


SARS-CoV-2-related Multisystem Inflammatory Syndrome in Adult complicated by myocarditis and cardiogenic shock

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Abstract

Multisystem Inflammatory Syndrome in Adult (MIS-A) is a rare COVID-19 complication, presenting as fever with laboratory evidence of inflammation, severe illness requiring hospitalization and multisystem organ involvement. We report on a 25-year-old man presenting with fever, rash, abdominal pain, diarrhoea and vomiting following prior asymptomatic COVID-19 infection. He developed refractory shock and type 1 respiratory insufficiency requiring mechanical ventilation. Diagnostic testing revealed significant inflammation, anemia, thrombocytopenia, acute kidney injury, hepatosplenomegaly, colitis, lymphadenopathy and myocarditis necessitating inotropy. Ventilatory, vasopressor and inotropic support was weaned following pulse corticosteroids and intravenous immunoglobulins. Heart failure therapy was started. Short-term follow-up shows resolution of inflammation and cardiac dysfunction.

Keywords Acute heart failure; Myocarditis; Covid-19; echocardiography; cardiac MRI; intensive care medicine

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Introduction

Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) is the causative agent of the current COVID-19 pandemic.¹ About 40% of adult COVID-19 infections are asymptomatic.² Clinical presentation of COVID-19 is heterogeneous ranging from a mild to severe respiratory phenotype.³ Gastro-intestinal and dermatological symptoms are also reported, suggesting multisystem involvement.⁴ Some patients present with critical respiratory disease, often complicated by acute respiratory distress syndrome, acute kidney injury, thrombo-embolism and secondary infections with septic shock, associated with high mortality.^{5–8} In children, clinical presentation is generally mild and rarely critical.^{9,10} An atypical Kawasaki disease or toxic shock-like syndrome was reported, occurring four weeks after an asymptomatic or mild COVID-19 infection in children

and adolescents up to 21 years old, termed Multisystem Inflammatory Syndrome (MIS-C).^{11–13} Rare reports of this syndrome were described in adults (MIS-A).^{14,15}

Case Report

A 25-year-old man, with a recent (four weeks earlier) asymptomatic COVID-19 infection, was referred to our Intensive Care Unit (ICU) for evaluation and treatment of an unexplained shock syndrome. There was no history of smoking, alcohol or drug use. There was no exposure to other infectious or toxic agents and he exercised recreationally. The patient was double BNT162b2 vaccinated with the last dose nine months before admission. He presented to his general practitioner with fever (>39°C), abdominal pain, vomiting

and diarrhoea for four days. Ambulatory biochemical evaluation revealed elevated Erythrocyte Sedimentation Rate and C-Reactive Protein (CRP) with normal white blood cell count (Supplementary Table S1). Chest radiography was normal (*Figure 1A*). Amoxicillin/clavulanic acid was prescribed which was switched to cefuroxime following the occurrence of a diffuse erythematous and maculopapular rash.

Worsening clinical condition caused the patient to present to the emergency department. Clinical examination showed an ill patient with dyspnoea and diffuse abdominal pain. Heart-lung auscultation was normal. Rash persisted with associated bilateral conjunctivitis without other mucosal lesions. Blood pressure was 141/80 mmHg, pulse 110 bpm, temperature 37.8°C and oxygen saturation 98% without supplemental oxygen. ECG showed sinus tachycardia with new, diffuse PR-depression (*Figure 2*). Blood analysis demonstrated neutrophilia, thrombocytopenia, lymphopenia, high ferritin and D-dimer test, CRP doubling since visiting his GP and increased serum creatinine, gamma-glutamyl transferase, alkaline phosphatase and total bilirubin (Supplementary Table S1). Thoraco-abdominal Computed Tomography (CT) was performed because of suspected intra-abdominal sepsis and revealed uncomplicated ileocaecal inflammation, mesenteric lymphadenopathy, splenomegaly, normal lung parenchyma and discrete pericardial effusion. Transthoracic echocardiography (TTE) showed normal cardiac morphology and function without significant pericardial effusion. Blood, sputum, stool and urine cultures were incubated and the patient was switched to intravenous ciprofloxacin and metronidazole because of suspected intra-abdominal sepsis. Over the next two days, the patient developed hypotension and high anion gap metabolic acidosis due to lactic acid accumulation, necessitating fluid resuscitation and norepinephrine. Concurrently, he developed type 1 respiratory insufficiency treated with High

Flow Nasal Oxygen and, finally, sedation, intubation and mechanical ventilation.

Because of further clinical deterioration, thoraco-abdominal CT was repeated upon arrival in our hospital and showed terminal ileitis and diffuse colitis with increased lymphadenopathy, hepatosplenomegaly, new ascites and bilateral pleural effusions (*Figure 3*). Failure of shock resolution and persistent inflammation prompted antimicrobial escalation to meropenem and vancomycin. With persistent suspicion for intra-abdominal septic shock and no etiological explanation on repeat imaging, an urgent exploratory laparoscopy was performed and showed moderate clear ascites without any signs of infection. Ascites was recovered for culture. Because of unexplained shock with increasing vasopressor doses, worsening peripheral perfusion and increasing lactate, a repeat TTE was performed. It showed a mildly dilated left ventricle with moderately decreased ejection fraction due to anteroseptal akinesia and hypokinesia of the other segments, as well as a 6 mm circumferential pericardial effusion without tamponade physiology (Supplementary Video S1 and Supplementary Table S2). New chest radiograph showed cardiomegaly, bilateral pleural effusions and pulmonary edema (*Figure 1B*). High sensitive troponin T was dynamically elevated up to 288 ng/L and NT-pro-BNP was 28,770 pg/mL (Supplementary Table S1). Because of suspected myocarditis and cardiogenic shock, dobutamine was associated, as well as levosimendan. Cardiac MRI (CMR) was performed four days after hospital admission and showed a moderately dilated left ventricle with moderately reduced systolic function, evidence for non-ischemic myocardial injury (increased myocardial extracellular volume by T1-mapping) and focal myocardial edema in the anterior and apicolateral segments on T2-weighted images, but no focal myocardial late gadolinium enhancement, fulfilling the 2018 Lake Louise criteria for myocarditis (*Figure 4*).¹⁶ Pericardial inflammation was

Figure 1 Ambulatory chest radiograph (panel A) and following transfer to the referral ICU department (panel B).

