Evidence check

5 August 2020

Rapid evidence checks are based on a simplified review method and may not be entirely exhaustive, but aim to provide a balanced assessment of what is already known about a specific problem or issue. This brief has not been peer-reviewed and should not be a substitute for individual clinical judgement, nor is it an endorsed position of NSW Health.

Vascular dysfunction and COVID-19

Rapid review question

- What are the symptoms and incidence for vascular events in patients with COVID-19?

In brief

Vascular dysfunction in COVID-19 literature can be described in four main forms: thrombotic events such as deep venous thrombosis (DVT) or venous thromboembolism (VTE); thrombotic events with neurological symptoms such as stroke; systemic vasculitis; and neurovascular involvement.

- **Thrombotic vasculopathy**
  - A systematic review of 11 studies including 1,765 COVID-19 positive patients reported the occurrence of venous thromboembolism (VTE) in approximately 20% of patients.(1)
- **Cerebrovascular manifestations**
  - A systematic review has reported occurrence of stroke in 3.5% of patients based on a pooled analysis of five studies including 973 patients.(1)
  - Many patients with cerebrovascular complications have cerebrovascular risk factors, such as hypertension, diabetes mellitus, hyperlipidaemia, high BMI, smoking or previous stroke history.(2-5)
- **Systemic vasculitis**
  - An association between COVID-19 infection and novel paediatric vasculitis, named later as multisystem inflammatory syndrome in children (MIS-C) has not yet been established, due to inconsistent testing of COVID-19, although it seems plausible, given the temporal association.(6)
  - In adults, the spectrum of complications following COVID-19 is broader than in children and includes autoimmune diseases, but their incidence is low.(7) Case reports describe a wide range of clinical presentations of COVID-19 related to systemic vasculitis including cutaneous manifestations, and possible vascular involvement in remote tissues.(8-12)
- **Neurovascular involvement**
  - In a retrospective study of 214 patients with COVID-19, neurologic symptoms were seen in 36% of patients and were more common in patients with severe infection. Apart from cerebrovascular disease and impaired consciousness, most neurologic manifestations occurred early in the illness.(13)

- Involvement of vascular endothelium in hyperinflammatory pro-thrombotic state has been proposed as a possible mechanism for neurologic manifestations in patients with severe COVID-19.(13-17)

Limitations

- Testing methods for COVID-19 vary and are inconsistent across and within studies. Diagnosis of deep vein thrombosis (DVT), pulmonary embolism (PE) and venous thromboembolism (VTE) were inconsistent in the literature.(18-20) In MIS-C, case studies are reporting inconsistent testing and have described various methods to test including antibodies and/or PCR, or have raised suspicion based on history of symptoms or close contact with a positive case.(7)

Background

Vascular dysfunction, as a complication of COVID-19 disease, can have varied manifestations including multisystem inflammatory syndrome in children (MIS-C), cerebrovascular accident (CVA), deep vein thrombosis (DVT), pulmonary embolism (PE) and venous thromboembolism (VTE) and arterial thrombotic events. However, pathophysiological changes are thought to be multifactorial and not yet well understood.(21)

The mechanism behind the vasculitis has been described to include escalation from type 2 T-helper immune response (humoral immunity) to type 3 hypersensitivity (immune complex disease) state with the subsequent deposition of antigen-antibody complexes, particularly inside the walls of blood vessels, to such an extent as to generate a systemic vasculitis in the context of an immune complex disease.(22) It has been postulated that this persistent inflammatory status and high plasma levels of several proinflammatory cytokines in severe and critical COVID-19 patients act as a trigger for the coagulation cascade. Certain cytokines including interleukin-6, the key myokine from the blood vessels, activate the coagulation system and a hypercoagulable state and supress the fibrinolytic system.(23, 24) In the setting of COVID-19, pulmonary and peripheral endothelial injury due to direct viral attack might be an equally important inducer of hypercoagulation; exhibiting all components of Virchow's triad hypercoagulable state, endothelial injury, and stasis of blood flow, resulting in vascular endothelial damage and thrombus formation leading to varied manifestations described in the result section.(23, 25) Consequently, several autopsy studies have reported findings of increased prothrombotic activity in COVID-19 patients.(26-28)

Methods (Appendix 1)

PubMed search on 10 and 15 June 2020. An additional study was added after being screened for eligibility during daily evidence digest searches.

Vascular conditions included were vasculitis, including vasculitis rash, Kawasaki-like disease, pulmonary embolism, deep vein thrombosis, venous thromboembolism, neurological manifestations and symptoms related to cardiovascular accidents.

A Critical Intelligence Unit evidence check has been previously published on large vessel occlusion stroke in COVID-19 patients here.

Single case reports for all vascular conditions were not included in the review. Pathophysiology articles were excluded from inclusion of reporting articles.(19) Included studies had a focus on thrombosis as a major complication of COVID-19 patients.

Results

1. Thrombotic vasculopathy

- A systematic review of 11 studies reported occurrence of VTE in 20% of patients in a pooled cohort of 1,765 patient. There is significant heterogeneity and limitations associated with diagnostic examinations being performed in these patients, and how they are assessed for DVT and how they are tested for COVID-19.(1)
- Among COVID-19 patients, thrombotic complications are higher in critically ill patients in the ICU compared to the ward.(29) Among COVID-19 critically ill patients, middle-aged and elderly people account for the majority of strokes.(5)
- Higher levels of serum D-dimer levels have been consistently reported in severely ill COVID-19, which predict the risk of venous thromboembolism. Although, the optimal cut-off level and prognostic value are not known.(1, 30-33)
- Consensus guidelines from Jin, et al suggest close monitoring of patients with pre-existing cerebrovascular risk factors such as hypertension, diabetes mellitus, hyperlipidaemia, smoking or previous stroke history.(5)

2. Cerebrovascular manifestations

- Five studies including 973 patients had a pooled proportion of 3.5% incidence of stroke (with a reported occurrence of stroke between 2.7% and 3.8% of patients).(1)
- The timing of and results of PCR tests for COVID-19 have not been consistently reported in many studies, which is relevant to the temporal development of respiratory and neurological signs and symptoms.(19) However, acute cerebrovascular disease has been reported in the later clinical symptomatic phase, when disease enters the severe infection phase.(13, 33)
- Many patients with cerebrovascular complications have cerebrovascular risk factors, such as hypertension, diabetes mellitus, hyperlipidaemia, high BMI, smoking or previous stroke history.(2-5)
- Consensus guidelines from Jin, et al suggest close monitoring of patients with pre-existing cerebrovascular risk factors such as hypertension, diabetes mellitus, hyperlipidaemia, smoking or previous stroke history.(5)

