RAPID COMMUNICATION

Epidemiologic and clinical characteristics of multisystem inflammatory syndrome in adults: a rapid review

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Abstract

Multisystem inflammatory disease in children (MIS-C) is one of the severe presentations of the coronavirus disease 2019 (COVID-19) that has been described in the literature since the beginning of the pandemic. Although MIS-C refers to children, cases with similar clinical characteristics have been recently described in adults. A description of the epidemiologic and clinical characteristics of multisystem inflammatory disease in adults (MIS-A) is a starting point for better knowledge and understanding of this emerging disease.

We identified nine case reports of MIS-A in the literature, five from the United States, two from France and two from the United Kingdom. The case descriptions revealed similarities in clinical features, including occurrence during post-acute disease phase, fever, digestive symptoms, cardiac involvement and elevated inflammatory markers. All the patients were hospitalized, three required admission to the intensive care unit and one died. The most common treatments were intravenous immunoglobulin, prednisolone and aspirin.

These findings suggest that MIS-A is a severe complication of COVID-19 disease that can lead to death. Further studies to improve our understanding of the pathogenesis of MIS-A, which will help improve treatment decisions and prevent sequelae or death.

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Introduction

The coronavirus disease 2019 (COVID-19) is a novel disease resulting from infection by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (1). As of May 29, 2021, the virus has infected more than 170 million people and caused more than 3.5 million deaths worldwide (2).

The clinical characteristics of COVID-19 disease vary from asymptomatic to severe. The most common symptoms are fever, cough, diarrhea and dyspnea (3). There are three clinical stages (4). The first stage is characterized by infection with SARS-CoV-2, with flu-like symptoms in certain cases. The second stage, characterized by viral pneumonia, possibly combined with pulmonary inflammation and coagulopathy, can require hospitalization and even mechanical ventilation. The third stage of the disease is characterized by fibrosis.

Multisystem inflammatory syndrome has been widely reported in children (5) and, more recently, in adults (6). In children, multisystem inflammatory syndrome (MIS-C) is a severe presentation that has been described in the literature since the beginning of the pandemic. Although MIS-C is defined as restricted to children, similar clinical characteristics have been described in adults. Knowing the epidemiologic and clinical characteristics of multisystem inflammatory syndrome cases in adults (MIS-A) provides a starting point to a better understanding of this emerging disease.

Methods

A database at the Public Health Agency of Canada is populated daily with new COVID-19 literature using standardized algorithms [e.g. "COVID-19" OR "SARS-CoV-2" OR "SARS-Coronoavirus-2"

OR "nCov" OR "novel CoV" OR ("novel AND coronavirus")] tailored to each searched database, that is, PubMed, Scopus, BioRxiv, MedRxiv, ArXiv, SSRN and Research Square. The literature is cross-referenced with the COVID-19 information centres run by the Lancet, the BMJ, Elsevier and Wiley.

Our search through the Public Health Agency of Canada database included studies published in English since the start of the pandemic until November 13, 2020. We gathered details about COVID-19–related studies in a RefWorks database and an Excel spreadsheet that are searchable by topic. Search terms used to retrieve the MIS-A literature from titles and abstracts in the Excel spreadsheet included "MIS-A," "Kawasaki," "multisystem inflam*," "multi-system inflam*," "inflammatory multisystem," "inflammatory multi-system," "inflammatory disease," "Kawasaki-like" and "COVID-19 linked disease." We screened articles (n=314) for relevance and included those that described MIS-A with a COVID-19 link (see **Appendix A** and **Appendix B**). We excluded paediatric cases and studies with cases similar to a MIS-A, but not formally diagnosed as MIS-A as per the authors. Since MIS-A is an emerging disease, a case definition does not yet exist. Authors of studies included in this review based case selection on the definition of MIS-C, while excluding the age criteria (see **Appendix C**).

Results

We identified nine case reports of MIS-A in the literature, five in the United States, two in France and two in the United Kingdom.

All nine cases of MIS-A occurred in relatively young adults, with a median age of 31 years (interquartile range [IQR]=25–45 years). Six patients were male (6–11). Six studies reported ethnicity: three patients were of African origin or African American (6,8,12), two were of Hispanic origin (11,13) and one was White (10). Seven out of nine studies reported on comorbidity. Two patients had both hypertension and obesity (6,12); one of these patients also had diabetes (12). Four patients had no known comorbidities (7,8,10,13); in three cases the comorbidity status was not reported (7,9,14).

