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Progress in Pediatric Cardiology 62 (2021) 101407

Contents lists available at ScienceDirect

Progress in Pediatric Cardiology

journal homepage: www.elsevier.com/locate/ppedcard

Editorial

COVID-19 associated Multisystem Inflammatory Syndrome in Children (MIS-C) guidelines; revisiting the Western New York approach as the pandemic evolves

ARTICLE INFO

Keywords
COVID-19
Pediatric
Fever
Inflammation
SARS-CoV-2
MIS-C

ABSTRACT

Multisystem inflammatory syndrome of children (MIS-C) continues to be a highly concerning diagnosis in those recently infected with SARS-CoV-2. The diagnosis of MIS-C cases will likely become even more challenging as vaccine uptake and natural immunity in previously infected persons leads to lower circulating rates of SARS-CoV-2 infection and will make cases sporadic. Febrile children presenting with cardiac dysfunction, symptoms overlapping Kawasaki disease or significant gastrointestinal complaints warrant a thorough screen in emergency departments, urgent care centers, and outpatient pediatric or family medicine practices. An increased index of suspicion and discussion regarding higher level of care (transferring to pediatric tertiary care centers or to intensive care) continues to be recommended. Herein we outline a broad approach with a multidisciplinary team for those meeting the case definition and believe such an approach is crucial for successful outcomes.

1. Introduction

COVID-19, the clinical presentation of acute disease associated with the betacoronavirus SARS-CoV-2, affects all age groups, yet is more severe in the elderly and individuals with co-morbidities. Severe respiratory disease is the most concerning clinical presentation in adult patients. Initial reports during the pandemic suggested children have milder illness during acute infection [1]. Soon after the pandemic spread throughout Europe, reports of a severe pediatric multi-system inflammatory syndrome emerged. We have adopted the Center for Disease Control and Prevention (CDC) case definition of multisystem inflammatory syndrome of children (MIS-C) (Fig. 1). Some children with MIS-C have features similar to Kawasaki disease (KD), toxic shock syndrome, and myocarditis with cardiogenic shock. Clinical presentation is variable, with most centers reporting significant gastrointestinal (GI) symptoms, cardiac disease, mild or absent respiratory symptoms, and variable incidence of rash, conjunctivitis, and oral mucous membrane changes [2–7]. In 2020, diagnostic and treatment guidelines were created at our institution to address these cases based on the few limited published reports at the time [8]. Since then, much more has been learned about this syndrome, but many questions remain. This review details how our multidisciplinary approach to MIS-C has evolved, discusses current knowledge on the epidemiology and clinical manifestations, and revises our guidelines on diagnosis, treatment and follow up.

2. Epidemiology and case definitions

After initial reports from Europe [9–11] and the United States (US) [12], others have confirmed the global nature of this condition [13–17]. It is unclear why there is a paucity of MIS-C cases reported in certain countries, but a number of factors could be contributing, such as local resources, host genetic background, and influence of genetic variation of circulating viruses. Studies in the US have shown that racial and/or ethnic minorities and socioeconomically disadvantaged children carry the highest burden of infection with COVID-19 [18,19]. A recent study comparing children with severe acute COVID-19 infection to those with MIS-C showed MIS-C patients were more likely to be age 6–12 years, non-Hispanic Black, and have more significant cardiovascular and mucocutaneous inflammation. [20]. MIS-C was also independently associated with lower socioeconomic background, Hispanic ethnicity, and Black race [21].

The cumulative MIS-C incidence in persons younger than 21 years is 2 per 100,000, with cases following acute infections by an average of

Abbreviations: ASO, anti-streptolysin O; AP, approved; BNP, brain-natriuretic peptide; CDC, Center for Disease Control; COVID-19, coronavirus disease 2019; CRP, C-reactive protein; CXCL10, C-X-C-motif chemokine ligand 10; DCBLD2, Discoidin, CUB and LCCL domain-containing protein 2; EKG, electrocardiogram; EM, emergency use; E, envelope protein; E.U., European Union; ECMO, extracorporeal membrane oxygenation; FDA, US Food and Drug Authority; GI, gastrointestinal; IL, interleukin; IVIG, intravenous immunoglobulin G; KD, Kawasaki disease; LDH, lactate dehydrogenase; LFTs, liver function tests; MIS-C, Multisystem Inflammatory Syndrome in Children; M, membrane protein; Mpred, methylprednisolone; NP, Nucleoprotein; PCR, polymerase chain reaction; PTT, partial thromboplastin time; PT, prothrombin time; RBD, receptor binding domain; TE, thromboembolic events; TNF, tumor necrosis factor; TWEAK, TNF-like weak inducer of apoptosis; U.S., United States of America; VA, veno-arterial; VTE, venous thromboembolic events; VLPs, virus-like particles.

https://doi.org/10.1016/j.ppedcard.2021.101407
Received 29 May 2021; Accepted 2 June 2021
Available online 6 June 2021