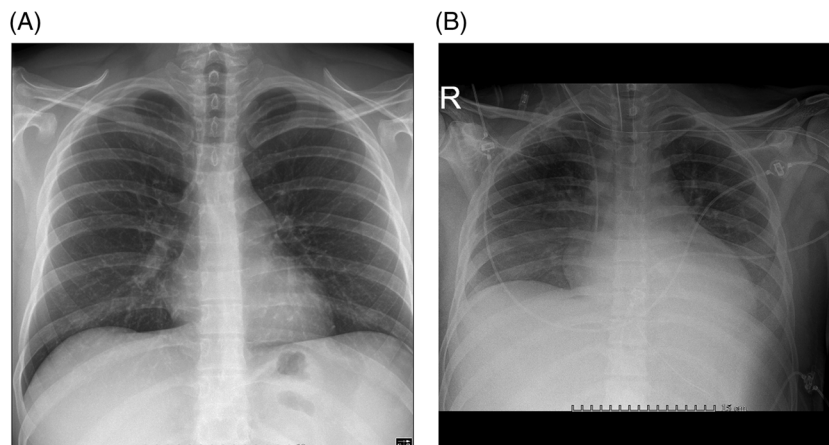


Figure 2 12-lead ECG showing sinus tachycardia and diffuse PR-depression. ECG recorded at 25 mm/s and 10 mm/mV.

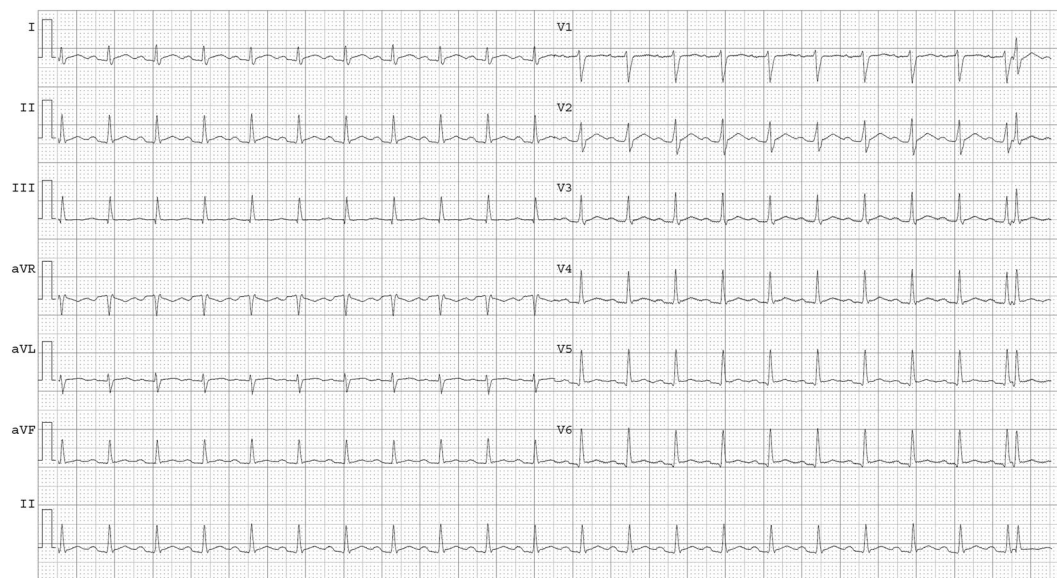
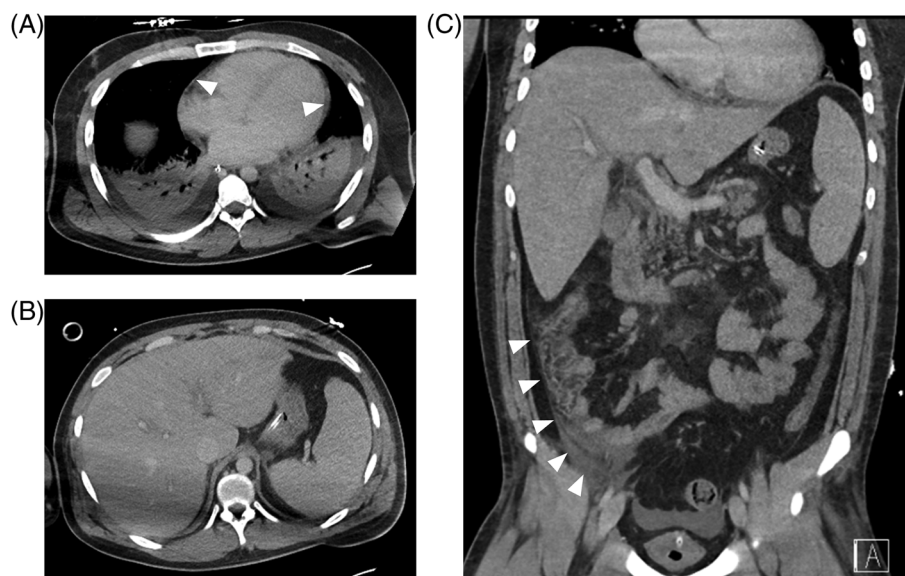


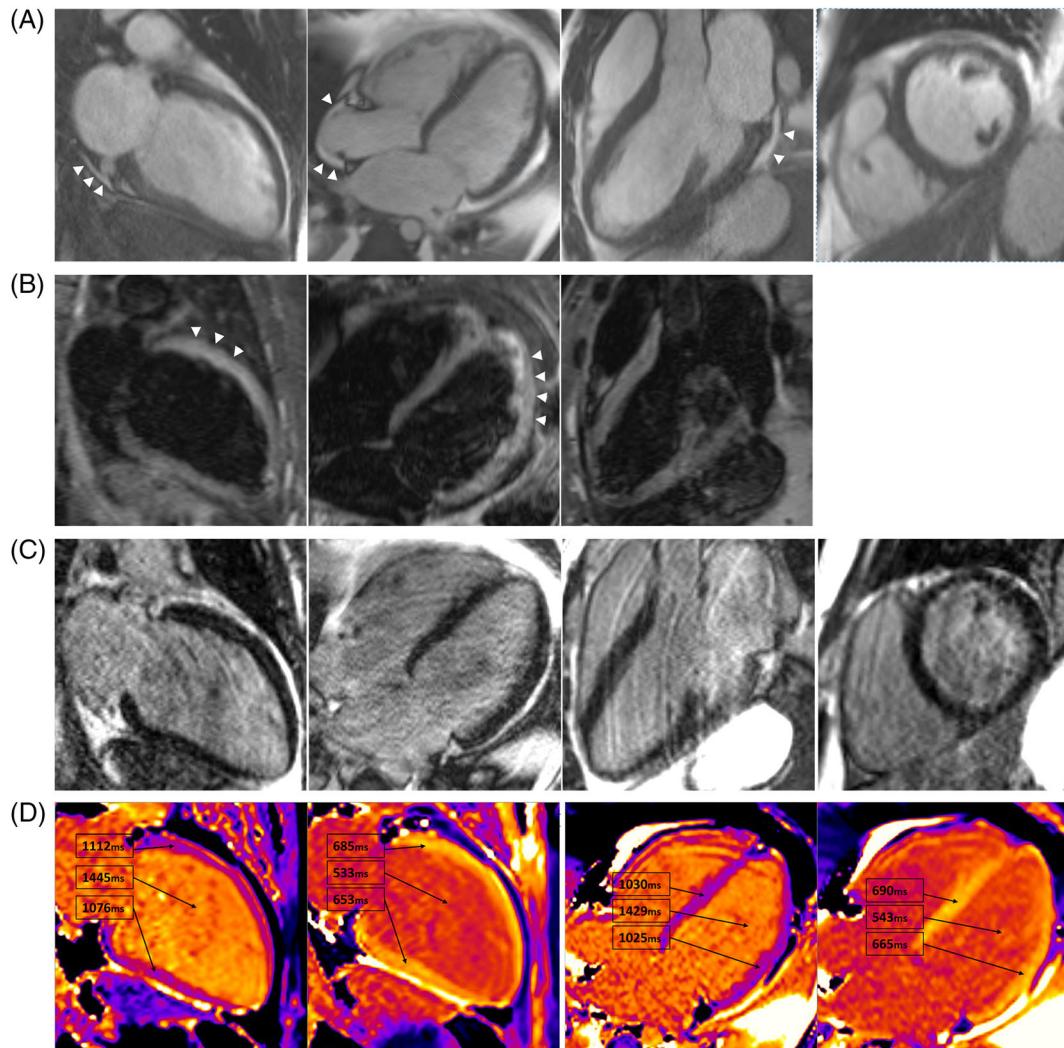
Figure 3 Computed tomography following transfer to the academic ICU department showing bilateral pleural effusion and mild pericardial effusion (white arrowheads) (panel A), hepatosplenomegaly (panel B) and colitis with adjacent ascites (white arrowheads) in the right lower quadrant (panel C).



