Le Infezioni in Medicina, n. 3, 344-352, 2022
doi: 10.53854/liim-3003-3

MIS-C related to SARS-CoV-2 infection: a narrative review of presentation, differential diagnosis, and management

Salika Gadiwala[1], Ayushi Mistry[2], Sejal Patel[3], Avanthika Chaithanya[4], Stuti Pathak[5], Travis Satnarine[6], Daria Bekina-Sreenivasan[7], Abdul Akim Bakarr[8], Bibhuti Bhusan Das[9], Raja Chandra Chakinala[10], Saurabhkumar Patel[11], Sathya Areti[12]

[1]Department of Public Health, Drexel University/Dornsife School of Public Health, Philadelphia, PA, USA;
[2]Department of Pediatrics, Dr. N. D. Desai Medical College and Research Center, Gujarat, India;
[3]Department of Pediatrics, Government Medical College, Surat, India;
[4]Department of Pediatrics, Karnataka Institute of Medical Sciences, Hubli, India;
[5]Gujarat Child Care Hospital, Ahmedabad, India;
[6]Port of Spain General Hospital, Trinidad and Tobago;
[7]Tyumen State Medical University, Tyumen, Russia;
[8]St. George's University Medical School, Grenada, West Indies;
[9]Department of Forensic Psychiatry, Central New York Psychiatric Center, OMH, NY, USA;
[10]Department of Internal Medicine, Guthrie Robert Packer Hospital, Sayre, Pennsylvania, USA;
[11]Department of Pediatrics, University of Illinois Hospital & Health Sciences System, Chicago, IL, USA;
[12]Department of Internal-Medicine-Pediatrics, Case Western University Hospitals/Rainbow Babies, Cleveland, OH, USA

Article received 25 7 2022, accepted 25 June 2022

SUMMARY

Multisystem Inflammatory Syndrome in Children (MIS-C), a rare condition, has been reported approximately 2-4 weeks after the onset of COVID-19 in children and adolescents, causing inflammation in multiple systems, including cardiovascular and respiratory, digestive, and central nervous systems. This condition is also known as hyperinflammatory shock, Kawasaki-like disease, and Pediatric Inflammatory Multisystem Syndrome (PIMS). The signs and symptoms include but are not limited to fever, rash, peripheral edema, gastrointestinal symptoms, conjunctivitis, and shock. Thirty-eight studies met our criteria, with a total of 5822 patients. The most affected population was between 5-18 years of age. We noted that MIS-C presented with a wide range of signs and symptoms that overlap with Kawasaki Disease, including high fever, sore throat, malaise, tachypnea, tachycardia, conjunctival injection, mucosal edema, cardiac involvement, and gastrointestinal symptoms. It causes an increase in IL-17A, IL-6, and arterial damage, a distinct difference from Kawasaki disease. The laboratory findings in MIS-C showed an increase in inflammatory markers like CRP, ESR, ferritin, leukocytes, and TNF-α. WHO stated that 23% of affected children with MIS-C had underlying conditions like chronic lung diseases, cardiovascular disease, and immunosuppression. In most affected children, aspirin and IVIG were successful, which resulted in a decrease in the inflammatory markers. We find that MIS-C is a rare, but potentially fatal pediatric complication, after COVID-19 infection. The aim of this article is to study the emerging relationship between COVID-19 and MIS-C in children and adolescents affected by this condition, to discuss the immunological mechanisms, and explore potential therapies.

Key Words: COVID-19, Kawasaki disease, MIS-C, pediatrics.

Corresponding author
Salika Gadiwala
E-mail: salikagadiwala13@gmail.com

INTRODUCTION

Since its discovery in China in late 2019, Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) has spread swiftly. COVID-19 was classified as a pandemic by the World Health Organization (WHO) on March 11, 2020 [1]. Previous studies suggested that young children were disproportionately spared, although it is unclear if this was due to a lack of detection, or due to the prevalence of asymptomatic or mild illness [2]. Many cases of children with hyper-inflammatory shock with symptoms comparable to Kawasaki Disease (KD) and Toxic Shock Syndrome were described in England in April 2020 [3]. Verdoni et al. observed a 30-fold rise in the incidence of KD in Bergamo, Italy [4]. On May 14, 2020, the Centers for Disease Control and Prevention (CDC) released a Health Advisory summarizing the symptoms of the reported multisystem inflammatory syndrome in children (MIS-C) [5].