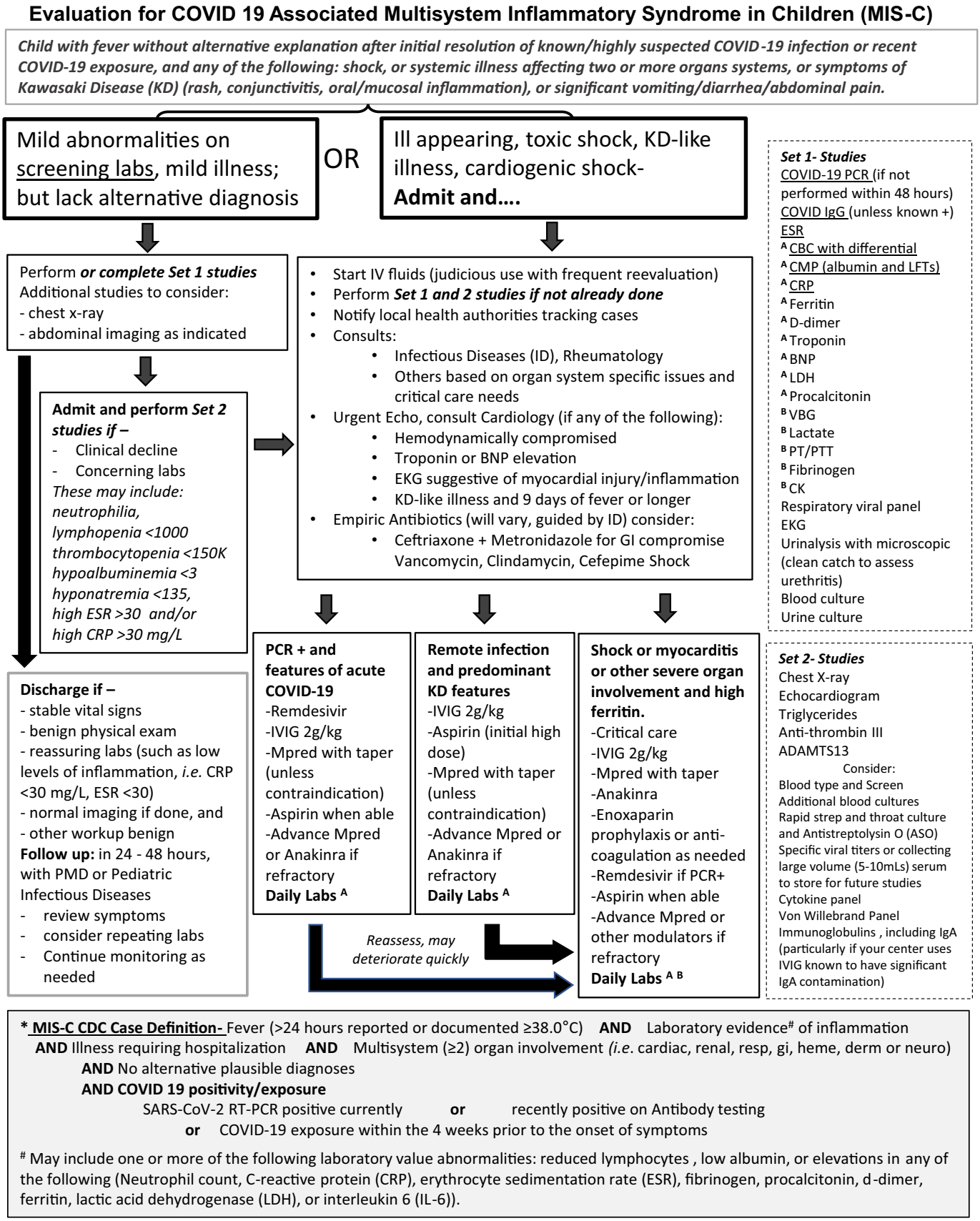

Fig. 1. Guidelines for evaluation of a child with suspected MIS-C.
Guideline was created following the CDC case definition, published cases, and other guidelines with input from emergency medicine physicians, hospitalists, intensivists, and specialists in the areas of critical care, infectious diseases, cardiology, rheumatology, and hematology. Screening labs we recommend in our hospital are underlined. "*Set 1* subset B" labs are followed in more severe cases. Mpred = Methylprednisolone.

2–5 weeks [2]. The CDC has an updated website on clinical information regarding MIS-C [22]. Over 3700 cases have been reported with a near 1% mortality rate and 99% with positive testing (by nucleic acid, antigen, and/or antibody) for SARS-CoV-2. The cases have a median age of 9 years (range ⟨1−20) and are predominantly 1–14 years of age. 63% of reported cases have occurred in children who are Hispanic/Latino or non-Hispanic Black. More than half (59%) of reported cases are male. Reports have emerged from young adults with similar presentations, a syndrome termed MIS-A (Adult) [23,24]. Generally, acute COVID-19 has distinct clinical signs and symptoms and laboratory findings [25], but some acute respiratory COVID-19 presentations may fulfill MIS-C criteria [9,26]. Interestingly, younger children with MIS-C are more likely than adolescents to be SARS-CoV-2 IgG positive (86% for cases 0–9 years of age versus 70% for 15–20 years), whereas the opposite is seen for polymerase chain reaction (PCR)-positivity (48% versus 64%, respectively) [2]. The age group most affected by MIS-C is those for which COVID-19 vaccines are not yet available for SARS-CoV-2 infection prevention.

The CDC definition of multisystem involvement includes ≥2 organ systems. The level of dysfunction that qualifies for a system to be included for MIS-C has not been specifically defined [27], but reports are consistent with organ dysfunction defined in guidelines for severe COVID-19 [20]. Many described cases of MIS-C have features of KD, including hand and foot inflammation/swelling, mucous membrane changes, non-exudative conjunctivitis, rash, and unilateral lymphadenopathy. However, MIS-C patients are generally outside the typical age group (older) and ethnic background (predominantly non-Asian) seen with classic KD. Patients with MIS-C frequently present with GI symptoms such as vomiting, diarrhea, and severe abdominal pain. Many have pulmonary infiltrates, although this is not part of the case definition [28]. Neurologic manifestations are not uncommon and involve both the central and peripheral nervous systems. Reports include encephalitis, meningitis, necrotizing encephalopathy, demyelinating disorders, intracerebral hemorrhage, and stroke [29]. Pathogenesis could be related to global illness, acute inflammation, vasculopathy, coagulopathy, or possibly direct central nervous system viral invasion or post-infection immune mediated disease [30]. MIS-C can present with multi-organ system failure with cardiogenic or vasoplegic shock [31]. The organ system involvement and treatment are complex and subsequently will be described in more detail.