3. Systemic vasculitis (Kawasaki-like disease, vasculitis rash)

- Multisystem inflammatory syndrome in children (MIS-C) has been reported throughout Europe and North America. The rate has been reported as 2 in 100,000 in persons <21 years of age.(34)
- According to Italian case reports, compared with classical Kawasaki disease (KD), COVID-19 patients with MIS-C were older and had gastrointestinal and meningeal signs, leukopenia with marked lymphopenia, thrombocytopenia, increased ferritin and markers of myocarditis. The presence of IgG antibody for SARS-CoV-2, which typically appears approximately two weeks after primary infection, suggests a delayed onset of paediatric MIS-C following primary infection of SARS-CoV-2.(35)
- Reports from the UK and France suggest that MIS-C following COVID-19 was more frequently found in patients of Afro-Caribbean descent, and to date, it has not been reported in Asian countries, where the incidence of Kawasaki disease is typically the highest, suggesting genetic predisposition could be a factor in the development of Kawasaki disease associated with COVID-19. (36-39)
- There are some reports of COVID-19 preceding the appearance of various autoimmune and autoinflammatory diseases, particularly in children. In adults, the spectrum of complications

following COVID-19 is broader than in children and includes autoimmune diseases, but their incidence is low. (7)

- Case reports describe a heightened immune response leading to systemic vasculitis and possible vascular involvement in remote tissues. Cutaneous manifestations include small vessel vasculitis, varicella-like exanthemas, dengue-like petechial rashes, urticarial eruptions and acro-ischemic lesions.(8-12) Many report evidence of prior COVID-19 infection, with a lag of up to a month between COVID-19 symptom onset and cutaneous lesions development.(24)

4. Neurovascular involvement and COVID-19

- In a retrospective study of 214 patients with COVID-19, neurologic symptoms were seen in 36.4% of patients and were more common in patients with severe infection (45.5%) according to their respiratory status, which included acute cerebrovascular events, impaired consciousness, and muscle injury.(13)
- Involvement of vascular endothelium in hyperinflammatory pro-thrombotic state has been proposed as a possible mechanism for neurologic manifestations in patients with severe COVID-19.(13-17)

Table 1: COVID-19 patients and thrombotic vasculopathy

Source	Summary
Peer reviewed sources	
Thrombosis Risk Associated With COVID-19 Infection. A Scoping Review Al-Ani, et al. 2020 (1)	• Eleven studies that include 1,765 patients reported the occurrence of VTE in approximately 20% of patients but with cumulative incidences up to 49% during hospitalisation. • The proportion of VTE is much higher in studies including mostly patients admitted to an intensive care unit. The estimates have a high statistical heterogeneity and there may be a risk for publication bias as suggested by a funnel plot analysis. • There were significant differences in screening strategies and definition of outcomes. • Five studies that include 973 patients with a pooled proportion of 3.5% (with a reported occurrence of stroke between 2.7% and 3.8% of patients). • Although an increase of biomarkers such as D-dimer has been consistently reported in severely ill COVID-19 patients, the optimal cut-off level and prognostic value are not known.
Venous thromboembolism and heparin use in COVID-19 patients: juggling between pragmatic choices, suggestions of medical societies and the lack of guidelines Porfridia and Pola, 2020 (40)	• This paper discusses that executing the diagnostic algorithm of utilising CTPA and D-dimer may have resulted in missing cases of PE in COVID-19 patients; COVID-19 patients staying at home with fever and respiratory symptoms for several days before being hospitalised and may have VTE at presentations. • Two studies published were on patients in ICU. A study from the Netherlands reported 27% incidence of VTE (including both DVT and PE) confirmed by computed tomography pulmonary angiography (CTPA) and/or venous ultrasonography of the legs, on a total of 184 evaluated patients. • A second study carried out in China reported a 25% incidence of DVT, assessed by venous ultrasonography of the legs, on a total of 81 evaluated patients.
Incidence of thrombotic complications in critically ill ICU patients with COVID-19 Klok, et al. 2020 (41)	• 184 patients with proven COVID-19 pneumonia who were admitted to ICU in three Dutch hospitals. • Of these patients, 23 died (13%), 22 were discharged alive (12%) and 139 (76%) were still in the ICU on 5 April 2020. • The cumulative incidence of the composite outcome was 31%, composite outcome consisted of PE, DVT, ischemic stroke, myocardial infarction or systemic arterial embolism.

Source	Summary
Peer reviewed sources	
	• Acute pulmonary embolism (PE) was the most frequent thrombotic complication (n = 25, 81%).
Venous and Arterial Thromboembolic Complications in COVID-19 Patients Admitted to an Academic Hospital in Milan, Italy Lodigiani, et al. 2020 (29)	• This study included consecutive symptomatic patients with laboratory-proven COVID-19 admitted to a university hospital in Milan, Italy. • There were 388 patients, 16% requiring intensive care (ICU). • Thromboembolic events occurred in 28 (7.7% of closed cases), corresponding to a cumulative rate of 21% (27.6% ICU, 6.6% general ward) and diagnosed within 24 hours of hospital admission. • Forty-four patients underwent VTE imaging tests and VTE was confirmed in 16 (36%). • Computed tomography pulmonary angiography (CTPA) was performed in 30 patients, corresponding to 7.7% of total, and pulmonary embolism was confirmed in 10 (33% of CTPA). • The rate of ischemic stroke and acute coronary syndrome/myocardial infarction was 2.5% and 1.1%, respectively. The high number of arterial and, in particular, venous thromboembolic events diagnosed within 24hr of admission and the high rate of positive VTE imaging tests among the few COVID-19 patients tested suggest that there is an urgent need to improve specific VTE diagnostic strategies.
Thrombotic risk in COVID-19: a case series and case–control study Stoneham, et al. 2020 (31)	• There were 21/274 (7.7%) COVID-19 patients diagnosed with VTE in this study. • Most COVID-19 patients had elevated D-dimers (56/60, 93%). However, levels were higher in patients with VTE.
High Incidence of Venous Thromboembolic Events in Anticoagulated Severe COVID-19 Patients Llitjos, et al. 2020 (2)	• Twenty-six consecutive patients with severe COVID-19 in ICU were screened for VTE. • Cumulative incidence of VTE in patients was 69% (n=18), pulmonary embolism was diagnosed in six patients (23%). • Results suggest considering both systematic screening of VTE and early therapeutic anticoagulation in severe ICU COVID-19 patients. • Patients were mostly men (n=20, 77%), had a previous history of arterial hypertension (n=22, 85%), and had an increased body mass index (median = 30.2kg/m^2, 25th-75th interquartile range [IQR]: 25.5, 33.5).