apparent by the presence of pericardial effusion, thickening and gadolinium enhancement on CMR (Figure 4). Retrospective CT evaluation confirmed normal coronary arteries. Rhythm monitoring revealed no arrhythmia. Cultures, auto-immune and viral serology remained negative. PCR revealed persistently high SARS-CoV-2 viral load, more than four weeks after the initial positive test, in the presence of anti-N IgG.

MIS-A was diagnosed because of the suggestive rash, conjunctivitis, gastro-intestinal symptoms, thrombocytopenia, fever, major inflammation, shock and severe myocarditis with cardiac failure and lack of any other explanation and underlying infection. Intravenous immunoglobulins (IVIGs, 2 g/kg for 1 day, maximum 100 g) and pulse corticosteroids (10 mg/kg/d for 3 days, maximum 1 g/d) were started.^{17,18} The patient improved and was weaned off ventilatory,

Figure 4 Cardiac MRI scan showing dilated left ventricle and mild pericardial effusion (white arrowheads) on cine images (panels A). Myocardial edema in the anterior and lateral apical segments (white arrowheads) on STIR-T2 weighted images (panels B). Pericardial enhancement, and no myocardial late gadolinium enhancement (panels C). Pre- and postcontrast T1 maps from which a myocardial extracellular volume of 31% (normally $25.3 \pm 3.5\%$) was calculated (panels D). Indexed myocardial mass was augmented (193 g/m^2 , normally $<107 \text{ g/m}^2$).



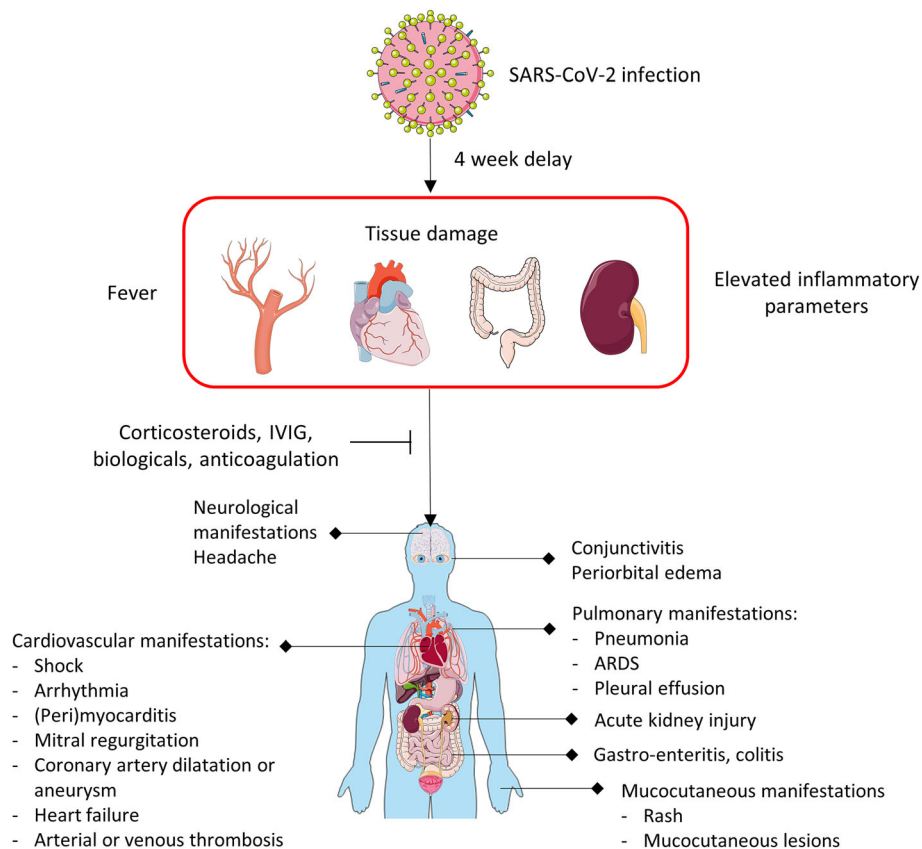
inotropic and vasopressor support within three days. Antibiotics were discontinued two days later. ECG showed regression of PR depression. TTE showed improved anteroapical contractility, increased LVEF and regressed pericardial effusion (Supplementary Table S2). Corticosteroids were continued orally (2 mg/kg/d) and slowly tapered over six weeks. Proton pump inhibitor and calcium/vitamin D supplements were associated. Heart failure therapy (bisoprolol 2.5 mg and lisinopril 10 mg daily) was titrated. Because left ventricular function improved rapidly following start of pulse corticosteroids and IVIGs, lisinopril was not escalated to valsartan-sacubitril and no mineralocorticoid receptor antagonist was associated. Low-dose aspirin was associated to prevent vascular events. At ambulatory

short-term follow-up following hospital discharge the patient was asymptomatic and without inflammation. Resting ECG was normal and TTE showed lower septum and posterior wall thicknesses, as well as normalisation of left ventricular diameters and systolic function (Supplementary Table S2 and Supplementary Video S2). Heart failure therapy and low dose aspirin will be discontinued in the future.

Discussion

COVID-19-associated MIS was first reported in children in April 2020 as a Kawasaki disease- and toxic shock-like hyperinflammatory syndrome.^{11–13} The Center for Disease

Figure 5 Development and clinical presentation of MIS-C/A. SARS-CoV-2-infection results in hyperinflammation with tissue damage resulting in multisystem organ damage and/or failure that may be treated with immunomodulatory agents.