All the children showed serologic evidence of infection with SARS-CoV-2 and their symptoms were temporally linked with COVID-19. Fever, rash, conjunctivitis, peripheral edema, gastrointestinal (GI) symptoms, shock, increased indicators of inflammation, and heart injury were all present in this cluster [6]. The signs and symptoms of MIS-C are similar to KD, though Whittaker et al. described a wider spectrum of symptoms in MIS-C [7]. MIS-C affected children older than 7 years while Kawasaki affected those under 5 years [7]. Most COVID-19 patients in the pediatric population are asymptomatic, but those who develop symptoms are more prone to hyper-inflammatory shock and hypotension with cardiac and other end-organ injuries [8]. In comparison to KD, which is commonly seen in East Asian populations, MIS-C is reported mainly in African and Hispanic populations [7].

Due to scattered and insufficient data on the epidemiology, clinical spectrum, and immunological profile of MIS-C associated with post-COVID-19 infection, diagnostics and treatment modalities are limited. This review aims to briefly summarize the clinical picture of MIS-C, the current perspectives on its clinical and immunological differentiation compared to KD, and discusses potential therapeutic interventions.

METHODS AND RESULTS

We performed a narrative review of articles, from April 2020 to July 2021, on the COVID-19 positive (RT-PCR confirmed) pediatric population in the following databases: PubMed, Elsevier, and Google Scholar. Our inclusion criteria were children less than 18 years of age with signs and symptoms of MIS-C post-COVID-19 infection, regardless of their country of origin, if the publications were in English or an English translation was available. We discussed the period between the COVID-19 onset and MIS-C, differentiated between MIS-C and Kawasaki, and explored therapeutic options, demographic variables, clinical features, and laboratory markers.

Our literature search identified 79 articles, of which 38 articles met our criteria, with a total of 5822 patients. The most affected population was 5-18 years of age. These included various case reports, case series, cross-sectional and cohort studies. These studies have been conducted from April 2020 to July 2021. The number of patients ranged from 1 to 1733 (median, 7). Each article was summarized based on presenting features, laboratory and radiological evaluations, diagnosis, and treatment protocols. (Refer to the section: Supplementary Information).

DISCUSSION

Epidemiology

According to the papers we reviewed, MIS-C can be seen in children of any age. The CDC has defined a child as anyone under the age of 21. However, the American Heart Association has not specified age [7]. The influence of gender on the incidence of MIS-C is debatable. Some experts narrate a significant difference between males and females such as a study by Riollano-Cruz et al., where 15 children were diagnosed with MIS-C, of which eleven (73%) were male and four (27%) female [9]. In our analysis, there were 2919 males and 2257 females (1.3:1 ratio). Observational studies in countries with multiple racial communities showed a higher incidence in Hispanic or Latino individuals (40.5%) and people of African ethnicity (33.1%), while a lower incidence was seen in non-Hispanic white children (13.2%) [6].

Clinical features

MIS-C in children has a wide range of features. In April 2020, Riphagen et al. described some of the first cases among children in the United Kingdom with features such as persistent fever, rash, conjunctivitis, edema, and pain of the extremities [3]. In May 2020, CDC gave a case definition for MIS-C:

- A person with age less than 21 years, with symptoms of fever, clinically severe illness which requires hospitalization, involvement of multi-organ systems (should be more than two of the following- cardiac, respiratory, renal, gastrointestinal, hematological, neurological, or dermatological) and lab evidence of inflammation; AND
- All other diagnoses are ruled out; AND
- COVID-19 positive by a rapid antigen test, RT PCR, or serology for current or recent infection; or exposure to COVID-19 has occurred 4 weeks before the onset of symptoms [5].

Among the symptoms listed by CDC, most notable were GI manifestations and Kawasaki-like features, including rash, red-eye, and rarely, coronary artery enlargement/aneurysm. Most worrisome were shortness of breath, concerning for congestive heart failure or pulmonary embolism, and a toxic shock-like syndrome with cytokine storm/macrophage activation [10].

Later Verdoni et al. studied cases in Bergamo, Italy comparing cases of KD in children during the COVID pandemic (Feb-April 2020) and a previously collected cohort [4]. They found major differences, leading them to classify the patients as "Kawasaki-like disease". The authors divided the patients, into two groups - classic and incomplete form. The 10 patients (4 to 11 years) were, on average, hospitalized on the 6th day of fever with the classic form presenting with the rash on hands and feet, conjunctivitis, associated changes in the lips and oral cavity, with one patient showing cervical lymphadenopathy. Patients in the incomplete form only had 3 or fewer of the clinical criteria, and some of them showed signs of hypoperfusion, meningeal irritation, and diarrhea [4].