All nine patients underwent a reverse transcription polymerase chain reaction (RT-PCR) test for COVID-19. Five had negative RT-PCR results but positive serology tests (6–8,10,13). One had a negative RT-PCR result despite having had a positive RT-PCR result a few days earlier (12). The results of RT-PCR swab test and serology were both positive in one case (14). The two remaining patients had a positive RT-PCR test but did not have serology tests (9,11). These findings suggested that MIS-A probably occurred during the post-acute phase of the disease.

All the patients presented with fever. Seven had a fever for 5 to 7 days prior to hospital admission, while two did not report fever duration. Most (n=7) had digestive symptoms upon admission (7,9–14), with the most common diarrhea (n=6), followed by vomiting (n=4) and bilateral enlarged parotid glands (n=1). Rash (n=4) (8–10,14) and neck pain (n=3) (11–13) with or without lymphadenopathy were also common.

There was multi-organ effect in all cases. Involvement of the cardiovascular system was the most common (n=7) (6,7,10,12–15) and was documented via echocardiography in four cases. The four cases had an acute myocardial dysfunction with left ventricular systolic dysfunction and pericardial effusion. Two had ventricular fibrillation (11,12) and two other a dilated inferior vena cava (10,14). One of these patients also had overloaded right ventricular pressure and mild enlargement of the main pulmonary artery and hyperkinetic left ventricle (14).

The other manifestations were digestive (n=7) (7,9–14), ophthalmic (n=6) (8–11,13,14), renal (n=4) (6,11,12,14), dermatologic (n=5) (6,8–10,13), pulmonary (n=2) (7,12) and neurologic (n=1) (6).

C-reactive protein (CRP) test results and lymphocyte counts were reported in eight cases, and D-dimers and troponin in six cases. All cases had elevated inflammatory markers. The inflammatory markers that were most commonly elevated were CRP (n=8) (6,7,9–14), followed by D-dimers (n=6) (7,9,11–14) and troponin (n=6) (6–11). Lymphopenia was also common (n=6) (7–9,11,12,14). Three authors excluded rheumatic disease, HIV and hepatitis infection (9,11,13).

Intravenous immunoglobulin (IVIG; n=4) (8,9,11,14), prednisolone (n=3) (8,9,13) and aspirin (n=3) (7,13,14) were the most common treatments. Immunoglobulin was not given in one case because the patient responded well to aspirin (7). In another case, prednisolone was not provided because the patient had a concomitant tracheal aspiration positive for *Klebsiella aerogenes* (syn: *Enterobacter aerogenes*) that was then treated with trimethoprim sulfamethoxazole (6). One patient did not receive any specific treatment; she died while being evaluated for admission (12).

Of the nine patients, one died (12) and the outcome of another was not reported (9). Three patients had severe symptoms, requiring admission to the intensive care unit (ICU), but recovered (6,7,14). Two patients presented with hypotension and tachycardia upon admission but did not require admission to ICU and recovered (11,13). One patient presented with vasoplegic shock upon admission, had a length of stay in hospital of eight days and recovered under treatment (8). One case did not demonstrate shock-like signs and recovered under treatment (9). The case that died had been previously hospitalized for COVID-19 and discharged 12 days earlier; upon readmission she presented with rapid onset of fever and developed hemodynamic instability and ventricular fibrillation and could not be resuscitated.

Discussion

MIS-A appears to be a rare complication of COVID-19 disease. The RT-PCR and serology results and the absence of pulmonary involvement in most cases are consistent with MIS-A occurring during the post-acute phase of COVID-19 disease.

The clinical characteristics of MIS-A share similarities with MIS-C. The pathogenesis of MIS-C involves immune dysregulation similar to Kawasaki disease, macrophage activation syndrome (MAS) and cytokine release syndrome (16,17). Kawasaki disease is theorized to be from an aberrant immune response to a possible infectious trigger; it is described in children and less often in adults (15,18). In the case of MIS-A, the pathogenesis is not fully understood (19). Endothelial damage seems to have led to serious complications with multi-organ involvement in the reported cases (12). This process probably occurs post-infection based on the timing of the rise of MIS-C cases and peak of COVID-19 in the communities in which these cases were found (16,17).

While we identified some common features, the clinical presentations in the case reports of the MIS-A patients varied. For example, ophthalmologic signs (9) were predominant in one case and cardiac signs in another (6). Further studies are required on MIS-C pathophysiology and how it contributes to MIS-A pathogenesis.