Control (CDC) released a MIS-C definition (*Box 1*) in May 2020.¹⁹ Since June 2020, a similar syndrome was described in adult patients.^{14,15,20} MIS is a rare COVID-19 complication: 316 per 1000000 SARS-CoV-2 infections in children.²¹ Currently, more than 221 MIS-A cases have been reported and analysed in two systematic reviews.^{22,23} Patients generally develop MIS-A four weeks after COVID-19 infection. Most are male (70%) and 21–34 years old, but the oldest is 84 years.²² Currently, COVID-19 vaccination is not associated with MIS.²⁴

MIS-A is diagnosed by exclusion. The CDC defines MIS-A in patients aged ≥ 21 years old hospitalized for ≥ 24 hours, or with an illness resulting in death, who meet the clinical criteria and laboratory evidence summarized in *Box 1*.²⁰ The criteria must be met by the end of the third hospital day. The patient should not have a more likely alternative diagnosis for the illness such as sepsis or exacerbation of a chronic medical condition. In this case, intra-abdominal sepsis was initially suspected and repeated cultures, assessments by computed tomography and a laparoscopy were performed to exclude sepsis before initiating immunomodulatory treatment for MIS-A. In this 25-year old man, MIS-A was diagnosed at the start of the third hospital day based on

the presence of two primary (severe cardiac illness in combination with rash and non-purulent conjunctivitis) and three secondary clinical criteria (shock, abdominal pain and thrombocytopenia) in the presence of elevated CRP and ferritin as well as recent positive SARS-CoV-2 PCR.

Although not mandatory for the diagnosis of MIS-A, endomyocardial biopsy (EMB) may be performed in suspected myocarditis and may provide differentiation between inflammatory, infectious and infiltrative causes.^{25,26} In MIS-A, EMB histopathology has shown an inflammatory infiltrate of macrophages, T lymphocytes and eosinophils.^{27–30} It may be particularly useful if histological evaluation is expected to impact therapy. In this case, we estimated EMB would not add diagnostic clues given the typical clinical course of MIS-A in the absence of a more likely alternative diagnosis, nor would it alter our therapeutic management. And indeed, the patient improved rapidly upon treatment with pulse corticosteroids and IVIGs.

The organ systems most affected in MIS-A are hematological (41.8–92%), cardiovascular (81–87%), gastro-intestinal (73.4–83%) and respiratory (29.1–74%). Mucocutaneous (46–52.1%), musculoskeletal (30.4%), neurological (16.4–47%) and renal (43%) manifestations are

less frequent.^{22,23} Organ system involvement is comparable between adults and children.³¹ Cardiovascular findings in MIS-C/A include perimyocarditis (11–33%), hypotension and shock (50–60%), coronary artery dilatation or aneurysm (4–8%), mitral regurgitation (14%) and arrhythmia (12–18%).^{22,23,31–33} Left ventricular dysfunction is present in 55% of adults with mean left ventricular ejection fraction (LVEF) 39%.^{22,23} Left ventricular dysfunction with ejection fraction <55% is present in 38% of MIS-C patients.^{31–33} Additionally, 28.6% of MIS-A patients and 3% of MIS-C patients show severe LV dysfunction with LVEF <30%.^{22,23,31–33} Patients with LVEF <45% are more likely to present in shock (60% vs 9%) and be admitted to ICU (100% vs 55%) as compared to patients with LVEF ≥45%.³⁴ Patients with lower LVEF also resided longer on ICU with more need for inotropy, but showed no significant differences in total hospital stay, ventilatory support or mortality. Treatment generally causes normalisation of LVEF after 1 week.^{22,23,31–33} Mortality is 1.9% in MIS-C and 7% in MIS-A and has been reported in patients that require mechanical circulatory support and do not show improvement in LVEF.^{22,35}

Early diagnosis is crucial since MIS-C/A is severe, but treatable. Cardiovascular complications triggered recommendations for immunomodulation and intensive cardiac observation.^{34,36} Cardiac complications generally regress with these interventions.^{22,23,31–33} Cardiac involve-

ment may be diagnosed by a combination of ECG, cardiac biomarkers, echocardiography and radiography. Very limited data (9 adults, 4 children) are available on CMR in MIS.^{37,38} This case report shows that the 2018 Lake Louise criteria may be performant for the diagnosis of MIS-associated myocardial inflammation. More research is needed to describe long term effects and identify risk factors or imaging criteria for MIS development and associated mortality.

MIS pathophysiology is currently incompletely understood. An immunopathological cascade is suggested based on natural history, immunological phenotyping and histopathology.^{39–43} Failure of the innate and adaptive immune response to SARS-CoV-2 causes hyperinflammation. Abnormal IFN γ production activates macrophages, natural killer cells and T-cells, activating inflammatory cytokine cascades that damage multiple organ systems (*Figure 5*). In MIS-C, several studies have shown activation of oligoclonally expanded T cells, reminiscent of disease driven by superantigen exposure such as in toxic shock syndrome. These T cells harbor the *TRBV11–2* gene, encoding for the T cell receptor V β 21.3, which seems to be a highly sensitive and specific feature.^{39,43,44} The resemblance with Kawasaki disease and toxic shock syndrome spurred experts to adopt analogous treatments including IVIGs, aspirin, corticosteroids, and anti-IL-1, -IL-6, or -TNF α .^{17,18} Evidence-based data remain scarce to date.

Box 1. CDC MIS-C/A definition.

MIS-C	MIS-A
An individual aged <21 years presenting with fever*, laboratory evidence of inflammation**, and evidence of clinically severe illness requiring hospitalization, with multisystem (>2) organ involvement (cardiac, renal, respiratory, hematologic, gastrointestinal, dermatologic or neurological);	A patient aged ≥21 years hospitalized for ≥24 hours, or with an illness resulting in death, who meets the following clinical and laboratory criteria. The patient should not have a more likely alternative diagnosis for the illness (e.g., bacterial sepsis, exacerbation of a chronic medical condition).
AND	I. Clinical Criteria
No alternative plausible diagnoses;	Subjective fever or documented fever (≥38.0 C) for ≥24 hours prior to hospitalization or within the first THREE days of hospitalization* and at least THREE of the following clinical criteria occurring prior to hospitalization or within the first THREE days of hospitalization*. At least ONE must be a primary clinical criterion.
AND	Primary clinical criteria
Positive for current or recent SARS-CoV-2 infection by RT-PCR, serology, or antigen test; or exposure to a suspected or confirmed COVID-19 case within the 4 weeks prior to the onset of symptoms.	1 Severe cardiac illness Includes myocarditis, pericarditis, coronary artery dilatation/aneurysm, or new-onset right or left ventricular dysfunction (LVEF<50%), 2nd/3rd degree A-V block, or ventricular tachycardia. (Note: cardiac arrest alone does not meet this criterion) 2 Rash AND non-purulent conjunctivitis
	Secondary clinical criteria
	1 New-onset neurologic signs and symptoms Includes encephalopathy in a patient without prior cognitive impairment,

(Continues)

MIS-C	MIS-A
	seizures, meningeal signs, or peripheral neuropathy (including Guillain-Barré syndrome) 2 Shock or hypotension not attributable to medical therapy (e.g., sedation, renal replacement therapy) 3 Abdominal pain, vomiting, or diarrhea 4 Thrombocytopenia (platelet count <150,000/microliter)
	II. Laboratory evidence The presence of laboratory evidence of inflammation AND SARS-CoV-2 infection.
	1 Elevated levels of at least TWO of the following: C-reactive protein, ferritin, IL-6, erythrocyte sedimentation rate, procalcitonin 2 A positive SARS-CoV-2 test for current or recent infection by RT-PCR, serology, or antigen detection
*Fever >38.0 °C for ≥24 hours, or report of subjective fever lasting ≥24 hours **Including, but not limited to, one or more of the following: an elevated C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), fibrinogen, procalcitonin, d-dimer, ferritin, lactic acid dehydrogenase (LDH), or interleukin 6 (IL-6), elevated neutrophils, reduced lymphocytes and low albumin	*These criteria must be met by the end of hospital day 3, where the date of hospital admission is hospital day 0.