3. Distinguishing MIS-C from KD

As the definitions of MIS-C are broad, both prolonged highly inflamed acute presentations and a post-infectious complication will be included [31]. Children with KD during this pandemic may also meet the definition of MIS-C posing a diagnostic challenge. Although MIS-C and KD share certain symptoms, the clinical presentations are generally distinguishable. KD is rare in ages over 8 years, whereas the median age in most studies on MIS-C is 8–10 years [32,33]. GI manifestations are a prominent clinical feature of MIS-C, but much less common, and if present less severe in KD. The children that fulfilled classic criteria of KD within early reports of MIS-C generally had less myocardial involvement (near-normal ventricular function, lower troponin and brain-natriuretic peptide (BNP) levels) than MIS-C and seemed to respond well to care directed at KD [9]. KD shock presentation has been reported in up to 7% of cases of KD previously and is known to have elevations in BNP and troponins consistent with myocarditis [34], which is more clinically similar to MIS-C cases. Initial MIS-C reports had a number of cases with coronary aneurysms [9,10,33]. Recent studies suggest persistent aneurysms are rare in MIS-C. In one series, only 1 of 28 MIS-C cases had a coronary artery diameter *Z*-score over 2.5, which resolved quickly on follow-up. Another case series reporting echocardiographic data showed that 0 of 21 cases of MIS-C developed aneurysms [25]. When coronary arteries are noted to be enlarged during MIS-C, the findings correspond to the peak of fever. In contrast, the aneurysms of KD usually are most prominent 2–3 weeks after onset of fevers, generally after fever has resolved [35]. In comparison to 20 classic KD cases, MIS-C cases had significantly worse ejection fractions, more significant mitral regurgitation, and higher rate of pleural effusions. Overall, MIS-C cases demonstrated worse left ventricle systolic and diastolic function by all echocardiographic parameters [36].

Clinical characteristics of 58 children with MIS-C were compared with historical KD controls, including those with KD shock syndrome [37]. Lymphopenia, thrombocytopenia, excessive C-reactive protein (CRP) elevation, hyperferritinemia, elevated troponins and elevated D-dimers correlated with MIS-C, with troponin and D-dimer elevations being most specific. Low albumin and relative anemia, although supplemental criteria for diagnosing KD, were in fact lower in MIS-C children overall. Thrombocytosis was also less commonly present in children with MIS-C than those with KD.

The immune system responses in MIS-C were directly compared to KD [38]. Principal components analysis of serum cytokine expression profiles showed distinct groupings. Children with KD showed significant elevations in cytokines interleukin (IL)-6, IL-17A, and C-X-C-motif chemokine ligand 10 (CXCL10) compared to MIS-C and adult COVID-19 patients. Serum proteins that were lower in KD included adenosine deaminase, stem cell factor, and tumor necrosis factor (TNF)-like weak inducer of apoptosis (TWEAK), which is a negative regulator of interferon-γ and Th1-type immune responses. Discoidin, CUB and LCCL domain-containing protein 2 (DCBLD2), an endothelial secreted protein associated with vascular injury [39], were also more elevated in KD than MIS-C. Matrix metalloproteinase 1 and 10, proteins involved in arterial disease, were also differentially expressed [40]. MIS-C and KD likely have overlapping immune profiles, as both have endothelial damage and IL-1β upregulation and significant downstream IL-6 elevation [41].

4. Proposed guidelines for evaluation

The following guidelines were created by a multidisciplinary team at our center consisting of pediatric emergency medicine physicians, hospitalists, intensivists, and pediatric subspecialists in the areas of infectious diseases, cardiology, rheumatology, and hematology [8]. This revision is based on studies published over the last year, recently published guidelines, and our collective clinical experience (see Fig. 1) [27].

5. Initial consideration in the emergency department

Health care providers in the emergency department face a challenge as fever in children is a common presentation. An additional challenge is that COVID-19 infection in children is often mild or asymptomatic, so the absence of a recent illness does not preclude one from the diagnosis of MIS-C. With an increased worldwide prevalence of COVID-19 in early 2021, many children have potentially been recently exposed to SARS-CoV-2. Some children may be diagnosed outpatient or may have family, daycare or school contacts who have been diagnosed.

Primary respiratory complaints can be seen in MIS-C. A number of cases of MIS-C are PCR-positive and have pulmonary involvement, including chest X-ray infiltrates. In MIS-C, GI complaints can be so severe, that patients may be suspected as having a surgical abdomen (e.g., potential appendicitis) prompting evaluation from a surgeon [42]. Patients in whom there is a low index of suspicion but present with some features of MIS-C should be considered for screening for inflammation with a complete metabolic panel, complete blood count with differential, sedimentation rate (ESR) and CRP.

Timely SARS-CoV-2 nasopharyngeal PCR and antibody testing should be done, both for diagnostic and infection control purposes. With continued evolution of the pandemic, genetic variants may influence the diagnostic accuracy of certain tests. Interpretation of results will depend on several factors including the type of antibody testing locally performed, country of residence, recent travel history, known exposures, and specific SARS-CoV-2 vaccine formulation if obtained. The

nucleoprotein (NP) is the antigen used in many commercial antibody assays. Antibodies against NP can distinguish natural infection from vaccination for those vaccines that produce or contain Spike or receptor binding domain (RBD) antigens (Table 1) [43–45]. There are assays available that measure antibodies against SARS-CoV-2 Spike protein or the RBD, but these would not distinguish natural infection from vaccination [46,47]. This differentiation by antibodies against NP is not applicable for the inactivated whole viral vaccines (Table 1) so interpretation of antibody testing in a patient who received these types of vaccines will be difficult [48]. It is anticipated that more vaccines using a variety of platforms with presentation of a variety of antigens will be approved. Clinicians should keep current on vaccine developments, testing available at their institution, and effects of viral variants currently circulating, to assist in interpretation of viral testing.

Patients with signs and symptoms fulfilling the case definition of MIS-C (see Fig. 1) should undergo a more extensive workup. Discussion with local pediatric emergency medicine or infectious disease physicians that serve one's area is encouraged for further guidance on the workup of suspected cases.

Published reports and our own experience show that patients can initially be well-appearing with reassuring laboratory workup, only to return to the hospital days later with worsening symptoms and rapid clinical deterioration [32]. We propose that the patients evaluated for this condition who are discharged from the emergency department are given MIS-C specific discharge instructions and have a follow-up clinic or telehealth visit (as well as a repeat of their MIS-C screening labs if their symptoms continue) within 24–72 h. Since a broad differential of infections can have overlapping manifestations, direct follow-up or discussion with local pediatric infectious disease physicians for questions that may arise during follow-up is recommended.