The approach to management of children with MIS-C is evolving; management does require multidisciplinary care and a case-by-case approach. Since MIS-C is most likely a post-infectious complication rather than an active infection, the role of antivirals is not clear (20). Those that meet the criteria for Kawasaki disease may benefit from IVIG, as might those with moderate to severe MIS-C (20). Patients who may benefit from this treatment may include those with cardiac involvement or in shock states. Steroids might be considered for those who have severe or refractory shock (20). Other adjunctive therapies (IL-1 inhibitors or convalescent plasma) and their place in the treatment of MIS-C is uncertain (20). How these treatment options can be applied to MIS-A patients is also currently unknown. We need further studies outside of controlled clinical trials to ascertain the role of IVIG, steroids and other immunomodulatory agents in treating suspected cases of MIS-A (21).

Limitations

We based this current review on nine case reports from three countries. Although case reports can help in identifying new trends or diseases, there are limitations. Information from the case reports is difficult to generalize because patients have different backgrounds and are not representative of the population.

Currently, there is no case definition for MIS-A. Using the MIS-C case definition (minus age) has its challenges, as there are at least four definitions (see Appendix C). In addition, how each case met the definition was not always clear. For example, authors of the case reports did not always specify how they excluded all other potential causes of the multisystem inflammatory syndrome or report the duration of fever or presence of comorbidities. There was also a lack of information about ethnicity and severity of the disease. For example, when hypotension was identified, the presence or absence of shock-like syndrome was not always specified.

These are preliminary findings; additional studies will lead to a better understanding of common epidemiologic and clinical characteristics of this condition.

Conclusion

The case descriptions revealed similarities in clinical features such as fever, digestive symptoms, cardiac involvement and elevated inflammatory markers. The RT-PCR and serology results and the absence of pulmonary involvement suggest that MIS-A occurred during the post-acute phase of COVID-19 disease. All patients were hospitalized, three required admission to the ICU and one died. The most common treatments were IVIG, prednisolone and aspirin.

The findings suggest that MIS-A is a severe complication of COVID-19 disease that can lead to death. Early recognition of MIS-A may improve outcomes. A case definition for MIS-A is needed to help standardize reporting and facilitate disease recognition. Further studies to improve our understanding of pathogenesis of MIS-A will help improve treatment decisions and prevent sequelae and death.

Authors' statement

NA — Methodology, investigation, writing–original draft
RE — Conceptualization, writing–review and editing, supervision
MS — Writing–review and editing
LW — Writing–review and editing
NB — Writing–review and editing
TD — Writing–review and editing

Competing interests

None.

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Appendices

Appendix A: Comparison of nine MIS-A cases in the COVID-19 literature published up to November 2020

Patient/studies characteristics		Boudhabhay *et al.*, 2020 (6)	Chowdhary *et al.*, 2021 (7)	Fox *et al.*, 2020 (12)	Jones *et al.*, 2020 (8)	Kofman 2020 (14)	Lidder *et al.*, 2020 (9)	Moghadam *et al.*, 2020 (10)	Sokolovsky *et al.*, 2020 (13)	Shaigany *et al.*, 2020 (11)
Background	Ethnicity	African	NR	African American	African	NR	NR	White	Hispanic	Hispanic
	Age, years	46	26	31	21	25	45	21	36	45
	Sex	Male	Male	Female	Male	Female	Male	Male	Female	Male
	Presence of comorbidity	X	NR	X	NR	–	–	NR	–	–
Symptoms and system/organ involved	Fever	X	X	X	X	–	X	X	X	X
	Cardiovascular	X	X	X	–	X	X	X	X	X
	Digestive	–	X	X	–	X	X	X	X	X
	Ophthalmic	–	–	–	X	X	X	X	X	X
	Renal	X	–	X	–	X	–	–	–	X
	Dermatologic	X	–	–	X	–	X	X	X	–
	Pulmonary	–	X	X	–	–	–	–	–	–
	Neurologic	X	–	–	–	–	–	–	–	–
RT-PCR and serology test results	RT-PCR	Negative	Negative	Negative	Negative	Positive	Positive	Negative	Negative	Positive
	Serology	Positive	Positive	NR	Positive	Positive	NR	Positive	Positive	NR
Elevated inflammatory markers and lymphopenia	CRP	X	X	X	NR	X	X	X	X	X
	Troponin	X	X	NR	X	–	X	X	NR	X
	D-dimers	NR	X	X	NR	X	X	NR	X	X
	Lymphopenia	NR	X	X	X	X	X	–	–	X
Exclusion of other infective and inflammatory conditions		NR	NR	NR	X	NR	X	X	X	X
Treatment	Immunoglobulin	–	–	–	X	X	X	–	–	X
	Prednisolone	–	–	–	X	–	X	–	X	–
	Aspirin	–	X	–	–	X	–	–	X	–
Outcome		Recovery	Recovery	Death	Recovery	Recovery	NR	Recovery	Recovery	Recovery