Source	Summary
Peer reviewed sources	
	• The median value of fibrinogen at admission was 7g/L (25th-75th IQR: 6.4, 7.4) and the median D-dimer value was 1750ng/mL (25th-75th IQR: 1130, 2850).
Venous Thrombosis Among Critically Ill Patients With Coronavirus Disease 2019 (COVID-19) Nahum, et al. 2020 (3)	• A total of 34 consecutive patients were included in this study. COVID-19 diagnosis was confirmed with PCR on nasopharyngeal swabs of 26 patients (76%); eight patients (24%) had a negative result on PCR but had a typical pattern of COVID-19 pneumonia on chest computed tomography scan. • Deep vein thrombosis was found in 22 patients (65%) at admission and in 27 patients (79%) when the venous ultrasonograms were performed 48 hours after ICU admission were included. • Mean (SD) age was 62.2 (8.6) years, and 25 patients (78%) were men. Major comorbidities were diabetes (15 [44%]), hypertension (13 [38%]), and obesity (mean [SD] body mass index, calculated as weight in kilograms divided by height in meters squared, 31.4 [9.0]).
Prevalence of venous thromboembolism in patients with severe novel coronavirus pneumonia Cuit, et al. (4)	• The incidence of VTE in intensive care unit of patients with severe COVID-19 was 25% (20/81). • Mean age (59.9), including 44 females (54%). • Thirty-three (41%) patients had chronic medical illness, including hypertension, diabetes and coronary heart disease, 35 (43%) patients had a history of smoking. • The level of D-dimer was a good index for predicting VTE in patients with severe COVID-19.
High risk of thrombosis in patients in severe SARS-CoV-2 infection: a multicenter prospective cohort study Helms, et al. (30)	• One hundred and fifty COVID-19 patients were included. • Sixty-four clinically relevant thrombotic complications were diagnosed. • Most patients (>95%) had elevated D-dimer and fibrinogen. • Comparison with non-COVID-19 acute respiratory distress syndrome (ARDS) patients (n=145) confirmed that COVID-19 acute respiratory distress syndrome patients (n=77) developed significantly more thrombotic complications, mainly pulmonary embolisms (11.7 vs 2.1%, p <0.008). • Despite anticoagulation, a high number of patients with ARDS secondary to COVID-19 developed life-threatening thrombotic complications.

Source	Summary
Peer reviewed sources	
Incidence and Consequences of Systemic Arterial Thrombotic Events in COVID-19 Patients Cantardor, et al. 2020 (16)	• Evidence of thrombosis is a common finding in severe COVID-19 patients. • There is very little data on the incidence and consequences of coronary, cerebrovascular and peripheral vascular thrombotic events. • In a large cohort of 1,419 COVID-19 patients, a 1% incidence was observed (stroke and TIA=8, ACS=3, acute limb ischemia=3) with total of 14 of systemic arterial thrombotic events. • Although SARS-CoV-2 infection may favour arterial thrombotic events, with grave consequences, it does not seem to be a frequent enough phenomena to warrant the need for specific systematic preventive measures.
Prevalence of Venous Thromboembolism in Critically Ill Patients with COVID-19 Hippensteel, et al. 2020 (15)	• Thrombotic complications, including venous thromboembolism (VTE), have been reported to occur in 27-69% of critically ill patients with SARS-CoV-2. • A total of 107 patients were evaluated for inclusion. Six patients were excluded as they received therapeutic anticoagulation for chronic atrial fibrillation (n=4), chronic VTE (n=2), or a mechanical heart valve (n=1). An additional 11 patients required extracorporeal membrane oxygenation (ECMO) therapy and were analysed separately for VTE presence and excluded from additional analyses. Based on these exclusions, a total of 91 patients were included in the analyses. VTE was defined by radiographic identification in the routine course of care either by doppler ultrasound of the extremities or computed tomography pulmonary angiography. Twenty-four patients (26.1%) were found to have VTE during their hospitalisation.
Scientific and Standardization Committee Communication: Clinical Guidance on the Diagnosis, Prevention and Treatment of Venous Thromboembolism in Hospitalized Patients With COVID-19.	• The diagnostic assessment of suspected VTE in hospitalised COVID-19 patients is challenging, especially for critically ill patients in whom, typically, it is important to reliably confirm or exclude VTE. • Imaging studies for deep vein thrombosis (DVT) or pulmonary embolism (PE) may be avoided due to concerns of transmitting infection in non-COVID-19 hospital wards or to healthcare workers. • The frequent finding of an elevated D-dimer in very ill hospitalised COVID-19 patients may prompt an aggressive diagnostic approach for VTE.

Source	Summary
Peer reviewed sources	
Spyropoulos, et al. 2020 (42)	
Systematic Assessment of Venous Thromboembolism in COVID-19 Patients Receiving Thromboprophylaxis: Incidence and Role of D-dimer as Predictive Factors Artifoni, et al. 2020 (43)	• In this retrospective French cohort study, patients hospitalised in medical wards with confirmed COVID-19 and adequate thromboprophylaxis were included. • A systematic low limb venous duplex ultrasonography was performed at hospital discharge or earlier if deep venous thrombosis (DVT) was clinically suspected. Chest angio-CT scan was performed when pulmonary embolism (PE) was suspected. • Of 71 patients, 16 developed VTE (22.5%) and 7 PE (10%) despite adequate thromboprophylaxis. D-dimers at baseline were significantly higher in patients with DVT ($p < 0.001$). • Demographics, comorbidities, disease manifestations, severity score and other biological parameters, including inflammatory markers, were similar in patients with and without VTE.

Table 2: Cerebrovascular accident (stroke) and neurovascular manifestations

Source	Summary
Peer reviewed sources	
Cerebrovascular Disease Is Associated with an Increased Disease Severity in Patients With Coronavirus Disease 2019 (COVID-19): A Pooled Analysis of Published Literature Aggarwal, et al. 2020 (14)	• There is a ~2.5-fold increase in odds of severe COVID-19 illness in patients with a history of cerebrovascular disease. • A total of 2,031 confirmed COVID-19 patients were included in this pooled analysis. • Four studies compared cerebrovascular disease in severe vs non-severe cases, with a sample of 1,829 confirmed COVID-19 patients (553, 30.2% being severe cases). A total number of 49 patients (2.6%) were classified as having a history of cerebrovascular disease or stroke. • Two studies with 202 patients (100, 49.5% being non-survivors) compared the rate of cerebrovascular disease in COVID-19 patients who did not survive vs survived, with 19 (9.4%) classified as non-survivors.