Rare presentation and differential diagnosis

At the peak of the pandemic in April 2020, there was a 30-fold increase in the incidence of KD with severe cardiac involvement and similar features like Macrophage Activation Syndrome (MAS) in the European region [4]. Researchers observed Kawasaki-like Disease associated with SARS-CoV-2 Infection, which started 2-4 weeks after the infection [4]. Ziaee et al. and Domniguez S. et al. described how viral infections can be a trigger for activating the immune system in KD. Earlier, human coronavirus (HCoV)-NL63 infection was linked with a higher incidence of KD but that study failed to establish an etiological relationship with Kawasaki Syndrome [11, 12].

According to a CDC report, on June 28, 2021, the total number of patients with MIS-C was 4196 and the total MIS-C deaths were 37 [13]. The patients' median age was 9 years, with half of the age range between 5-13 years. 62% of patients' race/ethnicity fell into either Hispanic, Latino, or Black. 99% of the patients with MIS-C were tested positive for COVID-19 infection and the other 1% had history of contact with a positive person [13].

The study published in Aug 2020 in CDC's Morbidity and Mortality weekly report with 570 MIS-C patients, showed that 35.6% of patients had similar clinical courses to previous reports. All patients had positive SARS-CoV-2 infection. The remaining 64.6% of patients had less severe clinical courses with symptoms overlapping with acute COVID-19 infection or KD [6]. Patients with MIS-C and COVID-19 Infection showed low WBC count in comparison to KD and healthy children. Consiglio C. et al. described lymphopenia as a hallmark of COVID-19 infection which is evident in MIS-C patients [14]. Thrombocytopenia, elevated CRP, and ferritin are also significant markers in MIS-C, while IL-17A-mediated hyperinflammation is evident only in KD [14].

MIS-C symptoms are overlapping with the following diseases:

Kawasaki Disease (KD)

KD is medium-sized artery vasculitis prevalent in children less than 5 years of age [11]. As per the American Heart Association, KD is divided into two types: Classical Type: Fever (≥5 days) plus four or more clinical criteria (includes bilateral bulbar non-exudative conjunctivitis, polymorphic rash, non-suppurative laterocervical lymphadenopathy, changes of the lips or oral cavity, erythema of the palms and soles, firm induration of the hands or feet, or both) or Incomplete Type: Fever (≥5 days) plus two or three of the clinical criteria mentioned above [15].

Kawasaki Disease Shock Syndrome (KDSS)
KD can be worsened by hemodynamic irregularities defined as KDSS [16]. Patients require intensive support due to severe hypotension and shock [16]. Other symptoms include lymphadenectasis, hypoalbuminemia, hyponatremia, hepatic insufficiency, anemia, and severe gastrointestinal symptoms [17]. It is also associated with a higher risk of coronary artery abnormalities with a high incidence of coronary artery dilatation, mitral regurgitation, and prolonged myocardial dysfunction [16-18].

Macrophage Activation Syndrome (MAS)
MAS or secondary Hemophagocytic Lymphohistiocytosis (HLH) is a phenomenon that occurs due to inappropriate activation of macrophages that leads to cytopenia, organ dysfunction, and coagulopathy [19]. Rheumatic diseases are most frequently associated with the complications of MAS, though there is evidence of association of MAS among KD patients [20-22]. In MAS, ESR usually begins to fall with major three cell lines in the blood. With laboratory evidence of liver dysfunction, coagulopathy, and hemophagocytosis, a sepsis-like picture develops [23].

Toxic Shock Syndrome (TSS)
TSS is a fulminant syndrome characterized by uncontrolled activation of the immune system by "superantigens", which are proteins that activate the T Cell cascade which leads to increased production and release of cytokines [24]. It presents with acute onset fever, rapidly progressive hypotension with renal failure, and multisystem organ involvement [25].