Abbreviations: CRP, C-reactive protein; NR, not reported; RT-PCR, reverse transcription polymerase chain reaction; –, not present characteristic; X, reported as present

Appendix B: Summary of case reports on multisystem inflammatory syndrome in adults (MIS-A) (n=9)

Case report/ demographic characteristics and past medical history	MIS-A clinical and laboratory characteristics	Treatment/severity and outcome
Boudhabhay *et al.*, 2020 (6) France 16 September 2020 The patient was a 46-year-old male of African descent with a history of hypertension and obesity	Fever and other signs and symptoms: • Admitted for hypertensive emergency (189/123 mmHg) and fever (duration not reported) Evidence of coagulopathy and renal involvement: • Acute kidney injury: Serum creatinine (sCr) level was 169 µmol/L associated with 1 g/day proteinuria, aseptic pyuria, no hematuria and low natriuresis (<20 mmol/L) • Renal biopsy light microscopy revealed typical lesions of thrombotic microangiopathy (TMA) including fibrin thrombi within glomeruli and myxoid intimal alterations of arterioles and small to medium-sized renal arteries • On Day 4, the patient presented evanescent facial erythema and developed acute myocardial dysfunction with reduced left ventricular ejection fraction to 40%, pericardial effusion • On Day 5, the patient presented with neurologic impairment. Abnormal supratentorial periventricular magnetic resonance imaging (MRI) signals responsible for a restriction of the diffusion due to an acute vasculitis PCR and serology for SARS-CoV-2: • RT-PCR negative, IgM negative and IgG positive (no previous COVID-19 symptoms were reported) Inflammatory markers: • CRP level was 312 mg/L • Thrombocytopenia: neutrophil count was 18.7 × 10^9/L • High sensitive troponin (hsTroponin) elevation	• No immunosuppressive treatment was introduced because of concomitant tracheal aspiration positive for *Klebsiella aerogenes* treated with trimethoprim sulfamethoxazole • Dobutamine and renal replacement therapy (RRT) • Specific complement inhibition with eculizumab therapy (900 mg) • On Day 5 of hospitalization, neurologic impairment presented with coma leading to intubation and mechanical ventilation The patient was discharged after 30 days in hospital
Chowdhary *et al.*, 2021 (7) United Kingdom September 2020 The patient was a 26-year-old male Ethnicity was not reported The presence or absence of comorbidity was not reported Exposure to SARS-CoV-2 was reported	Fever and other signs and symptoms: • Patient was admitted after five days of fever • Dry cough, myalgia, diarrhea, vomiting and abdominal pain • Patient was hypotensive and hypoxic upon admission One or more organs involved (pulmonary, cardiac, digestive): • CT showed bilateral pulmonary basal ground-glass changes and bowel edema • Initial transthoracic echocardiography demonstrated severe left ventricular systolic dysfunction with pericardial effusion • CT of the abdomen demonstrating mesenteric lymphadenopathy and small bowel edema PCR and serology for SARS-CoV-2: • RT-PCR negative, IgG and IgM positive serology Inflammatory markers: • CRP: 419 mg/L • Ferritin: 3,275 lg/L (normal <322 µg/L) • Procalcitonin: 164 lg/L (normal <50 µg/L) • Troponin I: 2,030 ng/L (normal <57 ng/L) • D-dimer: 2,722 ng/mL (normal <220 ng/mL)	• Vasopressor therapy, high-dose aspirin and broad-spectrum antibiotics in intensive care • Immunomodulatory therapy was not given due to the good response to aspirin The patient was admitted to the ICU and recovered over 10 days.