Source	Summary
Peer reviewed sources	
Neuropathogenesis and neurologic manifestations of the Coronaviruses in the age of Coronavirus disease 2019: A review Zubair, et al. 2020 (17)	• Although there are reports of neurological complications in patients with COVID-19, it is unclear if SARS-CoV-2 is neurotropic in humans. • Viral neuroinvasion could plausibly be achieved by several routes, including transsynaptic transfer across infected neurons, entry via the olfactory nerve, infection of vascular endothelium, or leukocyte migration across the blood-brain barrier. • The most common neurologic symptoms in COVID-19 are headache, anosmia, and ageusia. Other neurological findings include stroke, impairment of consciousness, coma, seizure and encephalopathy. • Severe cases are characterised by elevated inflammatory markers and hypercoagulability compared with moderate cases and with increased likelihood of stroke. • Infection of the vascular endothelial cells and subsequent damage to vasculature may increase the risk of ischemic and haemorrhagic infarcts.
Impact of Cerebrovascular and Cardiovascular Diseases on Mortality and Severity of COVID-19 – Systematic Review, Meta-analysis, and Meta-regression Pranata, et al. 2020 (44)	• The findings of this study showed that cerebrovascular and cardiovascular diseases were associated with an increased poor outcome in COVID-19. • The association was not influenced by gender, age, hypertension, diabetes, and respiratory comorbidities. • The association between cerebrovascular disease and poor outcome in COVID-19 patients was not affected by cardiovascular diseases and vice versa.
Clinical time course of COVID-19, its neurological manifestation and some thoughts on its management Zhou, et al. 2020 (33)	• Perspective on original research (Mao, et al), highlights that the clinical team has encountered cases of negative nucleic acid and later with confirmed diagnosis. This may be due to inadequate sampling, insensitivity of the test and sampling during the incubation period. • High index of suspicion and paying attention to clinical presentation can be very important. • Repeat nucleic acid test and/or obtain serology on antibodies of virus are warranted if a patient is suspected of COVID-19.
Neurologic Manifestations of Hospitalized Patients With	• Retrospective study of 214 patients with COVID-19, neurologic symptoms were seen in 36.4% of patients and were more common in patients with severe infection (45.5%) according to their respiratory status, which included acute cerebrovascular events, impaired consciousness, and muscle injury.

Source	Summary
Peer reviewed sources	
Coronavirus Disease 2019 in Wuhan, China Mao, et al. 2020 (13)	• Neurologic manifestations fell into three categories: central nervous system manifestations (dizziness, headache, impaired consciousness, acute cerebrovascular disease, ataxia and seizure), peripheral nervous system manifestations (taste impairment, smell impairment, vision impairment and nerve pain), and skeletal muscular injury manifestations. • Apart from cerebrovascular disease and impaired consciousness, most neurologic manifestations occurred early in the illness (median time, 1-2 days). Of the six patients with acute cerebrovascular disease, two arrived at the emergency department owing to sudden onset of hemiplegia but without any typical symptoms of COVID-19 (fever, cough, anorexia and diarrhea). • Some patients with fever and headache were admitted to the neurology ward after initially being ruled out of COVID-19 by routine blood test results and a screening lung CT in the clinic. However, several days later, they had typical COVID-19 symptoms such as cough, throat pain, lower lymphocyte count and ground-glass opacity appearance on lung CT. Their diagnosis of COVID-19 was confirmed by a positive nucleic acid test and then they were transferred to the isolation ward (testing is not consistent). • Neurovascular manifestations such as symptoms associated with central nervous system (CNS), peripheral nervous system (PNS) and skeletal muscular injury have been found to be prevalent.
Consensus for prevention and management of coronavirus disease 2019 (COVID-19) for neurologists Jin, et al. 2020 (5)	Symptoms related to the development of acute cerebrovascular diseases: • Among patients with SARS-CoV-2 infection, middle-aged and elderly people accounted for the majority of strokes, especially in critically ill patients. • Serum D-dimer level is generally increased, which could be the source of embolic vascular events. • Many of these patients may already have other cerebrovascular risk factors, such as hypertension, diabetes mellitus, hyperlipidaemia, smoking or previous stroke history. Some may develop their first-ever acute ischaemic stroke. Therefore, medical staff should pay close attention to the manifestation of neurological symptoms. • If an acute ischaemic stroke patient with suspected or confirmed diagnosis of COVID-19 are admitted, emergency treatment should be jointly offered by neurologists and infectious disease specialists. • For ischaemic stroke patients with a high D-dimer level, preventive anticoagulation is recommended. These patients should be transferred to the isolation ward and neurologists would assist in the management.

Source	Summary
Peer reviewed sources	
Coexistence of COVID-19 and Acute Ischemic Stroke Report of Four Cases Abdulkadir, et al. 2020 (45)	A case report of four patients, findings: • Diagnosis of COVID-19 and strokes were simultaneous and diagnosed using PCR and CT.
Thrombotic Neurovascular Disease in COVID-19 Patients Sweid, et al. 2020 (46)	• Case series for 14 patients. • 50.3% had neurological insult as the initial manifestation of COVID-19. The average duration between the onset of COVID-19 symptoms and the cerebrovascular insult was 3.5 days (range: 0-17). The cerebrovascular pathologies were 12 cases of acute ischemic stroke (AIS) and two cases of sinus thrombosis. • The SARS-CoV-2 is neuroinvasive and neurovirulent, it binds to ACE2 and reduces its downstream effect and induces a hyper-inflammatory response characterised by a cytokine storm. • This leads to vasculitis, increased sympathetic tone, arrhythmias and a hypercoagulable state.

Table 3: Systemic vasculitis (Kawasaki-like multisystem inflammatory syndrome)

Source	Summary
Peer reviewed sources	
Childhood Multisystem Inflammatory Syndrome – A New Challenge in the Pandemic Levin, 2020 (34)	• The CDC and WHO definitions require evidence of SARS-CoV-2 infection or exposure - a requirement that is problematic, since asymptomatic infections are common and antibody testing is neither universally available nor reliable. • MIS-C occurs 2 to 4 weeks after infection with SARS-CoV-2. • The disorder is uncommon (2 in 100,000 persons <21 years of age) as compared with SARS-CoV-2 infection diagnosed in people younger than 21 years of age over the same period (322 in 100,000).

Source	Summary
Peer reviewed sources	
	• Most patients with MIS-C have antibodies against SARS-CoV-2 and the virus is detected in a smaller proportion. • A relatively high proportion of cases have occurred among black, Hispanic, or South Asian persons. • Critical illness leading to intensive care develops in some patients, with prominent cardiac involvement and coronary-artery aneurysms in 10 to 20%.
Acute Heart Failure in Multisystem Inflammatory Syndrome in Children (MIS-C) in the Context of Global SARS-CoV-2 Pandemic Belhadjer, et al. 2020 (47)	• Report on a series of febrile paediatric patients with acute heart failure, potentially associated with SARS-CoV-2 infection and the multisystem inflammatory syndrome in children (MIS-C) as defined by the US Centers for Disease Control. Thirty-five children were identified and included in the study. • Median age at admission was 10 years (range 2-16 years). Co-morbidities were present in 28% including asthma and being overweight. • Thirty-one out of 35 (88%) patients tested positive for SARS-CoV-2 infection by PCR of nasopharyngeal swab or serology.
An outbreak of severe Kawasaki-like disease at the Italian epicentre of the SARS-CoV-2 epidemic: an observational cohort study Verdoni, et al. 2020 (35)	• Eight of ten (80%) patients were IgG positive, and three were also IgM positive for COVID-19. • Children diagnosed after the SARS-CoV-2 epidemic began and showing evidence of immune response to the virus were older, had a higher rate of cardiac involvement and features of macrophage activation syndrome (MAS). The SARS-CoV-2 epidemic was associated with high incidence of a severe form of Kawasaki disease. • Group 1 comprised 19 patients between 1 January 2015 and 17 February 2020. Group 2 included 10 patients diagnosed between 18 February and 20 April 2020; eight of 10 were positive for IgG or IgM, or both. • The two groups differed in disease incidence. Group 2 had more cardiac involvement, Kawasaki Disease Shock Syndrome, MAS and need for adjunctive steroid treatment.
Paediatric inflammatory multisystem syndrome and SARS-CoV-2 infection in children ECDC, 2020 (6)	• The presenting signs and symptoms are a mix of the ones for Kawasaki disease (KD) and toxic shock syndrome (TSS) and are characterised, among others, by fever, abdominal pain and cardiac involvement. Markers of inflammation were elevated: neutrophilia with lymphopenia, significantly increased C-reactive protein, D-dimer, IL-6 and ferritin levels and hypoalbuminaemia.