6. Criteria for hospitalization

Proposing detailed criteria for hospital admission is challenging and it will depend on multiple factors. In some children, a rapid decline in clinical status can occur [32]. Children suspected to have MIS-C that are initially being evaluated in a rural area or a local emergency department/urgent care center/hospital should be stabilized and transferred as quickly and safely as possible to a tertiary medical center. From our own experience and in published studies [31], there appear to be mild forms of this condition without cardiac involvement and with only mild laboratory abnormalities. These may resolve without medical intervention. It is unclear if the recognition of milder cases is from lack of initial reporting of such cases, change in the circulating strains, epidemiologic changes in groups affected, or from improvements in clinical care. Our center has been aggressive in our treatment strategy; we suspect this may be one possible explanation for relative lack of severe outcomes in our cohort.

7. Consultations

The multi-faceted nature of the disease course and various presentations underlines the need for multispecialty input and coordination of care. As a subset of children can become severely ill quickly, referral to a tertiary care center is paramount. Pediatric infectious diseases should be consulted early on in all cases being considered for MIS-C, as

Table 1
Notable COVID-19 vaccines approved, in emergency use, or expected to be approved in 2021.

Vaccine platform	Company or institute name	Vaccine	Antibody target contained in vaccine	Status	Region or countries used	Antibody target that distinguishes history of natural infection from vaccination
mRNA	Moderna	mRNA-1273	Spike	AP EM	Switzerland North America, E.U., Japan, Israel, others	NP
mRNA	Pfizer/BioNTech	BNT162b2	Spike	AP EM	Switzerland, Brazil, Saudi Arabia, New Zealand Americas, Australia, E.U., Japan, Israel, others	NP
mRNA	CureVac	CVnCoV	Spike	Phase III	E.U.	NP
Adenoviral	Oxford-AztraZeneca	ChAdOx1	Spike	AP EM halted	Brazil Many in Europe, Americas, Africa, Asia Norway, Denmark	NP
Adenoviral	Janssen/J&J	Ad26COVs1	Spike	EM	U.S., E.U.	NP
Adenoviral	CanSinoBIO	Ad5-nCoV/ Convidecia	Spike	AP EM	China, Chile, Mexico, Pakistan, Moldova, Hungary,	NP
Adenoviral	Gamaleya	Sputnik V	Spike	EM	Russia	NP
Protein	Anhui Zhifei Longcom/ Institute of Medical Biology	ZF2001	RBD portion of Spike	EM	China, Uzbekistan	NP
Protein on particles	Novavax	NVX-CoV2373	Spike on nanoparticles	Phase III	U.K., U.S., Mexico	NP
VLPs	Medicago	Co-VLP	Spike on VLPs tobacco produced	Phase III	Canada	NP
Inactivated	Beijing Institute/ Sinopharm	BBIBP-CorV	Spike, NP, E, M	AP EM	China, U.A.E, Bahrain many others	none
Inactivated	Wuhan Institute/ Sinopharm	Vero	Spike, NP, E, M	AP EM	China U.A.E.	none
Inactivated	Sinovac	Coronavac	Spike, NP, E, M	AP EM	China many others	none
Inactivated	Bharat Biotech	Covaxin	Spike, NP, E, M	EM	India, others	none
Inactivated	Chumakov Center	Covivac	Spike, NP, E, M	EM	Russia	none
Inactivated	Research Institute for Biological Safety Problems	QazVac	Spike, NP, E, M	EM	Kazakhstan	none
Peptide and protein	Bektop/ Vector Institute	EpiVacCorona	Spike peptide, NP-fusion	EM	Turkmenistan, others	none

Approved- AP, emergency use- EM, envelope protein-E, European Union- E.U., membrane protein-M, nucleoprotein- NP, receptor binding domain- RBD, United States- U.S., virus-like particles- VLPs.

bacterial and viral illness may present similarly. Pediatric rheumatology, if available, should be involved early, especially in cases with high clinical suspicion. Critical care is consulted as needed and, in our center, often informed of mild cases since care needs can change quickly. We recommend pediatric cardiology consultation if there are abnormalities in BNP or troponin levels, or on electrocardiogram (EKG) or echocardiogram. As the name implies, the multisystem inflammation seen in these cases may require seeking input from other subspecialties (pediatric neurology, gastroenterology, hematology, or surgery) as the need arises.

8. Treatments

MIS-C presentation among children admitted to the hospital falls under three distinctive categories for the purposes of treatment recommendations: i) MIS-C with features of acute COVID-19; ii) MIS-C with predominant KD features; and iii) MIS-C with shock, myocarditis or severe multisystem involvement. Children presenting with shock frequently require cardiac and respiratory support. Generally, antibiotic coverage should be empiric in patients diagnosed and/or hospitalized with MIS-C, with initial broad-spectrum antibiotics recommended as symptoms may overlap with severe bacterial infections. For patients with milder illness, we suggest ceftriaxone if there is concern for coinfection. As GI symptoms are a common presentation of MIS-C, addition of metronidazole may be considered in cases where ileitis or colitis is seen on imaging. In cases of severe illness or shock, we advise empiric coverage that targets methicillin-resistant *Staphylococcus aureus*, resistant Gram-negatives, and includes antibiotics that inhibit toxin production since toxic shock will be in the differential diagnoses. We often use vancomycin, cefepime, and clindamycin or vancomycin, meropenem, and gentamicin. We strongly encourage consultation with local pediatric infectious disease experts prior to transfer of care or quickly after initial evaluation (see Fig. 1).

The antiviral drug remdesivir should be considered for those known to be PCR-positive and/or with a presentation consistent with typical COVID-19. This should be guided by a pediatric infectious disease consultant and by current treatment guidelines. In particular, remdesivir is recommended in COVID-19 patients requiring supplemental oxygen, or oxygen through a high-flow device or non-invasive ventilation, but not in patients needing invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO). Remdesivir is not recommended in patients with abnormal liver function or severe renal compromise. For children under twelve years old, remdesivir has a U.S. Food and Drug Authority (FDA) emergency use authorization. The current remdesivir dosing for children is 5 mg/kg load IV (maximum 200 mg) on day 1, then 2.5 mg/kg (maximum 100 mg) IV daily for 4–9 days. There does not appear to be a role for convalescent serum or recombinant antibodies for these presentations, even for patients presenting with acute SARS-CoV-2 [49].