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Figure 5 was constructed using open source clipart from <https://smart.servier.com/>.

Conflict of interest

The authors have no conflicts of interest to disclose.

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Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Results of laboratory testing.

GP = General Practitioner, ER = Emergency Room, ICU = Intensive Care Unit, ESR = Erythrocyte Sedimentation

Rate, CRP = C-Reactive Protein, Hb = Hemoglobin, Hct = Hematocrit, PLC = Platelet Count, WBC = White Blood Cells Count, AST = Aspartate Aminotransferase, ALT = Alanine Aminotransferase, ?GT = Gamma-Glutamyl Transferase, AP = Alkaline Phosphatase, LDH = Lactate Dehydrogenase, PCT = Procalcitonin.

Table S2. Longitudinal analysis of transthoracic echocardiography.

IVSd = end-diastolic Interventricular Septum thickness, LVDd = Left Ventricular end-diastolic Diameter, LVPWd = end-diastolic Left Ventricular Posterior Wall thickness, LVDs = Left Ventricular end-systolic Diameter, LVEF = Left Ventricular Ejection Fraction, RWMA = Regional Wall Motion Abnormalities, LVCO = Left Ventricular Cardiac output, LA = Left Atrium, RA = Right atrium, DT = Deceleration Time, RVEDD = Right Ventricular End-Diastolic Diameter, TAPSE = Tricuspid Annular Plane Systolic Excursion, sPAP = systolic Pulmonary Artery Pressure, CVP = Central Venous Pressure.

Video S1. Parasternal short axis view from transthoracic echocardiography following transfer to academic ICU department.

Video S2. Parasternal short axis view from transthoracic echocardiography at one week follow-up.