Source	Summary
Peer reviewed sources	
	• To date, an association between SARS-CoV-2 infection and this new clinical entity of multisystem inflammation has not yet been established, although an association appears plausible. • In total, about 230 suspected cases of the new paediatric inflammatory multisystem syndrome, temporally associated with SARS-CoV-2 infection (PIMS-TS) have been reported in EU/EEA countries and the UK in 2020. • Some children were positive for SARS-CoV-2 by PCR, while others were positive for IgG antibodies. COVID-19 history or COVID-19-compatible symptoms could be either elicited in the history of the child or a household member.
SARS-CoV-2-related paediatric inflammatory multisystem syndrome, an epidemiological study, France, 1 March to 17 May 2020 Belot, et al. 2020 (48)	• French surveillance data supports a causal relationship between SARS-CoV-2 infection and Paediatric Multisystem Inflammatory Syndrome (PIMS), with 95 of the 156 notified cases confirmed or probable post-COVID-19 cases. Among the 48 excluded cases, 39 presented with Kawasaki-like disease (KLD) symptoms, probably reflecting the classical Kawasaki disease. • The epidemic curve of the PIMS cases followed that of COVID-19 with a lag time of 4–5 weeks, supporting the hypothesis of PIMS being a post-infectious manifestation. • The older age and the balanced sex ratio in SARS-CoV-2-associated KLD differed to that of the classical Kawasaki disease, which mainly affects younger and male children. • Macrophage activation syndrome and seritis with systemic inflammation are infrequent in Kawasaki disease and reminiscent of other autoinflammatory diseases.
Kawasaki-like multisystem inflammatory syndrome in children during the covid-19 pandemic in Paris, France: prospective observational study Toubiana, et al. 2020 (37)	• Twenty-one children and adolescents admitted with features of Kawasaki disease over 15 days. Presentations included Kawasaki disease shock syndrome (12) and myocarditis (16). • Nineteen of 21 had evidence of recent SARS-CoV-2 infection (positive RT-PCR result in 8/21, positive IgG antibody detection in 19/21).
Multisystem Inflammatory Syndrome Related to COVID-19 in	• Among 17 patients (8 male; median age, 8 years [range, 1.8-16 years]), most were white (n=12) and previously healthy (mild asthma in 3).

Source	Summary
Peer reviewed sources	
Previously Healthy Children and Adolescents in New York City Cheung, et al. 2020 (49)	• Eight patients tested positive for SARS-CoV-2 by RT-PCR and the other nine by serology. • All patients had been discharged home with no fatalities after a mean total length of hospital stay of 7.1 (range, 3-18) days.
Gastrointestinal symptoms as a major presentation component of a novel multisystem inflammatory syndrome in children (MIS-C) that is related to COVID-19: a single center experience of 44 cases Miller, et al. 2020 (50)	• All 44 patients had either documented SARS-CoV-2 exposure, or positive RT-PCR assay or positive antibodies. • Gastrointestinal (GI) signs and symptoms appear prominently as presenting features of multisystem inflammatory syndrome in children (MIS-C). • MIS-C should thus be considered in patients with prominent GI symptoms and a history of recent SARS-CoV-2 exposure or infection.
Clinical Characteristics of 58 Children With a Pediatric Inflammatory Multisystem Syndrome Temporally Associated With SARS-CoV-2 Whittaker, et al. 2020 (51)	• Fifty-eight children (median age, 9 years [interquartile range, 5.7-14]; 33 girls [57%]) were identified and met the criteria for PIMS-TS. • Results from SARS-CoV-2 PCR tests were positive in 15 of 58 patients (26%) and SARS-CoV-2 IgG test results were positive in 40 of 46 (87%). In total, 45 of 58 patients (78%) had evidence of current or prior SARS-CoV-2 infection. • All children presented with fever and non-specific symptoms, including vomiting (26/58 [45%]), abdominal pain (31/58 [53%]), and diarrhoea (30/58 [52%]). Rash was present in 30 of 58 (52%), and conjunctival injection in 26 of 58 (45%) cases. • Laboratory evaluation was consistent with marked inflammation, for example, C-reactive protein (229mg/L [IQR, 156-338], assessed in 58 of 58) and ferritin (610µg/L [IQR, 359-1280], assessed in 53 of 58).
Multisystem Inflammatory Syndrome in Children During the Coronavirus 2019 Pandemic: A Case Series	• The study presents case series of six multisystem inflammatory syndrome in children (MIS-C) in which in addition to persistent fever, diarrhoea, and variably rash, conjunctivitis, and extremity oedema, appear to often be associated with severe illness including shock and myocardial dysfunction. MIS-C potentially driven by a disordered immunological response following SARS-CoV-2 infection.

Source	Summary
Peer reviewed sources	
Chiotos, et al. 2020 (52)	• Evidence of prior infection, including positive antibody testing for SARS-CoV-2 IgG antibodies in all but one patient (who was not tested) and weakly positive SARS-CoV-2 nasopharyngeal PCRs in three patients. None of these patients had a close contact with a documented SARS-CoV-2 infection, though these cases presented several weeks after the start of documented community transmission of SARS-CoV-2 in the UK region. • Despite the constellation of symptoms and signs that resemble features of Kawasaki disease, there are several features that *may* distinguish this syndrome based on this case series and the other published series, including prominent cardiac dysfunction with troponin leak and extremely elevated brain type natriuretic peptides (BNPs); frequent and often severe enteropathy.
Hyperinflammatory shock in children during COVID-19 pandemic Riphagen, et al. 2020 (36)	• During a period of 10 days in mid-April 2020, the study noted a cluster of eight children with hyperinflammatory shock, showing features similar to atypical Kawasaki disease, Kawasaki disease shock syndrome or toxic shock syndrome. • All children were previously fit and well. Six of the children were of Afro-Caribbean descent, and five of the children were boys. Four children had known family exposure to COVID-19.
SARS-CoV-2-Induced Kawasaki-Like Hyperinflammatory Syndrome: A Novel COVID Phenotype in Children Licciardi, et al. 2020 (53)	• This case study describes two patients with SARS-CoV-2-induced Kawasaki-like hyperinflammatory syndrome developed in the late phase of viral infection, when SARS-CoV-2 was not detectable in upper airway but they had high titres of IgG and IgM against SARS-CoV-2.
Septic shock presentation in adolescents with COVID-19 Dallan, et al. 2020 (54)	• A study of three adolescent patients. • The first patient with the final diagnosis was COVID-19-compensated septic shock. The patient re-presented to the emergency department on day three with a non-specific non-petechial pruritic maculopapular rash on the trunk and arms, without systemic symptoms, thought to be of viral aetiology, probably related to COVID-19 as SARS-CoV-2 nasopharyngeal swab PCR was positive.