A number of adjunct therapies have been used because of the profound inflammatory response and KD-like features, although few studies support their use. Many centers have treated children that present most similarly to KD with traditional therapy used for KD, as detailed in recent guidelines [35]. For those who qualify as a case of KD, including concern for coronary artery involvement on echocardiogram, we recommend giving IV immunoglobulin G (IVIG) 2 g/kg and oral high dose aspirin 20–25 mg/kg/dose every 6 h (80–100 mg/kg/day) until the fever resolves. Daily low dose aspirin 3–5 mg/kg/day (maximum 81 mg) is then prescribed after initial improvement and maintained until coronary arteries are assessed during outpatient follow-up with pediatric cardiology. Acute aspirin dosage may also vary at individual centers.

Recent data from a retrospective review supports the use of corticosteroids in MIS-C cases [50]. Patients treated with IVIG alone were compared to IVIG and methylprednisolone. Most cases received 0.8 to 1 mg/kg (maximum 30 mg) methylprednisolone every 12 h for 5 days, while the remaining children received a bolus of 15 to 30 mg/kg/day of methylprednisolone for 3 days. All primary (fever) and secondary endpoints (additional therapy, hemodynamic support, left ventricular dysfunction, and length of pediatric intensive care unit stay) favored inclusion of corticosteroids. Initiation of three-day pulse methylprednisolone with the initial IVIG infusion for children with KD can be considered for children at high risk (infants, KD shock syndrome, CRP $>$ 130 mg/L, admission echo Z score $>$ 2.5 or aneurysms, and Asian race).

Current data supports the use of both IVIG and corticosteroids in all three categories of MIS-C. Dexamethasone has been used as an adjunctive treatment for hospitalized patients with active COVID-19 infection with prominent respiratory features and/or shock; however, methylprednisolone is more commonly used for MIS-C. A recently-published randomized controlled trial and retrospective trials suggest superiority of methylprednisolone over dexamethasone for acute/respiratory COVID-19 [51,52]. We would recommend use of methylprednisolone in all cases of MIS-C, unless there is a high index of suspicion for concomitant infection or if steroids are contraindicated.

Many centers, including ours, will use the IL-1 receptor antagonist anakinra if additional immune modulation is required. However, no formal studies support or refute this approach [53]. If the clinical presentation is most consistent with KD, and there is failure of first line treatment, a second dose of IVIG or infliximab (a TNF-α inhibitor) could be considered, per KD guidelines [35]. Other immunomodulators are not recommended [27], but can be used if a patient is refractory to optimized methylprednisolone, anakinra, and IVIG treatment. In our experience, early initiation of aggressive treatment has led to short hospitalization time, minimal organ damage, and good short- and long-term outcomes (see Rheumatology section for details).

9. Subspecialty approaches

9.1. Gastrointestinal presentation and findings

MIS-C frequently presents with prominent gastrointestinal (GI) signs and symptoms (70–90% of reported cases) [9–11,13–17] including abdominal pain, diarrhea, nausea, vomiting, constipation, and GI bleeding [54,55]. GI manifestations are not surprising since enterocytes, including those lining the appendix, are rich in angiotensin-converting enzyme 2 (ACE2), the receptor used by SARS-CoV-2 [56]. GI manifestations in MIS-C may be severe and prompt surgical intervention. Appendicitis has been described in PCR-negative/antibody-positive case reports [57,58] and a case series where all were PCR-positive but had other characteristics consistent with MIS-C [42]. The clinical presentation may also resemble inflammatory bowel disease and include severe abdominal pain and GI bleeding [54,55]. GI symptoms may initially be mild before progressing to signs of acute abdomen [59,60]. Cases presenting with severe abdominal pain or evidence of GI bleed must be approached cautiously, as cases of unrelated isolated acute appendicitis may also appear to be MIS-C at first glance [61] and a number of children with bacterial gastroenteritis due to *Campylobacter* or *Salmonella* have been misdiagnosed as MIS-C [62]. In addition to bowel pathology, acute hepatitis has also been reported in MIS-C. In the majority of cases, acute hepatitis is associated with severe disease, including shock, and it may be a secondary severe MIS-C rather than a primary MIS-C hepatic disorder [63].

For those with significant GI manifestations, testing beyond "*Set 1*" labs (Fig. 1) should include pancreatic enzymes and specific imaging. A plain abdominal X-ray can evaluate for signs of perforation, and abdominal CT will be helpful for acute abdomen presentations due to inflammatory bowel disease-like disorder, appendicitis, or bowel perforation. Pediatric GI and/or surgical consultation is critical to address appropriate evaluation, as well as medical and/or surgical treatment.

9.2. Cardiology

Prior to the COVID-19 pandemic, it was very uncommon for children presenting with KD to have shock or myocardial involvement [64]. Cardiac findings in KD typically manifest with coronary artery changes and rarely with depression of ventricular function. Initial published and non-published reports of COVID-19-associated MIS-C cases describe ventricular dysfunction, coronary artery changes, atrioventricular valve regurgitation and pericardial effusions [9–11,26]. Therefore, it is prudent for cardiac screening to be completed early in the hospital course. This should include measures of cardiac injury and ventricular dysfunction. We recommend obtaining an EKG and echocardiogram on all children with suspected MIS-C during hospitalization.

In children presenting with shock (most have reported vasodilatory shock), fluid resuscitation is imperative in the initial management. As there is a high potential for underlying cardiac dysfunction, patients should be frequently reassessed during fluid resuscitation for evidence of fluid overload, such as pulmonary edema or hepatomegaly. In centers with bedside ultrasound available, evaluation of cardiac function may be considered early in resuscitation to determine best management. Complete transthoracic echocardiograms should be performed urgently in all patients with clinical or laboratory evidence of cardiac injury and/or shock (see Fig. 1). In children with reassuring initial cardiac evaluation or mild to moderate disease, it is reasonable to consider ongoing cardiac screening throughout hospitalization due to reports of rapid decompensation. It is also reasonable to follow serum troponin and/or BNP levels and consider repeating echocardiograms in children with significant laboratory or clinical changes.