References

- Zhu N, Zhang D, Wang W, Li X, Yang B, Song J, Zhao X, Huang B, Shi W, Lu R, Niu P, Zhan F, Ma X, Wang D, Xu W, Wu G, Gao GF, Tan W. A Novel Coronavirus from Patients with Pneumonia in China, 2019. *N Engl J Med.* 2020; **382**: 727–733.
- Ma Q, Liu J, Liu Q, Kang L, Liu R, Jing W, Wu Y, Liu M. Global Percentage of Asymptomatic SARS-CoV-2 Infections Among the Tested Population and Individuals With Confirmed COVID-19 Diagnosis: A Systematic Review and Meta-analysis. *JAMA Netw Open.* 2021; **4**: e2137257.
- Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, Zhang L, Fan G, Xu J, Gu X, Cheng Z, Yu T, Xia J, Wei Y, Wu W, Xie X, Yin W, Li H, Liu M, Xiao Y, Gao H, Guo L, Xie J, Wang G, Jiang R, Gao Z, Jin Q, Wang J, Cao B. Clinical features of patients infected with 2019 novel coronavirus in Wuhan. *China Lancet.* 2020; **395**: 497–506.
- Gupta A, Madhavan MV, Sehgal K, Nair N, Mahajan S, Sehrawat TS, Bikdeli B, Ahluwalia N, Ausiello JC, Wan EY, Freedberg DE, Kirtane AJ, Parikh SA, Maurer MS, Nordvig AS, Accili D, Bathon JM, Mohan S, Bauer KA, Leon MB, Krumholz HM, Uriel N, Mehra MR, Elkind MSV, Stone GW, Schwartz A, Ho DD, Bilezikian JP, Landry DW. Extrapulmonary manifestations of COVID-19. *Nat Med* 2020 267. 2020; **26**: 1017–1032.
- Grasselli G, Zangrillo A, Zanella A, Antonelli M, Cabrini L, Castelli A, Cereda D, Coluccello A, Foti G, Fumagalli R, Iotti G, Latronico N, Lorini L, Merler S, Natalini G, Piatti A, Ranieri MV, Scandroglio AM, Storti E, Cecconi M, Pesenti A. Baseline Characteristics and Outcomes of 1591 Patients Infected With SARS-CoV-2 Admitted to ICUs of the Lombardy Region. *Italy JAMA.* 2020; **323**: 1574–1581.
- Richardson S, Hirsch JS, Narasimhan M, Crawford JM, McGinn T, Davidson KW, Barnaby DP, Becker LB, Chelico JD, Cohen SL, Cookingham J, Coppa K, Diefenbach MA, Dominello AJ, Duer-Hefele J, Falzon L, Gitlin J, Hajizadeh N, Harvin TG, Hirschwerk DA, Kim EJ, Kozel ZM, Marrast LM, Mogavero JN, Osorio GA, Qiu M, Zanos TP. Presenting Characteristics, Comorbidities, and Outcomes Among 5700 Patients Hospitalized With COVID-19 in the New York City Area. *JAMA.* 2020; **323**: 2052–2059.
- Yang X, Yu Y, Xu J, Shu H, Xia J, Liu H, Wu Y, Zhang L, Yu Z, Fang M, Yu T, Wang Y, Pan S, Zou X, Yuan S, Shang Y. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. *Lancet Respir Med.* 2020; **8**: 475–481.
- Grasselli G, Greco M, Zanella A, Albano G, Antonelli M, Bellani G, Bonanomi E, Cabrini L, Carlesso E, Castelli G, Cattaneo S, Cereda D, Colombo S, Coluccello A, Crescini G, Forastieri Molinari A, Foti G, Fumagalli R, Iotti GA, Langer T, Latronico N, Lorini FL, Mojoli F, Natalini G, Pessina CM, Ranieri VM, Rech R, Scudeller L, Rosano A, Storti E, Thompson BT, Tirani M, Villani PG, Pesenti A, Cecconi M. Risk Factors Associated With Mortality Among Patients With COVID-19 in Intensive Care Units in Lombardy, Italy. *JAMA Intern Med.* 2020; **180**: 1345–1355.
- Castagnoli R, Votto M, Licari A, Brambilla I, Bruno R, Perlini S, Rovida F, Baldanti F, Marseglia GL. Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Infection in Children and Adolescents: A Systematic Review. *JAMA Pediatr.* 2020; **174**: 882–889.
- Göttinger F, Santiago-García B, Noguera-Julían A, Lanasa M, Lancella L, Calò Carducci FI, Gabrovská N, Velizarova S, Prunk P, Osterman V, Krivec U, Lo Vecchio A, Shingadia D, Soriano-Arandes A, Melendo S, Lanari M, Pierantoni L, Wagner N, L'Huillier AG, Heininguer U, Ritz N, Bandi S, Krajcar N, Roglič S, Santos M, Christiaens C, Creuven M, Buonsenso D, Welch SB, Bogyi M, Brinkmann F, Tebruegge M, Pfefferle J, Zacharasiewicz A, Berger A, Berger R, Strenger V, Kohlfürst DS, Zschocke A, Bernar B, Simma B, Haberlandt E, Thir C, Biebl A, Vanden Driessche K, Boiy T, Van Brusselen D, Bael A, Debulpaep S, Schelstraete P, Pavic I, Nygaard U, Glenthoj JP, Heilmann Jensen L, Lind I, Tistsenko M, Uustalu Ü, Buchtala L, Thee S, Kobbe R, Rau C, Schwerk N, Barker M, Tsolia M, Eleftheriou I, Gavin P, Kozdoba O, Zsigmond B, Valentini P, Ivaškevičienė I, Ivaškevičius R, Vilc V, Schölvinck E, Rojahn A, Smyrniaos A, Klingenberg C, Carvalho I, Ribeiro A, Starshinova A, Solovic I, Falcón L, Neth O, Minguell L, Bustillo M, Gutiérrez-Sánchez AM, Guarch Ibáñez B, Ripoll F, Soto B, Kötz K, Zimmermann P, Schmid H, Zucol F, Niederer A, Buettcher M, Cetin BS, Bilogortseva O, Chechenyeva V, Demirjan A, Shackley F, McFetridge L, Speirs L, Doherty C, Jones L, McMaster P, Murray C, Child F, Beuvink Y, Makwana N, Whittaker E, Williams A, Fidler K, Bernatoniene J, Song R, Oliver Z, Riordan A. COVID-19 in children and adolescents in Europe: a multinational, multicentre cohort study. *Lancet Child Adolesc Heal.* 2020; **4**: 653–661.
- Riphagen S, Gomez X, Gonzalez-Martinez C, Wilkinson N, Theocharis P. Hyperinflammatory shock in children during COVID-19 pandemic. *Lancet.* 2020; **395**: 1607–1608.
- Verdoni L, Mazza A, Gervasoni A, Martelli L, Ruggeri M, Ciuffreda M, Bonanomi E, D'Antiga L. An outbreak of severe Kawasaki-like disease at the Italian epicentre of the SARS-CoV-2 epidemic: an observational cohort study. *Lancet (London, England).* 2020; **395**: 1771–1778.
- Toubiana J, Poirault C, Corsia A, Bajolle F, Fourgeaud J, Angoulvant F, Debray A, Basmaci R, Salvador E, Biscardi S, Frange P, Chalumeau M, Casanova JL, Cohen JF, Allali S. Kawasaki-like multisystem inflammatory syndrome in children during the covid-19 pandemic in Paris, France: prospective observational study. *BMJ.* 2020; **3**: m2094.
- Shaigany S, Gnirke M, Guttman A, Chong H, Meehan S, Raabe V, Louie E, Solitar B, Femia A. An adult with Kawasaki-like multisystem inflammatory syndrome associated with COVID-19. *Lancet (London, England).* 2020; **396**: e8–e10.
- Hékimian G, Kerneis M, Zeitouni M, Cohen-Aubart F, Chommeloux J, Bréchet N, Mathian A, Lebreton G, Schmidt M, Hié M, Silvain J, Pineton de Chambrun M, Haroche J, Burrel S, Marot S, Luyt CE, Leprince P, Amoura Z, Montalescot G, Redheuil A, Combes A. Coronavirus Disease 2019 Acute Myocarditis and Multisystem Inflammatory Syndrome in Adult Intensive and Cardiac Care Units. *Chest.* 2021; **159**: 657–662.
- Ferreira VM, Schulz-Menger J, Holmvang G, Kramer CM, Carbone I, Sechtem U, Kindermann I, Gutberlet M, Cooper LT, Liu P, Friedrich MG. Cardiovascular Magnetic Resonance in Nonischemic Myocardial Inflammation: Expert Recommendations. *J Am Coll Cardiol.* 2018; **72**: 3158–3176.
- Henderson LA, Canna SW, Friedman KG, Gorelik M, Lapidus SK, Bassiri H, Behrens EM, Ferris A, Kernan KF, Schulert GS, Seo P, Son MBF, Tremoulet AH, Yeung RSM, Mudano AS, Turner AS, Karp DR, Mehta JJ. American College of Rheumatology Clinical Guidance for Multisystem Inflammatory Syndrome in Children Associated With SARS-CoV-2 and Hyperinflammation in Pediatric COVID-19: Version 2. *Arthritis Rheumatol.* 2021; **73**: e13–e29.
- Harwood R, Allin B, Jones CE, Whittaker E, Ramnarayan P, Ramanan AV, Kaleem M, Tulloh R, Peters MJ, Almond S, Davis PJ, Levin M, Tometzki A, Faust SN, Knight M, Kenny S, Agbeko R, Aragon O, Baird J, Bamford A, Bereford M, Bharucha T, Brogan P, Butler K, Carroll E, Cathie K, Chikermane A, Christie S,