Appendix B: Summary of case reports on multisystem inflammatory syndrome in adults (MIS-A) (n=9) (*continued*)

Case report/ demographic characteristics and past medical history	MIS-A clinical and laboratory characteristics	Treatment/severity and outcome
Fox *et al.*, 2020 (12) United States July 2020 The patient was a 31-year-old African American female Her comorbidities included hypertension treated with lisinopril, diabetes with poor adherence to metformin and glizide, and obesity (body mass index [BMI]= 36.1 kg/m^2) She had been discharged 12 days earlier after a hospitalization for COVID-19 disease with a positive RT-PCR	The patient was admitted for sudden fever 39.8°C (duration not specified), tachycardia (120 beats/min), left-sided neck pain, nausea and vomiting Inflammatory markers: • D-dimer level of 2.48 nmol/L (normal <1.37 nmol/L) • CRP levels 165 mg/L, then 580 mg/L (normal <9 mg/L) • Ferritin level, 411.2 µg/L (normal 10–150 µg/L) • Lactic acid level, 3.1 mmol/L (normal 0.3–2.0 mmol/L) • Lymphopenia One or more organs involved (pulmonary, cardiac, parotids, renal): • CT scan of her neck showed bilaterally enlarged parotid glands and swelling in the posterior nasopharynx to oropharynx • CT scan of her chest showed interval improvement of bibasilar ground-glass opacities, with cervical and anterior mediastinal lymphadenopathy • Creatinine level 202.44 µmol/L (44.20–97.24 µmol/L); glomerular filtration rate 32 mL/min/1.73 m^2 (>89 mL/min/1.73 m^2) PCR and serology for SARS-CoV-2: • RT-PCR was positive 12 days prior to readmission • MISC-A, RT-PCR was negative at readmission and serology was not performed	Patient developed hemodynamic instability and ventricular fibrillation during evaluation for hospital admission and died.
Jones *et al.*, 2020 (8) United Kingdom The date the study was conducted was not reported September 2020 The patient was a 21-year-old male of African descent The presence or absence of comorbidity was not reported	Fever and other signs or symptoms: • Six days of fever • Admitted for abdominal pain associated with constipation, anorexia • Transient maculopapular palmar rash four days into illness • Non-exudative conjunctivitis • Cervical lymphadenopathy • Cracked lips and prominent lingual papillae PCR and serology for SARS-CoV-2: • RT-PCR negative and serology was strongly positive, suggesting recent exposure to SARS-CoV-2 One or more organs involved: • Rash • Conjunctivitis • Cervical lymphadenopathy • Cracked lips and prominent lingual papillae Inflammatory markers: • Lymphopenia • Elevated inflammatory and elevated troponin T • Other infective and inflammatory conditions were excluded	• IVIG • Methylprednisolone The patient was discharged after a length of hospital stay of eight days.

Appendix B: Summary of case reports on multisystem inflammatory syndrome in adults (MIS-A) (n=9) (*continued*)