Source	Summary
Peer reviewed sources	
	• The second patient was a previously healthy 10-year-old mixed-race (Asian and white) male with obesity and COVID-19 induced hypotensive septic shock associated with multiple organ dysfunction syndrome (MODS). • The third patient was a previously healthy 10-year-old black male with obesity with marked inflammatory marker elevation with lymphopenia and evidence of MODS. • Nasopharyngeal PCRs for SARS-CoV-2 was negative for patient two and three. SARS-CoV-2 infection was confirmed serologically.
Acute Myocarditis and Multisystem Inflammatory Emerging Disease Following SARS-CoV-2 Infection in Critically Ill Children Grimaud, et al. 2020 (55)	• SARS-CoV-2 PCR and serology were positive for 10 and 15 children, respectively. One child had both negative SARS-CoV-2 PCR and serology, but had a typical SARS-CoV-2 chest tomography scan. The first symptoms before PICU admission were intense abdominal pain and fever for 6 days (1-10). All children had highly elevated inflammatory markers.
Complement Associated Microvascular Injury and Thrombosis in the Pathogenesis of Severe COVID-19 Infection: A Report of Five Cases Magro et al. 2020 (56)	• Skin and lung tissues from five patients with severe COVID-19, characterised by respiratory failure (n=5) and purpuric skin rash (n=3). • Using pulmonary and cutaneous biopsy and autopsy samples from 5 individuals with severe COVID-19, some SARS-CoV-2-infected patients who become critically ill, suffered a generalised thrombotic microvascular injury. • Pathology involves at least the lung and skin, and appears mediated by intense complement activation. • Does not report clinical management or outcomes of the five patients.
Vascular skin symptoms in COVID-19: a French observational study Bouaziz, et al. 2020 (11)	• Retrospective observational nationwide study of skin lesions encountered during COVID-19 epidemic in France in an ambulatory dermatology setting. All 14 patients had previously PCR confirmed COVID-19 infection, using on samples collected using nasopharyngeal swabs. Skin symptoms started a few days after first COVID-19 general symptoms unless specified.
Autoimmune and inflammatory diseases following COVID-19	• Emerging reports show that severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection precedes the appearance of various autoimmune and autoinflammatory diseases.

Source	Summary
Peer reviewed sources	
Galeotti, et al. 2020 (7)	• The clinical history of patients with PIMS suggests that many had previously experienced mild symptoms of COVID-19 or had contact with COVID-19-positive family members. • In adults, the spectrum of complications following COVID-19 is broader than in children and includes autoimmune diseases but their incidence is very rare. • Although a causal link between SARS-CoV-2 and the appearance of autoimmune and autoinflammatory diseases has not yet been firmly established, it is suggested by the temporal association with the current COVID-19 pandemic and the history of exposure of affected patients to SARS-CoV-2.

Appendix

PubMed search terms

((((2019-nCoV[title/abstract] or nCoV*[title/abstract] or covid-19[title/abstract] or covid19[title/abstract] OR "covid 19"[title/abstract] OR "coronavirus"[MeSH Terms] OR "coronavirus"[title/abstract] OR sarscov-2[title/abstract] OR “severe acute respiratory syndrome coronavirus 2”[Supplementary Concept])) AND ((('multisystem inflammatory syndrome') OR (Kawasaki-like'[Title/Abstract])) OR (vasculitis[Title/Abstract]))

((((2019-nCoV[title/abstract] or nCoV*[title/abstract] or covid-19[title/abstract] or covid19[title/abstract] OR "covid 19"[title/abstract] OR "coronavirus"[MeSH Terms] OR "coronavirus"[title/abstract] OR sarscov-2[title/abstract] OR “severe acute respiratory syndrome coronavirus 2”[Supplementary Concept])) AND "stroke"[Title/Abstract] (2019:2020[pdat]

((((2019-nCoV[title/abstract] or nCoV*[title/abstract] or covid-19[title/abstract] or covid19[title/abstract] OR "covid 19"[title/abstract] OR "coronavirus"[MeSH Terms] OR "coronavirus"[title/abstract] OR sarscov-2[title/abstract] OR “severe acute respiratory syndrome coronavirus 2”[Supplementary Concept])) AND "neurological symptoms"[Title/Abstract]

((((2019-nCoV"[Title/Abstract] OR "ncov*"[Title/Abstract]) OR "covid-19"[Title/Abstract]) OR "covid19"[Title/Abstract]) OR "covid-19"[Title/Abstract]) OR "coronavirus"[MeSH Terms]) OR "coronavirus"[Title/Abstract]) OR "sarscov-2"[Title/Abstract]) OR "severe acute respiratory syndrome coronavirus 2"[Supplementary Concept])) AND ("incidence"[All Fields] OR "prevalence"[All Fields]) ("pulmonary embolism"[All Fields] OR "pe"[All Fields]))

(("2019-nCoV"[Title/Abstract] OR "ncov*"[Title/Abstract] OR "covid-19"[Title/Abstract] OR "covid19"[Title/Abstract] OR "covid-19"[Title/Abstract] OR "coronavirus"[MeSH Terms] OR "coronavirus"[Title/Abstract] OR "sarscov-2"[Title/Abstract] OR "severe acute respiratory syndrome coronavirus 2"[Supplementary Concept])) AND ((DVT[Title/Abstract] OR "Deep vein thrombosis"[Title/Abstract] OR "Venous thromboembolism"[Title/Abstract] OR VTE[Title/Abstract])) Filters: from 2019 - 2020

References

1. Al-Ani F, Chehade S, Lazo-Langner A. Thrombosis risk associated with COVID-19 infection. A scoping review. Thrombosis research. 2020;192:152-60.
2. Llitjos JF, Leclerc M, Chochois C, Monsallier JM, Ramakers M, Auvray M, et al. High incidence of venous thromboembolic events in anticoagulated severe COVID-19 patients. Journal of Thrombosis and Haemostasis. 2020;18(7):1743-1746. doi:10.1111/jth.14869.
3. Nahum J, Morichau-Beauchant T, Daviaud F, Echegut P, Fichet J, Maillet J-M, et al. Venous Thrombosis Among Critically Ill Patients With Coronavirus Disease 2019 (COVID-19). JAMA Network Open. 2020;3(5):e2010478-e.
4. Cui S, Chen S, Li X, Liu S, Wang F. Prevalence of venous thromboembolism in patients with severe novel coronavirus pneumonia. Journal of Thrombosis and Haemostasis. 2020;18(6):1421-4.
5. Jin H, Hong C, Chen S, Zhou Y, Wang Y, Mao L, et al. Consensus for prevention and management of coronavirus disease 2019 (COVID-19) for neurologists. Stroke and vascular neurology. 2020:svn-2020-000382.
6. European Centre for Disease Prevention and Control. Paediatric inflammatory multisystem syndrome and SARS-CoV-2 infection in children. Solna: ECDC; 2020.