Similarity with KD
In genetically susceptible people, infection appears to cause a dysregulated immunological response in KD [9]. Rowley et al. proposed that the etiology of KD might be connected to a respiratory pathogen with vascular tissue tropism, most likely a virus [26]. Another Japanese team used serological testing to investigate the link between coronaviruses (HCoV-NL63 and HCoV-229E) and KD. SARS-CoV-2, a highly virulent strain capable of eliciting a robust immunological response might be one of the causes of KD [4].
Symptoms and organ dysfunction in KD and MIS-C both are caused by cytokine storm, which causes systemic inflammation [9, 26, 27]. In MIS-C, the inflammatory storm is more severe [28]. S-100 and IL-18 concentrations are similar in MIS-C and KD, according to Rodriguez-Smith et al. However, INF-γ-induced chemokine ligand 9 (CXCL9) is a biomarker that can help distinguish MIS-C from KD [29]. Another significant distinction is the cytokine profile that leads to an inflammatory process between the two. IL-1 is the major mediator of coronary artery inflammation in individuals with KD, and IL-1 inhibition has been utilized to treat resistant KD. MIS-C, on the other hand, appears to be primarily driven by IL-6 and IL-8 [9].
Immunochemistry of mucosal biopsy from a COVID-19 patient with GI symptoms manifested SARS-CoV-2 in endothelial cells. There were similar changes in small and medium-vessel vasculitis as in KD patients [26]. Some new studies have identified autoantibody targeting antigens on mucosal and cardiac tissues in MIS-C patients. Patients with KD have also been shown to have these auto-antigens [26].
Some clinical features are common between KD and MIS-C, such as conjunctival injection, mucositis, and edema of the hands and feet [29]. The distinct features of MIS-C are stomach discomfort, cardiac dysfunction, and hypotension [2]. The symptoms of MIS-C resemble KDSS. Ahmed et al. described that 60.2% of children with MIS-C suffer from shock [27].
Blondiaux et al.'s research suggest similarity in pathophysiology between KD and MIS-C. Cardiac MRI of MIS-C patient showed myocardial edema and hyperemia, which correlated with a histological finding of KD hearts, revealing macrophage and neutrophil infiltration in the myocardial interstitium [30]. Hameed et al. did prospective observational research suggesting comparable x-ray and CT chest features (ground-glass opacities, local patchy shadowing, and interstitial abnormalities (44%) between KD and MIS-C children [31].

Diagnosis
If a patient is suspected to have MIS-C, based on history and physical findings, testing is warranted to establish the diagnosis [32]. Tests include laboratory evidence of inflammation (can give examples of the inflammatory labs since this section is mainly diagnosis) and COVID-19 tests [32]. Nakra et al., suggest tests may be beneficial in the

evaluation of generalized inflammation, multisystem involvement, and possible infection [2].
Based on the American College of Rheumatology (ACR) task-force evaluation, an algorithm has been established for the diagnosis of MIS-C [33]. The guidance suggests that if the child presents with unremitting fever, a link to COVID-19, and suggestive clinical features, to first consider other overlapping syndromes, then consider if the child presents with shock of unclear etiology. If present, a full diagnostic evaluation occurs. If not, the diagnosis can be done in stages, with Complete Blood Count, Comprehensive Metabolic Panel, Erythrocyte Sedimentation Rate, C-Reactive Protein, and COVID-19 PCR (Polymerase Chain Reaction) first, followed by other investigations, such as BNP (Brain Natriuretic Peptide), electrocardiogram and echocardiogram. [33]. It has been seen that only pro-BNP and IL-6 were elevated in association with coronary artery abnormalities [34].

Treatment Protocols

According to the CDC, treatments thus far have been primarily supportive and aimed at reducing inflammation to stabilize critical patients and prevent long-term sequelae [32]. Treatment is started based on severity. The ACR task force agreed that in those without life-threatening manifestations like shock, treatment with immunomodulatory agents is deferred until evaluation for other causes has occurred [33]. However, in life-threatening circumstances, treatment may be required first [35]. In these patients, early supportive care, immunomodulatory treatment, and antiviral medication are recommended [33]. MIS-C requires a multidisciplinary team of pediatric cardiologists, rheumatologists, immunologists, intensivists, and others relevant to the individual patient [36]. Supportive measures should include close monitoring of vital signs, fluid resuscitation and inotropic support to maintain adequate organ perfusion, renal replacement therapy, respiratory support, and extracorporeal membranous oxygenation (ECMO) [32, 37]. ECMO has been beneficial in patients with presentations such as cytokine storm of shock [36]. Empiric antibiotic use has been common [32]. Patients with MIS-C who meet the criteria for KD should be treated according to established guidelines for KD [35].
Anti-inflammatory measures for KD have often been through the use of glucocorticoids and IVIG (intravenous immunoglobulin). These are first-tier agents [32, 33, 38]. Glucocorticoids at a low-to-moderate dose of 1-2 mg/kg/day have been sufficient in the treatment of MIS-C [33]. Anakinra (interleukin-1 receptor antagonist) is suggested for use in patients refractory to IVIG and/or glucocorticoids [33]. Faster initiation of glucocorticoids and IVIG can lead to a reduction in the length of the Pediatric Intensive Care Unit and hospital stay [37].
The recommended dose of IVIG is 1-2 g/kg in stable patients, while unstable patients usually need higher doses [36]. There has been inconsistent evidence in proving if tocilizumab (humanized monoclonal antibody against the interleukin-6 receptor) was responsible for clinical improvement [33]. Given the associated hypercoagulable state, thrombotic prophylaxis is required, such as other antiplatelet and anticoagulant treatments [32]. Patients may receive prophylactic therapy with low-dose aspirin but may require therapeutic enoxaparin based on the involvement of their coronary arteries, or an ejection fraction <35% [33]. In a subset of patients with KD features, coronary artery aneurysms, and thrombosis, aspirin is recommended once daily at a low dose of 3-5mg/kg/day, up to maximum of 81 mg once daily [33]. It has been seen that vaccination with the Pfizer-BioNTech vaccine was found to be protective, with 95% of patients requiring hospitalization being unvaccinated, and fully vaccinated children not requiring respiratory or cardiovascular support, as compared to 39% of their unvaccinated counterparts [39].