Case report/ demographic characteristics and past medical history	MIS-A clinical and laboratory characteristics	Treatment/severity and outcome
Kofman *et al.*, 2020 (14) United States The date the study was conducted was not reported September 2020 The patient was a 25-year-old female; her ethnicity was not reported She was a non-smoker, did not use drugs, was not taking any prescription medications and had no known allergies She had taken ibuprofen and acetaminophen over the previous week for symptom relief	Fever and other signs and symptoms: • One week of low grade fever, weakness, dyspnea, fatigue • Also developed mild cough, sore throat, vomiting, diarrhea and lymph node swelling Upon admission: • She was afebrile, with mild hypotension (blood pressure 98/56 mmHg) • Oxygen saturation was normal on room air • She appeared ill, with tender cervical lymphadenopathy • Significant conjunctival injection without perilimbal sparing; injected, erythematous and cracked lips • Tenderness to palpation in the left lower abdominal quadrant One or more organs involved (renal, cardiac, digestive, ocular): • Acute kidney injury: Creatinine 7.74 mg/dL (normal: 0.5–1.2 mg/dL) and leukocytosis • Point-of-care echocardiogram revealed a dilated inferior vena cava and overloaded right ventricular pressure • CT angiogram of the chest showed mild enlargement of the main pulmonary artery • CT abdomen/pelvis demonstrated mild peripancreatic fat stranding, felt to possibly represent acute uncomplicated pancreatitis, as well as nonspecific bilateral perinephric fat stranding • Conjunctivitis PCR and serology for SARS-CoV-2: • Positive RT-PCR and IgG serology Inflammatory markers: • CRP: 90 mg/L (normal: 0–10 mg/L) • D-dimer: 960 mg/L (normal: 0–574 mg/L) • Ferritin: 798 ng/ml (normal: 11–307 ng/mL) • Lymphocytes: 3% (normal: 19–53)	• Aggressive fluid resuscitation and vasopressor • IVIG, 2 g/kg split equally between hospital days 2 and 3 • Aspirin 325 mg daily for seven days • Patient was offered remdesivir under an Emergency Use Authorization (EUA) basis, but declined • At discharge she was prescribed a seven-day course of apixaban for COVID-19–associated coagulopathy per Emory University Hospital COVID-19 treatment guidelines The patient was admitted to the ICU twice during her hospital stay. She was discharged on Day 5.
Lidder *et al.*, 2020 (9) United States May 2020 The case was a 45-year-old male with no comorbidities Ethnicity was not reported	Fever and other signs and symptoms: • Fever for five days, sore throat, diarrhea, eye redness, eyelid swelling and a diffuse rash including bilateral upper and lower eyelids One or more organs involved (renal, cardiac, digestive, ophthalmologic): • A transthoracic echocardiogram demonstrated global hypokinesis and a reduced ejection fraction of 40% • CT imaging showed unilateral cervical lymphadenopathy with a lymph node measuring 1.8 cm • Photophobia and swollen eyelids; no vision changes including blurry vision and eye pain • Uncorrected near visual acuity was 20/20 bilaterally • Bilateral superficial punctate keratitis, symmetric anterior chamber inflammation with 10–15 cells per high power field, and normal intraocular pressure. Dilated fundus exam was notable only for one small peripheral cotton wool spot in each eye • Punch biopsy of his erythema multiforme-like rash • Showed sparse superficial perivascular infiltrate of lymphocytes with neutrophils and scattered eosinophils, suggestive of toxic shock syndrome Excluding other cause: • Testing for myositis and HIV was negative • An exhaustive rheumatologic workup, including ANA, RF, anti-CCP, anti-Smith, anti-dsDNA, p-ANCA/MPO, c-ANCA/PR3, was negative • Blood cultures were negative PCR and serology for SARS-CoV-2: • Positive RT-PCR Inflammatory markers: • Lymphopenia • Ferritin, CRP, ESR, D-dimer and troponin were elevated	• Ophthalmic lubricating therapy in addition to prednisolone acetate 1% eye drops four times daily for his photophobia in the setting of anterior chamber inflammation • IVIG and an interleukin-6 (IL-6) inhibitor (tocilizumab) in addition to using a topical triamcinolone ointment for his diffuse rash The length of hospital stay was not reported, but the patient did not demonstrate shock-like signs.

Appendix B: Summary of case reports on multisystem inflammatory syndrome in adults (MIS-A) (n=9) (*continued*)

Case report/ demographic characteristics and past medical history	MIS-A clinical and laboratory characteristics	Treatment/severity and outcome
Moghadam *et al.*, 2020 (10) France The date the study was conducted was not reported July 2020 21-year-old White male who did not smoke or use drugs The presence or absence of comorbidity was not reported	Fever and other signs and symptoms: • Fever and non-bloody watery diarrhea lasting for seven days • Asymptomatic rash over his trunk and palms, consisting of erythematous round-shaped macules with a darker and raised rim, 1–3 cm in diameter • Bilateral conjunctivitis • Blood pressure 80/40 mmHg • Respiratory rate was 38 breaths/min, and oxygen saturation was 97% on ambient air One or more organs involved (cardiac, digestive, pleural): • Electrocardiogram showed diffuse negative T-waves, and echocardiography displayed hyperkinetic left ventricle with normal ejection fraction, normal right cavities and dilated non-compressible inferior vena cava • Thoraco-abdominal CT scan showed: ° Signs of congestive heart failure ° Bilateral pleural effusion ° Wall thickening of the right colon ° Respiratory function deterioration PCR and serology for SARS-CoV-2: • Negative RT-PCR and IgG-positive serology Inflammatory markers: • Lymphocytes: 900/mm^3 • CRP: 365 mg/L • Procalcitonin: 3.4 ng/mL • Ferritin: 1,282 mg/L (normal <30) • Lactate: 2.4 mmol/L (normal <1.6) • Troponin level: 550 ng/L (normal <34) • Cutaneous biopsy showed a slightly inflammatory infiltrate in upper dermis. Direct cutaneous immunofluorescence was negative Exclusion of other causes: • Extensive infectious inquiry and search for antinuclear antibodies were negative • The rash was particular and diagnosis of erythema multiforma and subacute lupus erythematosus were ruled out	• Volume resuscitation • Noradrenaline • Antibiotics (i.e. ceftriaxone and amikacin) • High-flow nasal oxygenation The patient stayed in the ICU for eight days and recovered.
Sokolovsky *et al.*, 2020 (13) United States The date the study was conducted was not reported June 2020 The case was a 36-year-old Hispanic female with no known comorbidity	Fever and other signs and symptoms: • One week of fever, abdominal pain, vomiting and diarrhea • Two days of a diffuse rash and arthralgias • Tachycardia, tachypnea, hypotensive • Classic phenotype of complete Kawasaki disease: bilateral nonexudative conjunctivitis mucositis with cracked lips, edema of the bilateral hands and feet, diffuse maculopapular rash and cervical lymphadenopathy One or more organs involved (cardiac, digestive): • CT angiogram of the chest: normal lung parenchyma and a trace right pleural effusion • CT abdomen/pelvis illustrated mild circumferential gallbladder wall thickening and a small area of colitis • Echocardiogram after treatment with IVIG revealed an ejection fraction of 65% with moderate tricuspid valve regurgitation. Subsequent coronary computed tomography angiography (CCTA) was normal except for a trace pericardial effusion PCR and serology for SARS-CoV-2: • Negative RT-PCR and IgG-positive serology Inflammatory markers: • CRP: 30 mg/dL (normal 0.0–0.9) • D-dimer: 652 ng/mL (normal <318) Exclusion of other cause: • Anti-dsDNA, anti-Smith, anti-RNP, SSB, RF, CCP, ANCA, ASO and anti-Jo-1 antibodies were negative • HIV and hepatitis panels were negative	• Fluid resuscitation for shock • A single dose of aspirin 650 mg • IVIG 2 g/kg • Methylprednisolone 2 mg/kg for five days followed by a prednisone taper The patient stayed at least six days in hospital and recovered.