7. Galeotti C, Bayry J. Autoimmune and inflammatory diseases following COVID-19. Nat Rev Rheumatol. 2020:1-2.

8. de Perosanz-Lobo D, Fernandez-Nieto D, Burgos-Blasco P, Selda-Enriquez G, Carretero I, Moreno C, et al. Urticarial vasculitis in COVID-19 infection: a vasculopathy-related symptom? J Eur Acad Dermatol Venereol. 2020.
9. Vanegas Ramirez A, Efe D, Fischer M. Drug-induced vasculitis in a patient with COVID-19. Journal of the European Academy of Dermatology and Venereology. 2020. DOI: 10.1111/jdv.16588.
10. Joob B, Wiwanitkit V. Chilblains-like lesions and COVID-19. Pediatr Dermatol. 2020;37. DOI: 10.1111/pde.14238.
11. Bouaziz JD, Duong T, Jachiet M, Velter C, Lestang P, Cassius C, et al. Vascular skin symptoms in COVID-19: a french observational study. Journal of the European Academy of Dermatology and Venereology. 2020:10.1111/jdv.16544.
12. Castelnovo L, Capelli F, Tamburello A, Faggioli PM, Mazzone A. Symmetric cutaneous vasculitis in COVID-19 pneumonia. Journal of the European Academy of Dermatology and Venereology. 2020:10.1111/jdv.16589.
13. Mao L, Jin H, Wang M, Hu Y, Chen S, He Q, et al. Neurologic manifestations of hospitalized patients with coronavirus disease 2019 in Wuhan, China. JAMA neurology. 2020.
14. Aggarwal G, Lippi G, Michael Henry B. Cerebrovascular disease is associated with an increased disease severity in patients with Coronavirus Disease 2019 (COVID-19): A pooled analysis of published literature. International journal of stroke : official journal of the International Stroke Society. 2020;15(4):385-9.
15. Hippensteel JA, Burnham EL, Jolley SE. Prevalence of Venous Thromboembolism in Critically Ill Patients with COVID-19. British Journal of Haematology. 2020. DOI: 10.1111/bjh.16908.
16. Cantador E, Núñez A, Sobrino P, Espejo V, Fabia L, Vela L, et al. Incidence and consequences of systemic arterial thrombotic events in COVID-19 patients. Journal of thrombosis and thrombolysis. 2020:1-5.
17. Zubair AS, McAlpine LS, Gardin T, Farhadian S, Kuruvilla DE, Spudich S. Neuropathogenesis and Neurologic Manifestations of the Coronaviruses in the Age of Coronavirus Disease 2019: A Review. JAMA Neurology. 2020. DOI:10.1001/jamaneurol.2020.2065.
18. Tal S, Spectre G, Kornowski R, Perl L. Venous Thromboembolism Complicated with COVID-19: What Do We Know So Far? Acta Haematologica. 2020. DOI: 10.1159/000508233.
19. Romoli M, Jelcic I, Bernard-Valnet R, García Azorín D, Mancinelli L, Akhvlediani T, et al. A systematic review of neurological manifestations of SARS-CoV-2 infection: the devil is hidden in the details. European Journal of Neurology. 2020. DOI:10.1111/ene.14382.
20. World Health Organization. Multisystem inflammatory syndrome in children and adolescents with COVID-19 Scientific brief. Geneva: WHO; 2020.
21. Becker RC. COVID-19 update: Covid-19-associated coagulopathy. Journal of Thrombosis and Thrombolysis. 2020:1-14.
22. Roncati L, Ligabue G, Fabbiani L, Malagoli C, Gallo G, Lusenti B, et al. Type 3 hypersensitivity in COVID-19 vasculitis. Clinical Immunology. 2020:108487.
23. Moores LK, Tritschler T, Brosnahan S, Carrier M, Collen JF, Doerschug K, et al. Prevention, diagnosis and treatment of venous thromboembolism in patients with COVID-19: CHEST Guideline and Expert Panel Report. Chest. 2020.
24. Mayor-Ibarguren A, Feito-Rodriguez M, Quintana Castanedo L, Ruiz-Bravo E, Montero Vega D, Herranz-Pinto P. Cutaneous small vessel vasculitis secondary to COVID-19 infection: A case report. Journal of the European Academy of Dermatology and Venereology.2002. DOI:10.1111/jdv.16670.
25. Cao W, Li T. COVID-19: towards understanding of pathogenesis. Cell Research. 2020;30(5):367-9.
26. Ackermann M, Verleden SE, Kuehnel M, Haverich A, Welte T, Laenger F, et al. Pulmonary Vascular Endothelialitis, Thrombosis, and Angiogenesis in Covid-19. N Engl J Med. 2020; 383:120-128 DOI: 10.1056/NEJMoa2015432.
27. Wichmann D, Sperhake JP, Lütgehetmann M, Steurer S, Edler C, Heinemann A, et al. Autopsy Findings and Venous Thromboembolism in Patients With COVID-19. Ann Intern Med. 2020. DOI: 10.7326/M20-2003.