- Clark M, Deri A, Doherty C, Drysdale S, Duong P, Durairaj S, Emonts M, Evans J, Fraser J, Hackett S, Hague R, Heath P, Herberg J, Iliina M, Jay N, Kelly D, Kerrison C, Kraft J, Leahy A, Linney M, Lyall H, McCann L, McMaster P, Miller O, O'Riordan S, Owens S, Pain C, Patel S, Pathan N, Pauling J, Porter D, Prendergast A, Ravi K, Riorden A, Roderick M, Scholefield BR, Semple MG, Sen E, Shackley F, Sinha I, Tibby S, Verganano S, Welch SB, Wilkinson N, Wood M, Yardley I. A national consensus management pathway for paediatric inflammatory multisystem syndrome temporally associated with COVID-19 (PIMS-TS): results of a national Delphi process. *Lancet Child Adolesc Heal*. 2021; 5: 133–141.
19. HAN Archive - 00432|Health Alert Network (HAN) [Internet]. [cited 2022 Jan 17]. Available from: <https://emergency.cdc.gov/han/2020/han00432.asp>
 20. Multisystem Inflammatory Syndrome in Adults (MIS-A) Case Definition Information for Healthcare Providers [Internet]. [cited 2022 Jan 17]. Available from: <https://www.cdc.gov/mis/mis-a/hcp.html>
 21. Payne AB, Gilani Z, Godfred-Cato S, Belay ED, Feldstein LR, Patel MM, Randolph AG, Newhams M, Thomas D, Magleby R, Hsu K, Burns M, Dufort E, Maxted A, Pietrowski M, Longenberger A, Bidol S, Henderson J, Sosa L, Edmundson A, Tobin-D'Angelo M, Edison L, Heidemann S, Singh AR, Giuliano JS, Kleinman LC, Tarquinio KM, Walsh RF, Fitzgerald JC, Clouser KN, Gertz SJ, Carroll RW, Carroll CL, Hoots BE, Reed C, Dahlgren FS, Oster ME, Pierce TJ, Curns AT, Langley GE, Campbell AP, Balachandran N, Murray TS, Burkholder C, Brancard T, Lifshitz J, Leach D, Charpie I, Tice C, Coffin SE, Perella D, Jones K, Marohn KL, Yager PH, Fernandes ND, Flori HR, Koniccki ML, Walker KS, Di Pentima MC, Li S, Horwitz SM, Gaur S, Coffey DC, Harwayne-Gidansky I, Hymes SR, Thomas NJ, Ackerman KG, Cholette JM. Incidence of Multisystem Inflammatory Syndrome in Children Among US Persons Infected With SARS-CoV-2. *JAMA Netw Open*. 2021; 4: e2116420.
 22. Patel P, Decuir J, Abrams J, Campbell AP, Godfred-Cato S, Belay ED. Clinical Characteristics of Multisystem Inflammatory Syndrome in Adults: A Systematic Review. *JAMA Netw Open*. 2021; 4: e2126456–e2126456.
 23. Kunal S, Ish P, Sakthivel P, Malhotra N, Gupta K. The emerging threat of multisystem inflammatory syndrome in adults (MIS-A) in COVID-19: A systematic review. *Hear Lung*. 2022; 1: 7–18.
 24. Belay ED, Godfred Cato S, Rao AK, Abrams J, Wyatt Wilson W, Lim S, Newton-Cheh C, Melgar M, DeCuir J, Webb B, Marquez P, Su JR, Meng L, Grome HN, Schlaudecker E, Talaat K, Edwards K, Barnett E, Campbell AP, Broder KR, Bamrah MS. Multisystem Inflammatory Syndrome in Adults After Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Infection and Coronavirus Disease 2019 (COVID-19) Vaccination. *Clin Infect Dis*. 2021; ciab936.
 25. Caforio ALP, Adler Y, Agostini C, Allanore Y, Anastasakis A, Arad M, Böhm M, Charron P, Elliott PM, Eriksson U, Felix SB, Garcia-Pavia P, Hachulla E, Heymans S, Imazio M, Klingel K, Marcolongo R, Mautucci Cerinic M, Pantazis A, Plein S, Poli V, Rigopoulos A, Seferovic P, Shoenfeld Y, Zamorano JL, Linhart A. Diagnosis and management of myocardial involvement in systemic immune-mediated diseases: a position statement of the European Society of Cardiology Working Group on Myocardial and Pericardial Disease. *Eur Heart J*. 2017; 38: 2649–2662.
 26. Cooper LT, Baughman KL, Feldman AM, Frustaci A, Jessup M, Kuhl U, Levine GN, Narula J, Starling RC, Towbin J, Virmani R. The role of endomyocardial biopsy in the management of cardiovascular disease: a scientific statement from the American Heart Association, the American College of Cardiology, and the European Society of Cardiology. Endorsed by the Heart Failure Society of America and the Heart Failure Association of the European Society of Cardiology. *J Am Coll Cardiol*. 2007; 50: 1914–1931.
 27. Gurin MI, Lin YJ, Bernard S, Goldberg RI, Narula N, Faillace RT, Alviar CL, Bangalore S, Keller NM. Cardiogenic shock complicating multisystem inflammatory syndrome following COVID-19 infection: a case report. *BMC Cardiovasc Disord*. 2021; 21: 522.
 28. Aldeghaither S, Qutob R, Assanangkornchai N, Issa-Chergui B, Tam M, Larotondo R, Samoukovic G. Clinical and Histopathologic Features of Myocarditis in Multisystem Inflammatory Syndrome (Adult)-Associated COVID-19. *Crit Care Explor*. 2022; 4: e0630.
 29. Vannella KM, Oguz C, Stein SR, Pittaluga S, Dikoglu E, Kanwal A, Ramelli SC, Briese T, Su L, Wu X, Ramos-Benitez MJ, Perez-Valencia LJ, Babyak A, Cha NR, Chung JY, Ylaya K, Madathil RJ, Saharia KK, Scalea TM, Tran QK, Herr DL, Kleiner DE, Hewitt SM, Notarangelo LD, Grazioli A, Chertov DS. Evidence of SARS-CoV-2-Specific T-Cell-Mediated Myocarditis in a MIS-A Case. *Front Immunol*. 2021; 12: 1.
 30. Bemtgen X, Klingel K, Hufnagel M, Janda A, Bode C, Staudacher DL, Supady A, Jandova I. Case Report: Lymphohistiocytic Myocarditis With Severe Cardiogenic Shock Requiring Mechanical Circulatory Support in Multisystem Inflammatory Syndrome Following SARS-CoV-2 Infection. *Front Cardiovasc Med*. 2021; 8: 716198.
 31. Feldstein LR, Rose EB, Horwitz SM, Collins JP, Newhams MM, Son MBF, Newburger JW, Kleinman LC, Heidemann SM, Martin AA, Singh AR, Li S, Tarquinio KM, Jaggi P, Oster ME, Zackai SP, Gillen J, Ratner AJ, Walsh RF, Fitzgerald JC, Keenaghan MA, Alharash H, Doymaz S, Clouser KN, Giuliano JS, Gupta A, Parker RM, Maddux AB, Havalad V, Ramsingh S, Bukulmez H, Bradford TT, Smith LS, Tenforde MW, Carroll CL, Riggs BJ, Gertz SJ, Daube A, Lansell A, Coronado Munoz A, Hobbs CV, Marohn KL, Halasa NB, Patel MM, Randolph AG. Multisystem Inflammatory Syndrome in U.S. Children and Adolescents. *N Engl J Med*. 2020; 383: 334–346.
 32. Matsubara D, Kauffman HL, Wang Y, Calderon-Anyosa R, Nadaraj S, Elias MD, White TJ, Torowicz DL, Yubbu P, Giglia TM, Hogarty AN, Rossano JW, Quartermain MD, Banerjee A. Echocardiographic Findings in Pediatric Multisystem Inflammatory Syndrome Associated With COVID-19 in the United States. *J Am Coll Cardiol*. 2020; 76: 1947–1961.
 33. Belhadjer Z, Méot M, Bajolle F, Khraiche D, Legendre A, Abakka S, Auriau J, Grimaud M, Oualha M, Beghetti M, Wacker J, Ovaert C, Hascoet S, Selegny M, Malekzadeh-Milani S, Maltret A, Bosser G, Giroux N, Bonnemains L, Bordet J, Di Filippo S, Mauran P, Falcon-Eicher S, Thambo JB, Lefort B, Moceri P, Houyel L, Renolleau S, Bonnet D. Acute Heart Failure in Multisystem Inflammatory Syndrome in Children in the Context of Global SARS-CoV-2 Pandemic. *Circulation*. 2020; 142: 429–436.
 34. Mannarino S, Raso I, Garbin M, Ghidoni E, Corti C, Goletto S, Nespoli L, Santacesaria S, Zoia E, Camporesi A, Izzo F, Dilillo D, Fiori L, D'Auria E, De SA, Dolci A, Calcaterra V, Zuccotti G. Cardiac dysfunction in Multisystem Inflammatory Syndrome in Children: An Italian single-center study. *Ital J Pediatr*. 2022; 48: 1–9.
 35. McArdle AJ, Vito O, Patel H, Seaby EG, Shah P, Wilson C, Broderick C, Nijman R, Tremoulet AH, Munblit D, Ulloa-Gutierrez R, Carter MJ, De T, Hoggart C, Whittaker E, Herberg JA, Kaforou M, Cunningham AJ, Levin M. Treatment of Multisystem Inflammatory Syndrome in Children. 2021; 385: 11–22.
 36. Son MBF, Murray N, Friedman K, Young CC, Newhams MM, Feldstein LR, Loftis LL, Tarquinio KM, Singh AR, Heidemann SM, Soma VL, Riggs BJ, Fitzgerald JC, Kong M, Doymaz S, Giuliano JS, Keenaghan MA, Hume JR, Hobbs CV, Schuster JE, Clouser KN, Hall MW, Smith LS, Horwitz SM, Schwartz SP, Irby K, Bradford TT, Maddux AB, Babbitt CJ, Rowan CM, McLaughlin GE, Yager PH, Maamari M, Mack EH, Carroll CL, Montgomery VL, Halasa NB, Cvijanovich NZ, Coates BM, Rose CE, Newburger

