharged with oral direct factor Xa inhibitor	Heterozygous factor V Leiden mutation in thrombophilia screening. Clinical improvement after thrombectomy and angioplasty
Schroder et al. [64]	Case report	1 (17 yr M)	MIS-C	Left ventricular thrombus	Anticoagulant treatment provided	Clinical improvement
Whitworth et al. [88]	Multicenter retrospective cohort study	20/814 (11 F and 9 M; 18 patients aged 10–21, 2 patient <1 yr)	9 COVID-19, 9 MIS-C, 2 asymptomatic COVID-19	3 pulmonary TE, 7 upper extremity DVT, 5 lower extremity DVT, 3 intracardiac thrombosis, 1 cerebral sinovenous thrombosis, 1 acute ischemic stroke	11 patients with UFH, 9 patients without thromboprophylaxis	10 patients critically ill, 6 patients deceased
Tiwari et al. [91]	Case report	1 (14 yr F)	PCR test positive	Acute ischemic stroke	UFH	Continuation of psychomotor rehabilitation

MIS-C — multisystem inflammatory syndrome in children; mo — month; yr — years old; F — female; M — male; PCR — polymerase chain reaction; SARS-CoV2 — severe acute respiratory syndrome coronavirus 2; UFH — unfractionated heparin; ASA — acetylsalicylic acid; IVIg — intravenous immunoglobulin; TE — thromboembolism; DVT — deep vein thrombosis

it will be interesting to assess whether COVID-19 infection in pregnancy predisposes to an increased frequency of severe thromboembolic incidents in neonates.

Conclusions

Thromboembolic complications can be categorized as another medical condition that develops in children after COVID-1 (Table I). Adolescents over 12 years of age are particularly vulnerable, but these complications can also occur in younger children and even infants. Most often the consequences take the form of deep vein thrombosis or pulmonary embolism. Coagulopathy may develop during infection, several weeks afterwards, or in the course of MIS-C. The treatment of thrombotic complications in children includes low and high molecular weight heparins

and in some cases acetylsalicylic acid. Pediatricians and general practitioners should pay particular attention to the possibility of multiple complications of varying severity associated with COVID-19 infection in children.

Authors' contributions

AJ, MC, NC, KC, MRP — design of the study. AJ, MC, NC — literature search and analysis of data. AJ, MC, NC, KC, MRP — writing manuscript. MRP, AJ — editorial preparation of the manuscript. All authors — critical revision and final approval.

Conflict of interest

Nothing to disclose.

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Ethics

The work described in this article has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans; EU Directive 2010/63/EU for animal experiments; uniform requirements for manuscripts submitted to biomedical journals.

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