All children with MIS-C should have outpatient follow-up with pediatric cardiology. We recommend follow-up about one month after diagnosis for children without evidence of cardiac involvement during their hospital course. Closer follow-up is needed for children with myocardial involvement. Recommendations from the American Academy of Pediatrics is to treat all children with MIS-C similarly to children who have had viral myocarditis [65]. This includes exercise restriction for 3–6 months and obtaining specific cardiology clearance prior to resuming training or competition. During those visits, repeat cardiologic testing may include electrocardiogram, cardiac MRI, and stress testing to evaluate for any evidence of myocardial injury or scarring depending on the individual case and available testing modalities.

9.3. Critical care

Critical care evaluation and management are warranted in most cases [10,11,37,66]. Early recognition of a shock state (vasoplegic vs cardiogenic), proper and judicious fluid resuscitation, early establishment of invasive monitoring, intubation and mechanical ventilation, optimization of oxygen delivery (DO_2), minimization of oxygen consumption (VO_2), and appropriate initiation of inotropes and vasopressors are key factors to successful and favorable outcomes [11,67,68]. This initial approach combined with multidisciplinary management and initiation of early but comprehensive diagnostics help to guide further therapeutic choices (e.g., antithrombotic agents, antibiotics, and immune modulating medications). There is an increasing recognition of neurological manifestations including seizure, headache, meningitis, encephalopathy, muscle weakness, brain stem and cerebellar signs that also support critical care involvement [69].

Extracorporeal therapies like plasmapheresis (therapeutic plasma exchange) [70] and ECMO [11,66] may have a role in treating and supporting these patients especially in cases of severe inflammation, refractory ventricular arrhythmia, refractory vasoplegia, cardiogenic and septic shock. An earlier report from Switzerland and France supports such an approach [11]. This study described the experience of 35 critically ill children with MIS-C presenting with acute myocardial injury/myocarditis and cardiogenic shock. Initial symptoms on presentation were mainly fever, fatigue and GI manifestations. Inotropic support was required in 80% of cases, while veno-arterial (VA) ECMO was initiated in 28% in this cohort. Despite the rapid deterioration at presentation, a rapid resolution of the systolic myocardial function was noted. All patients survived and none had embolic or thrombotic events. All patients received IVIG and 65% received heparin for anticoagulation. Patients with this severity of decompensation should be considered for aggressive immunomodulation and antithrombotic management, as these interventions have clinically been shown to alter the course of these patients rapidly.

A meta-analysis of 27 case series which included 917 MIS-C cases showed a third of patients required intubation and mechanical ventilation, while 6.3% received ECMO. Left ventricular dysfunction or myocarditis was present in 55.3% (95% CI, 42.4–68.2) and the pooled prevalence of coronary artery aneurysm or dilatation was 21.7% (95% CI, 12.8–30.1) [66]. The recent updated COVID-192021 ECMO guidelines from the Extracorporeal Life Support Organization (ELSO) recommends applying similar known principles that are currently published in ELSO guidelines for patient selection of pediatric COVID-19 associated respiratory failure and cardio-circulatory failure related to MIS-C [71]. While mortality was similar in acute pulmonary COVID-19 and MIS-C requiring ECMO, organ support requirements and therapeutic strategy certainly differ between the two syndromes.

9.4. Hematology

COVID-19 infection in adults has been associated with high rates of thromboembolic events (TE) including deep vein thrombosis, pulmonary embolism, digital ischemia, arterial thrombosis, microvascular thrombosis and strokes despite prophylactic anticoagulation [72]. Prophylactic anticoagulation for adults hospitalized with COVID has been widely accepted and endorsed by the American Society of Hematology, the NIH, the CDC, the International Society for Hematology and Thrombosis, and the American College of Chest Physicians. A number of clinical trials are examining the benefit, if any, of the intensity of anticoagulation in adults hospitalized with COVID (ATTACC: NCT# 04372589, ACTIV-4a trial: NCT# 04505774, and REMAP-CAP: NCT#02735707).

Strategies regarding prophylactic anticoagulation in pediatric patients with COVID-19 and MIS-C vary institutionally, but many have elected for a minimum prophylactic anticoagulation strategy in adolescents and the critically ill. Expert consensus guidelines [73] support prophylactic anticoagulation for pediatric patients with COVID or MIS-C who have elevated D-dimer levels > five times the upper limit of normal, age above twelve years, or with risk factors including a central line, mechanical ventilation, obesity, hospital stay > three days, immobility, active malignancy, nephrotic syndrome, cystic fibrosis exacerbation, sickle cell exacerbation, inflammatory disease (e.g., lupus, juvenile idiopathic arthritis, inflammatory bowel disease) with exacerbation, congenital/acquired cardiac disease with impaired venous return, or a personal or first-degree relative with a history of VTE, known thrombophilia and others. Decisions regarding post-hospital discharge prophylaxis should be individualized and considered for patients with existing risk factors (as above), an elevated D-dimer on discharge, or those who have not returned to previous level of functioning. Patients with expanding or large coronary artery aneurysms will require therapeutic anticoagulation and antiplatelet therapy, following established guidelines for KD [35]. The effect of these interventions in ameliorating disease severity needs further study.

In an analysis of 814 children hospitalized with MIS-C, COVID-19 or asymptomatic SARS-CoV-2 infection, 20 children had TE. MIS-C had the highest rate of TE (6.5%), followed by COVID-19 and asymptomatic SARS-CoV-2 (2.1% and 0.7% respectively). 89% of TE occurred in children 12 years of age and older, with 19% of children with MIS-C in this age group having TE. No children with MIS-C under 12 years old had a TE. 68% of TE were symptomatic and 20% were present on admission. Risk factors identified by multivariate analysis included MIS-C, the

presence of a central venous catheter (47% of TE were line associated), age 12 years or older and diagnosis of cancer. Other conditions associated by univariate analysis included Hispanic ethnicity, African American racial background, prolonged length of stay, intensive care unit admission, mechanical ventilation, elevated fibrinogen, reduced platelet count, D-dimer > five times the upper limit of normal, low platelet counts and death. In cases that lacked TE on admission, 71% of cases of TE occurred despite thromboprophylaxis. Mortality was 28% for patients with TE and MIS-C or COVID-19, although most patients had concomitant co-morbidities [74].