Appendix B: Summary of case reports on multisystem inflammatory syndrome in adults (MIS-A) (n=9) (*continued*)

Case report/ demographic characteristics and past medical history	MIS-A clinical and laboratory characteristics	Treatment/severity and outcome
Shaigany *et al.*, 2020 (11) United States The date the study was conducted was not reported July 2020 The case was a 45-year-old Hispanic male He had no known comorbidity	Fever and other signs and symptoms: • Six days of fever, sore throat, diarrhea, bilateral lower extremity pain, conjunctivitis and diffuse exanthema • Exposure to SARS-CoV-2 infection two weeks earlier • Respiratory rate was 25–33 breaths per min • Hypotension (systolic blood pressure 80–90 mmHg) • Tachycardia with episodes of atrial fibrillation with rapid ventricular response • Bilateral, nonexudative conjunctival injection • Tender left neck swelling with palpable lymphadenopathy, periorbital edema with overlying erythema, lip cheilitis and targetoid erythematous papules and plaques with central duskiness involving the back, palms, neck, scalp, anterior trunk and upper thighs One or more organs involved (renal, cardiac, digestive, ophthalmologic): • CT of the neck revealed inflammation and edema involving the bilateral lower eyelid and pre-septal space, as well as sub-occipital reactive lymphadenopathy • Electrocardiogram demonstrated: ° ST elevations in the anterolateral leads ° Global hypokinesis of the left ventricular wall with a mild to moderately reduced ejection fraction of 40% • Diffuse conjunctivitis with chemosis as well as the presence of inflammatory cells within the anterior chamber, indicative of uveitis ° A 4-mm punch biopsy of the skin was performed on a papule on the back, with histology revealing rare intraepithelial collections of neutrophils with necrotic keratinocytes and a sparse interstitial, mixed-cell dermal infiltrate with vacuolar interface changes PCR and serology for SARS-CoV-2: • Positive RT-PCR Inflammatory markers: • Lymphopenia (0–700 lymphocytes per µL) • ESR of 120 mm/hour • Ferritin of 21,196 ng/mL • CRP of 546.7 mg/L • D-dimer of 2,977 ng/mL • Procalcitonin of 31.79 ng/mL • Interleukin-6 (IL-6) 117 pg/mL • Troponin 8.05 g/mL Exclusion of other causes: • HIV-1 and HIV-2 antibodies were negative • Bacterial blood cultures were negative	• Therapeutic dose low molecular weight heparin • IVIG of 2 g/kg over two days • A single intravenous dose of the interleukin-6 (IL-6) inhibitor tocilizumab (400 mg) The patient was in hospital for eight days and did not require vasopressor support or ICU level of care, and recovered.