- JW, Patel MM, Randolph AG. Multisystem Inflammatory Syndrome in Children - Initial Therapy and Outcomes. *N Engl J Med.* 2021; **385**: 23–34.
37. Blondiaux E, Parisot P, Redheuil A, Tzaroukian L, Levy Y, Sileo C, Schnuriger A, Lorrot M, Guedj R, Le Pointe HD. Cardiac MRI in children with multisystem inflammatory syndrome associated with COVID-19. *Radiology.* 2020; **297**: E283–E288.
 38. Bajaj R, Sinclair HC, Patel K, Low B, Pericao A, Manisty C, Guttmann O, Zemrak F, Miller O, Longhi P, Proudfoot A, Lams B, Agarwal S, Marelli-Berg FM, Tiberi S, Cutino-Moguel T, Carr-White G, Mohiddin SA. Delayed-onset myocarditis following COVID-19. *Lancet Respir Med.* 2021; **9**: e32–e34.
 39. Hoste L, Roels L, Naesens L, Bosteels V, Vanhee S, Dupont S, Bosteels C, Browaeys R, Vandamme N, Verstaen K, Roels J, Van Damme KFA, Maes B, De Leeuw E, Declercq J, Aegerter H, Seys L, Smole U, De Prijck S, Vanheerswynghels M, Claes K, Debacker V, Van Isterdael G, Backers L, Claes KBM, Bastard P, Jouanguy E, Zhang S-Y, Mets G, Dehoorne J, Vandekerckhove K, Schelstraete P, Willems J, Willekens J, Schaballie H, Van Daele S, Dierickx L, David S, Dhont E, Verrijckt A, de Jaeger A, Beel E, Matthijs I, Minne A, Decaestecker K, John J, Crijnen TEM, Koninckx M, Verbruggen J, Nys G, Akhnikh S, Vanlede K, Coppens A, Thijs J, Ryckaert I, Covents A, Duval ELIM, Verschelde A, De Keyzer L, Van Ackere T, Verbist A, Daeze C, Becue C, De Paepe J, Keepers J, Bruylants B, Kuypers S, Daelemans S, van der Werff ten Bosch J, van Berlaer G, Dreesman A, Florkin B, Heijmans C, Papadopoulos J, Stordeur P, Janssens S, Beyaert R, Saeys Y, Casanova J-L, Lambrecht BN, Haerynck F, Tavernier SJ. TIM3+ TRBV11-2 T cells and IFN γ signature in patrolling monocytes and CD16+ NK cells delineate MIS-C. *J Exp Med.* 2022; **219**: 219.
 40. Gruber CN, Patel RS, Trachtman R, Lepow L, Amanat F, Krammer F, Wilson KM, Onel K, Geanon D, Tuballes K, Patel M, Mouskas K, O'Donnell T, Merritt E, Simons NW, Barcessat V, Del Valle DM, Udondem S, Kang G, Gangadharan S, Ofori-Amanfo G, Laserson U, Rahman A, Kim-Schulze S, Charney AW, Gnjjatic S, Gelb BD, Merad M, Bogunovic D. Mapping Systemic Inflammation and Antibody Responses in Multisystem Inflammatory Syndrome in Children (MIS-C). *Cell.* 2020; **183**: 982–995.e14.
 41. Carter MJ, Fish M, Jennings A, Doores KJ, Wellman P, Seow J, Acors S, Graham C, Timms E, Kenny J, Neil S, Malim MH, Tibby SM, Shankar-Hari M. Peripheral immunophenotypes in children with multisystem inflammatory syndrome associated with SARS-CoV-2 infection. *Nat Med* 2020 2611. 2020; **26**: 1701–1707.
 42. Consiglio CR, Cotugno N, Sardh F, Pou C, Amodio D, Rodriguez L, Tan Z, Zicari S, Ruggiero A, Pascucci GR, Santilli V, Campbell T, Bryceson Y, Eriksson D, Wang J, Marchesi A, Lakshmi Kanth T, Campana A, Villani A, Rossi P, Landegren N, Palma P, Brodin P. The Immunology of Multisystem Inflammatory Syndrome in Children with COVID-19. *Cell.* 2020; **183**: 968–981.e7.
 43. Ramaswamy A, Brodsky NN, Sumida TS, Comi M, Asashima H, Hoehn KB, Li N, Liu Y, Shah A, Ravindra NG, Bishai J, Khan A, Lau W, Sellers B, Bansal N, Guerrero P, Unterman A, Habet V, Rice AJ, Catanzaro J, Chandnani H, Lopez M, Kaminski N, Dela Cruz CS, Tsang JS, Wang Z, Yan X, Kleinstein SH, van Dijk D, Pierce RW, Hafler DA, Lucas CL. Immune dysregulation and autoreactivity correlate with disease severity in SARS-CoV-2-associated multisystem inflammatory syndrome in children. *Immunity.* 2021; **54**: 1083–1095.e7.
 44. Porritt RA, Paschold L, Rivas MN, Cheng MH, Yonker LM, Chandnani H, Lopez M, Simnica D, Schultheiß C, Santiskulvong C, Van Eyk J, McCormick JK, Fasano A, Bahar I, Binder M, Arditì M. HLA class I-associated expansion of TRBV11-2 T cells in multisystem inflammatory syndrome in children. *J Clin Invest.* 2021; **131**: 131.