Coagulopathy and cytopenias are also observed with MIS-C. In critically-ill adults with acute COVID, bleeding complications have become increasingly recognized [75]. Other post-infectious complications including the development of autoimmune hemolytic anemias (warm, cold, direct antiglobulin test-negative, or cold agglutinin disease), immune thrombocytopenia, autoimmune thrombotic thrombocytopenia purpura have also been observed [76].

9.5. Infectious diseases

Sepsis and/or toxic shock should be considered and addressed in all cases presenting with cardiovascular compromise, and empiric antibiotics are recommended as previously detailed (see Fig. 1). Also previously discussed, acute SARS-CoV-2 infection may need to be treated. A number of children with suspected MIS-C may also fall into KD classification. We approach both conditions similarly in follow-up with visits scheduled 2 weeks and 4–6 weeks after initial presentation, with repeating of abnormal lab values to document normalization. Not uncommonly, we are faced with the challenge of considering multiple alternative diagnoses concurrent with initiating treatment for MIS-C. IVIG has low risk with other concurrent infections. If non-MIS-C diagnoses, such as focal bacterial infection or enteritis, become more likely, steroid therapy is either used sparingly or held until other conditions are ruled out.

During the acute presentation, our center pursues testing for other causes of infectious cardiac and systemic inflammation. This includes respiratory viral PCR testing (influenza, parainfluenza, rhinovirus, respiratory syncytial virus, metapneumovirus, SARS-CoV-2) and specific testing for adenovirus, coxsackievirus, cytomegalovirus, Epstein-Barr virus, parvovirus B19, and group A streptococcus. Hepatitis should be ruled out if liver function tests are abnormal. Serologic testing should be sent before IVIG treatment is initiated. HIV and other sexually-transmitted diseases should be screened for in patients 13 years of age or older or with risk factors. Conventional blood and urine cultures should be sent. Throat and sputum cultures may be sent to help rule out streptococcal or staphylococcal involvement. Endotracheal cultures done during initial intubation or with significant change in respiratory status may be helpful, particularly if nosocomial secondary infections are considered. Next generation sequencing modalities are used on a case-by-case basis and should be considered in patients with unexplained prolonged symptomatology or cases refractory to management.

9.6. Rheumatology

The role of a pediatric rheumatologist in the assessment and management of children with MIS-C has become more prominent over time, due to their experience with hyper-inflammatory conditions and with immunomodulatory therapies. At the present time, there is insufficient evidence to suggest that children with rheumatic diseases or those treated with immunomodulatory agents are at increased risk of developing MIS-C or of having a more severe outcome from SARS-CoV-2 infection [77]. Many children with MIS-C exhibit symptoms and laboratory findings consistent with hyper-inflammation, most likely due to an overproduction of pro-inflammatory cytokines including TNF, IL-6, and IL-1β. The clinical symptoms of high fevers, rashes, subcutaneous edema combined with laboratory abnormalities of elevated CRP, ESR and ferritin levels are indicative of this [41].

We agree with a stepwise approach to treatment for hospitalized patients. We suggest patients that meet MIS-C criteria and are admitted to the hospital receive IVIG 2 g/kg as a first line treatment. Reasoning for this includes a relatively low risk if other conditions (infection or malignancy) are missed, the widespread use and efficacy demonstrated in KD for prevention of coronary artery aneurysms, and the anti-inflammatory properties it exhibits in other immune mediated conditions (dermatomyositis, immune thrombocytopenic purpura, chronic inflammatory demyelinating polyneuropathy, myasthenia gravis, and other vasculitis syndromes). Due to the medication volume, patients with cardiac dysfunction will need to be monitored more closely during and after infusion, and consideration given to split the dose to 1 g/kg/day over 2 days. We also suggest that corticosteroids be given as an adjunctive therapy. Methylprednisolone IV (2–30 mg/kg/day, max 1 g) is preferred and used most often on presentation and doses will depend on severity of disease. Once a patient improves and can tolerate PO this can be switched to an oral form of prednisone (1–2 mg/kg/day, max 60 mg). This approach is supported by a recent study from France that showed that combined treatment with IVIG and steroids led to a lower risk of treatment failure [50]. Classifying patients in terms of severity of disease has proven difficult and subjective based on the evaluating clinician, the timing of the evaluation (as changes can occur rapidly within hours and daily), and timing of treatments given. It is reasonable to give IVIG and corticosteroids soon after diagnosis and reassess if higher doses of steroids are needed, or if anakinra needs to be added to the regimen. We propose the use of IVIG, high-dose corticosteroids and anakinra as early as possible among patients with shock, cardiac dysfunction or evidence of other severe organ dysfunction or respiratory failure. This approach in our center has anecdotally led to relatively short hospitalizations and good overall outcomes.

Anakinra, a recombinant human IL-1 receptor antagonist, has a quick onset, a short half-life (4 h), a large therapeutic window, and a good safety profile [78]. Dosing ranges from 2 to 20 mg/kg/day, depending on severity of disease [27]. This can be considered as first-line treatment for patients with severe disease, or added to patients that are refractory to use of IVIG and/or corticosteroids, or to those with contraindication to use of corticosteroids. IL-1 blocking agents are FDA approved for several autoinflammatory syndromes and systemic onset juvenile idiopathic arthritis [79] and they have an excellent safety profile [78,80–82]. As with any immune modulating agent, the main risk is infection. However, with its short half-life, anakinra may be discontinued and its effects short lived if a concurrent infection is found, or if the clinical condition worsens. There are case descriptions of anakinra use in a small number of MIS-C patients and anakinra has been used successfully in a small number of patients with IVIG-resistant KD [83–85]. Children with MIS-C require a prolonged course of corticosteroids to avoid rebound inflammation. Once afebrile and stable in the hospital and medication is changed to oral form, the doses can be tapered most often over a 2–3 week time period.