28. Lax SF, Skok K, Zechner P, Kessler HH, Kaufmann N, Koelblinger C, et al. Pulmonary arterial thrombosis in COVID-19 with fatal outcome: results from a prospective, single-center, clinicopathologic case series. Annals of Internal Medicine. 2020. DOI: 10.7326/M20-2566.
29. Lodigiani C, Iapichino G, Carenzo L, Cecconi M, Ferrazzi P, Sebastian T, et al. Venous and arterial thromboembolic complications in COVID-19 patients admitted to an academic hospital in Milan, Italy. Thromb Res. 2020;191:9-14.
30. Helms J, Tacquard C, Severac F, Leonard-Lorant I, Ohana M, Delabranche X, et al. High risk of thrombosis in patients with severe SARS-CoV-2 infection: a multicenter prospective cohort study. Intensive Care Med. 2020;46(6):1089-98.
31. Stoneham SM, Milne KM, Nuttal E, Frew GH, Sturrock BR, Sivaloganathan H, et al. Thrombotic risk in COVID-19: a case series and case–control study. Clinical Medicine. 2020. DOI: https://doi.org/10.7861/clinmed.2020-0228
32. Artifoni M, Danic G, Gautier G, Gicquel P, Boutoille D, Raffi F, et al. Systematic assessment of venous thromboembolism in COVID-19 patients receiving thromboprophylaxis: incidence and role of D-dimer as predictive factors. Journal of Thrombosis and Thrombolysis. 2020:1.
33. Zhou Y, Li W, Wang D, Mao L, Jin H, Li Y, et al. Clinical time course of COVID-19, its neurological manifestation and some thoughts on its management. Stroke and Vascular Neurology. 2020. DOI: 10.1136/svn-2020-000398.
34. Levin M. Childhood Multisystem Inflammatory Syndrome — A New Challenge in the Pandemic. New England Journal of Medicine. 2020. DOI: 10.1056/NEJMe2023158.
35. Verdoni L, Mazza A, Gervasoni A, Martelli L, Ruggeri M, Ciuffreda M, et al. An outbreak of severe Kawasaki-like disease at the Italian epicentre of the SARS-CoV-2 epidemic: an observational cohort study. The Lancet. 2020. DOI:https://doi.org/10.1016/S0140-6736(20)31103-X.
36. Riphagen S, Gomez X, Gonzalez-Martinez C, Wilkinson N, Theocharis P. Hyperinflammatory shock in children during COVID-19 pandemic. The Lancet. 2020;395(10237):1607-8.
37. Toubiana J, Poirault C, Corsia A, Bajolle F, Fourgeaud J, Angoulvant F, et al. Outbreak of Kawasaki disease in children during COVID-19 pandemic: a prospective observational study in Paris, France. medRxiv. 2020. DOI: 10.1101/2020.05.10.20097394.
38. Kim YJ, Park H, Choi YY, Kim YK, Yoon Y, Kim KR, et al. Defining Association between COVID-19 and the Multisystem Inflammatory Syndrome in Children through the Pandemic. J Korean Med Sci. 2020;35(22):e204-e.
39. Xu S, Chen M, Weng J. COVID-19 and Kawasaki disease in children. Pharmacol Res. 2020;159:104951-.
40. Porfidia A, Pola R. Venous thromboembolism and heparin use in COVID-19 patients: juggling between pragmatic choices, suggestions of medical societies. Springer; 2020.
41. Klok F, Kruip M, Van der Meer N, Arbous M, Gommers D, Kant K, et al. Incidence of thrombotic complications in critically ill ICU patients with COVID-19. Thrombosis research. 2020. DOI: 10.1016/j.thromres.2020.04.013.
42. Spyropoulos AC, Levy JH, Ageno W, Connors JM, Hunt BJ, Iba T, et al. Scientific and Standardization Committee Communication: Clinical Guidance on the Diagnosis, Prevention and Treatment of Venous Thromboembolism in Hospitalized Patients with COVID-19. Journal of thrombosis and haemostasis. 2020. DOI: 10.1111/jth.14929.
43. Artifoni M, Danic G, Gautier G, Gicquel P, Boutoille D, Raffi F, et al. Systematic assessment of venous thromboembolism in COVID-19 patients receiving thromboprophylaxis: incidence and role of D-dimer as predictive factors. Journal of thrombosis and thrombolysis. 2020:1-6.
44. Pranata R, Huang I, Lim M, Wahjoepramono P, July J. Impact of Cerebrovascular and Cardiovascular Diseases on Mortality and Severity of COVID-19 – Systematic Review, Meta-analysis, and Meta-regression. Journal of Stroke and Cerebrovascular Diseases. 2020;29:104949.
45. Abdulkadir T, ÜNLÜBAŞ Y, ALEMDAR M, AKYÜZ E. Coexistence of COVID-19 and acute ischemic stroke report of four cases. Journal of Clinical Neuroscience. 2020;77:227-229. DOI: 10.1016/j.jocn.2020.05.018.
46. Sweid A, Hammoud B, Weinberg JH, Oneissi M, Raz E, Shapiro M, et al. Thrombotic Neurovascular Disease in COVID-19 Patients. Neurosurgery. 2020.

47. Belhadjer Z, Méot M, Bajolle F, Khraiche D, Legendre A, Abakka S, et al. Acute heart failure in multisystem inflammatory syndrome in children (MIS-C) in the context of global SARS-CoV-2 pandemic. Circulation. 2020. DOI: 10.1161/CIRCULATIONAHA.120.048360.
48. Belot A, Antona D, Renolleau S, Javouhey E, Hentgen V, Angoulvant F, et al. SARS-CoV-2-related paediatric inflammatory multisystem syndrome, an epidemiological study, France, 1 March to 17 May 2020. Eurosurveillance. 2020;25(22):2001010.
49. Cheung EW, Zachariah P, Gorelik M, Boneparth A, Kernie SG, Orange JS, et al. Multisystem Inflammatory Syndrome Related to COVID-19 in Previously Healthy Children and Adolescents in New York City. JAMA. 2020;324(3):294-296. doi:10.1001/jama.2020.10374.
50. Miller J, Cantor A, Zachariah P, Ahn D, Martinez M, Margolis K. Gastrointestinal symptoms as a major presentation component of a novel multisystem inflammatory syndrome in children (MIS-C) that is related to COVID-19: a single center experience of 44 cases. Gastroenterology. 2020.
51. Whittaker E, Bamford A, Kenny J, Kaforou M, Jones CE, Shah P, et al. Clinical Characteristics of 58 Children With a Pediatric Inflammatory Multisystem Syndrome Temporally Associated With SARS-CoV-2. JAMA. 2020;324(3):259-269. DOI:10.1001/jama.2020.10369.
52. Chiotos K, Bassiri H, Behrens EM, Blatz AM, Chang J, Diorio C, et al. Multisystem Inflammatory Syndrome in Children during the COVID-19 pandemic: a case series. Journal of the Pediatric Infectious Diseases Society. 2020;9(3);393-398. DOI: 10.1093/jpids/piaa069.
53. Licciardi F, Pruccoli G, Denina M, Parodi E, Taglietto M, Rosati S, et al. SARS-CoV-2-Induced Kawasaki-Like Hyperinflammatory Syndrome: A Novel COVID Phenotype in Children. Pediatrics. 2020:2020-1711.
54. Dallan C, Romano F, Siebert J, Politi S, Lacroix L, Sahyoun C. Septic shock presentation in adolescents with COVID-19. The Lancet Child & Adolescent Health. 2020;4(7):479-554.
55. Grimaud M, Starck J, Levy M, Marais C, Chareyre J, Khraiche D, et al. Acute myocarditis and multisystem inflammatory emerging disease following SARS-CoV-2 infection in critically ill children. Ann Intensive Care. 2020;10(1):69-.
56. Magro C, Mulvey JJ, Berlin D, Nuovo G, Salvatore S, Harp J, et al. Complement associated microvascular injury and thrombosis in the pathogenesis of severe COVID-19 infection: a report of five cases. Translational Research. 2020;220:1-13. doi:10.1016/j.trsl.2020.04.007.

Evidence checks are archived a year after the date of publication

SHPN: (ACI) 210321 | ISBN: 978-1-76081-714-5 | TRIM: ACI/D20/2511-18