Abbreviations: ANA, antinuclear antibody; ANCA, antineutrophil cytoplasmic antibodies; c-ANCA; cytoplasmic antineutrophil cytoplasmic antibodies; anti-RNP, antinuclear ribonucleoprotein; ASO, anti-streptolysin O, CCP, cyclic citrullinated peptide; COVID-19, coronavirus disease 2019; CRP, C-reactive protein; CT, computed tomography; ESR, erythrocyte sedimentation rate; ICU, intensive care unit; HIV, human immunodeficiency virus; IG, immunoglobulin; IgG; immunoglobulin G; IgM, immunoglobulin M; IVIG, Intravenous immunoglobulin; MIS-A, multisystem inflammatory disease in adults; MPO, myeloperoxidase; p-ANCA, perinuclear antinuclear antibody; PR3, proteinase 3; RF, rheumatoid factor; RT-PCR, reverse transcription polymerase chain reaction [test]; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SSB, Sjögren's syndrome type B

Appendix C: Definitions of multisystem inflammatory syndrome in children

Authors	Definitions of MIS-C
World Health Organization (WHO) (22)	Diagnosis of MIS-C in children and adolescents aged less than 19 years includes a positive COVID-19 test or likely contact with COVID-19-positive individuals and several signs and symptoms. These include fever lasting for more than three days and two of the following: • Rash • Bilateral non-purulent conjunctivitis • Signs of muco-cutaneous inflammation (in the mouth or on the hands or feet) • Hypotension or shock • Myocardial dysfunction, pericarditis, valvulitis or coronary abnormalities (including echocardiogram findings or elevated troponin/NT-proBNP) • Coagulopathy (increased prothrombin time, activated partial thromboplastin time, elevated D-dimers) • Acute gastrointestinal problems (diarrhea, vomiting or abdominal pain) There must be laboratory evidence of inflammation, such as an elevated erythrocyte sedimentation rate (ESR), CRP or procalcitonin. Other obvious microbial causes of inflammation such as bacterial sepsis and staphylococcal or streptococcal shock syndromes must be excluded as a plausible diagnosis.
Centers for Disease Control (CDC) (23)	An individual below the age of 21 years presenting with fever lasting for more than 24 hours and laboratory evidence of inflammation, such as an elevated CRP, ESR, fibrinogen, procalcitonin, D-dimer, ferritin, lactic acid dehydrogenase (LDH) or interleukin-6, elevated neutrophils, reduced lymphocytes and low albumin. The patient must also have an evidence of clinically severe illness requiring hospitalization, with multisystem organ involvement and no alternative plausible diagnoses. The patient must be positive for current or recent SARS-CoV-2 infection by RT-PCR, serology or antigen test; or must have been exposed to a suspected or confirmed COVID-19 case within the four weeks prior to the onset of symptoms.
Royal College of Paediatrics and Child Health (RCPCH) (24)	A child presenting with persistent fever, inflammation (neutrophilia, elevated CRP and lymphopenia) and evidence of single or multi-organ dysfunction (shock, cardiac, respiratory, renal, gastrointestinal or neurologic disorder) with persistent fever over 38.5°C most of the time, oxygen requirement, hypotension and other features. The laboratory tests must show abnormal fibrinogen, absence of potential causative organisms (other than SARS-CoV-2), high CRP, high D-dimers, high ferritin, hypoalbuminemia and/or lymphopenia. This may include children fulfilling full or partial criteria for Kawasaki disease. Any other microbial cause, including bacterial sepsis, staphylococcal or streptococcal shock syndromes, infections associated with myocarditis such as enterovirus must be excluded. The SARS-CoV-2 PCR testing may be positive or negative.
Canadian Pediatric Society (CPS) (25)	The presence of high and persistent fever (≥3 days) unexplained by other causes. Fever together with laboratory evidence of marked systemic inflammation and temporal association with COVID-19 having been present in the community should raise the index of suspicion for MIS-C. The clinical presentations described to date have included fever with hyperinflammation; a Kawasaki-like syndrome; and shock or toxic shock-like states, with signs of hypotension and poor perfusion related to severe myocardial dysfunction. Gastrointestinal distress, that may or may not occur with neurologic signs such as neck stiffness, altered mental status or lethargy.

Abbreviations: COVID-19, coronavirus disease 2019; CRP, C-reactive protein; MIS-C, multisystem inflammatory syndrome in children; NT-proBNP, N-terminal pro-hormone B-type natriuretic peptide; RT-PCR, reverse transcription polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2