9.7. Hospital course

The hospital course can be highly variable. We recommend daily clinical and laboratory evaluation be done on all hospitalized children depending on the disease classification (see Fig. 1). We advise stopping antibiotics after 48 h unless bacteremia is diagnosed, or localized secondary infection is suspected. Children should be continuously monitored for fevers or evidence of ongoing or increasing inflammation. If clinical inflammation continues or worsens, retreatment or alternative therapy should be considered, as guided by infectious diseases and rheumatology. Aspirin dosing is similar to American College of Rheumatology MIS-C guidelines [27]. All children with MIS-C receive daily low-dose aspirin. Our center will hold on aspirin for children with thrombocytopenia until platelets are near normalization. If high-dose aspirin was begun due to presentation similar to KD, our center

decreases aspirin dosing to 3–5 mg/kg daily once the child is afebrile for more than 24 h. This will continue after discharge until follow-up with pediatric cardiology.

9.8. Discharge criteria and follow-up

To confirm clinical recovery and prevent readmission, we recommend the following criteria for hospital discharge: 3–4 days of downtrending inflammatory markers (ferritin, CRP, D-dimer), troponin consistently declining and < 1.0 ng/mL, 48 h without need for supplemental oxygen, 48 h without fever, 48 h off vasopressors, a normal EKG, therapeutic anti-factor-Xa level if going home on enoxaparin, eating and drinking adequately, heart failure symptoms controlled with oral medications (if applicable), and stable or improved findings on repeat echocardiogram (stable or improved ventricular function, coronary artery abnormalities, and valve function).

Recent data from 46 cases on 6 month follow-up suggests a reduction in functional exercise capacity, but few long-term organ specific morbidities after recovery [86]. We continue to recommend close follow-up. Follow-up visits should be scheduled with the child's primary care provider within 24–72 h after discharge. Rheumatology follow-up at our institution is usually 1–2 weeks after discharge and includes repeat of pertinent laboratory markers, and if corticosteroids were used, a slow tapering off guided by clinical and laboratory parameters. Cardiology follow-up will vary depending on degree of cardiac involvement, but at minimum, all patients should follow up 4 weeks after discharge [27]. We have children follow-up with infectious disease to review similarities to KD convalescence (such as peeling rash or reactive thrombocytosis) and for consideration of measurement of convalescent titers for any alternative diagnoses. These visits typically coincide with cardiology clinic visits. Other follow-up visits are dependent on the child's clinical course. There is little data to guide the optimal timing for vaccination after recovery from a case of MIS-C. Currently, the CDC suggests considering delaying vaccination until three months after MIS-C diagnosis if full recovery has been achieved [87].

10. Discussion

As most reports of MIS-C are in persons under 21 years of age, this emerging condition presents a challenge for general pediatricians and pediatric subspecialists. For children that fall into the case definition, a multi-disciplinary team approach is necessary to decide ongoing care as the disease manifestations can be significantly different. Advancing the level of care (transferring to tertiary care and intensive care) of children that fulfill the criteria for MIS-C remains a strong consideration due to the multidisciplinary nature of care and potential severe outcomes.

Our group agrees with the majority of the current recommendations proposed by the panel from the American College of Rheumatology [27]. Our approach differs slightly in a few areas. With the recent data supportive of improvements in fever, cardiac function, and hospital course [50] we have treated all cases of suspected MIS-C warranting hospital admission with IVIG and methylprednisolone. We are likely to continue this practice except in cases with specific contraindications or a strong suspicion of alternative acute infections. For cases that present with a wider differential that includes invasive bacterial disease, initiating treatment with IVIG alone or IVIG with low dose methylprednisolone should be considered. In severe presentations including those with shock, we would start with high doses of methylprednisolone (10–30 mg/kg/day) and have a low threshold to add anakinra early in the course.

As cases of MIS-C continue to temporally follow local disease spread, we advise continued vigilance in the approach to febrile children with recent history of or close exposure to SARS-CoV-2. Vaccination of persons of all ages, including children, is necessary to prevent continuous spread and should, in effect, prevent MIS-C. Rare cases of transient myocarditis in adolescents and young adults following the second dose of mRNA-based vaccines do not appear to have symptomatic overlap with MIS-C, but details are not yet published. Despite the rarity of these reports, they may affect the uptake of vaccine in pediatric populations. The diagnosis of MIS-C cases will become even more challenging as vaccination and natural immunity lead to lower circulating rates of SARS-CoV-2 infection as cases are likely to be more sporadic.

11. Conclusion

MIS-C continues to be a highly concerning diagnosis in those recently infected with SARS-CoV-2. Febrile children presenting with cardiac dysfunction, symptoms overlapping KD or significant GI complaints warrant a thorough screen in emergency departments, urgent care centers, and outpatient pediatric or family medicine practices. An increased index of suspicion and discussion regarding higher level of care (transferring to pediatric tertiary care centers or to intensive care) continues to be recommended. As outlined herein, a broad initial approach with a multidisciplinary team for those meeting the case definition is crucial for successful outcomes.

Funding

This work did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

CRediT authorship contribution statement

Teresa R. Hennon: Conceptualization, Writing – original draft, Writing – review & editing, Visualization. **Karl O.A. Yu:** Visualization, Writing – review & editing. **Michelle D. Penque:** Conceptualization, Writing – original draft, Writing – review & editing. **Rabheh Abdul-Aziz:** Writing – review & editing. **Arthur C. Chang:** Writing – review & editing. **Megan B. McGreevy:** Writing – review & editing. **John V. Pastore:** Writing – review & editing. **Andrew J. Prout:** Writing – review & editing. **Beverly A. Schaefer:** Writing – review & editing. **Omar S. Alibrahim:** Writing – review & editing. **Oscar G. Gomez-Duarte:** Visualization, Writing – review & editing. **Mark D. Hicar:** Conceptualization, Writing – original draft, Writing – review & editing, Visualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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