CONCLUSIONS

Our study review shows that MIS-C is a rare but potentially fatal complication of COVID-19 infection. Multiple studies describing pathophysiology, diagnostic features, and management of MIS-C have been conducted. Protocols and guidelines have been released by WHO, CDC, and AAP based on extensive research. Further studies and especially periodic reviews of articles are warranted to understand the detailed mechanisms of MIS-C, the best strategies to approach the diagnosis and treatment in the context of other inflammatory conditions that may present similarly, and ways to ameliorate MIS-C in those affected by COVID-19.

Grant support/funding
The study had no internal or external funding source.

Disclosure of potential conflict of interest
Authors declare no conflict of interest.

Ethical approval
Though this article does not contain any studies with direct involvement of human participants or animals performed by any of the authors, all procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Availability of data and material
The data is collected from the studies published online, publicly available, and specific details related to data and/or analysis will be made available upon request.

Authors' contributions
Conceptualization: Salika Gadiwala; Methodology: Salika Gadiwala, Avanthika Chaithanya; Acquisition of data: Salika Gadiwala, Ayushi Mistry, Avanthika Chaithanya, Sejal Patel, Stuti Pathak, Bhibhui B Das, Writing - original draft preparation: Salika Gadiwala, Ayushi Mistry, Avanthika Chaithanya, Sejal Patel, Stuti Pathak, Travis Satnarine, Abdul Akim Bakarr; Writing - review, critical feedback, and editing: Daria Bekina-Sreenivasan, Raja Chandra Chakinala, Sathya Areti; Supervision: Saurabhkumar Patel.

REFERENCES

[1] WHO, "Coronavirus disease (COVID-19) Weekly Epidemiological Update and Weekly Operational Update," 2020. https://www.who.int/emergencies/diseases/novel-coronavirus-2019/situation-reports
[2] Nakra NA, Blumberg DA, Herrera-Guerra A, Lakshminrusimha S. Multi-System Inflammatory Syndrome in Children (MIS-C) Following SARS-CoV-2 Infection: Review of Clinical Presentation, Hypothetical Pathogenesis, and Proposed Management. *Children (Basel)*. 2020; 7 (7), 69. doi: 10.3390/children7070069.
[3] Riphagen S, Gomez X, Gonzalez-Martinez C, Wilkinson N, Theocharis P. Hyperinflammatory shock in children during COVID-19 pandemic. *Lancet*. 2020; 395 (10237), 1607-8. doi: 10.1016/S0140-6736(20)31094-1.
[4] Verdoni L, Mazza A, Gervasoni A, et al. An outbreak of severe Kawasaki-like disease at the Italian epicentre of the SARS-CoV-2 epidemic: an observational cohort study. *Lancet*. 2020; 395 (10239): 1771-8. doi: 10.1016/S0140-6736(20)31103-X
[5] CDC Health Alert Network, "Multisystem Inflammatory Syndrome in Children (MIS-C) Associated with Coronavirus Disease 2019 (COVID-19)." 2020. https://emergency.cdc.gov/han/2020/han00432.asp
[6] Godfred-Cato S, Bryant B, Leung J, et al. COVID-19-Associated Multisystem Inflammatory Syndrome in Children - United States, March-July 2020 [published correction appears in MMWR Morb Mortal Wkly Rep. 2020 Sep 04; 69 (35), 1229]. *MMWR Morb Mortal Wkly Rep*. 2020; 69 (32), 1074-80. doi: 10.15585/mmwr.mm6932e2.
[7] Jiang L, Tang K, Levin M, et al. COVID-19 and multisystem inflammatory syndrome in children and adolescents. *Lancet Infect Dis*. 2020; 20 (11), e276-e288. doi: 10.1016/S1473-3099(20)30651-4.
[8] Blumfield E, Levin TL, Kurian J, Lee EY, Liszewski MC. Imaging findings in multisystem inflammatory syndrome in children (MIS-C) associated with Coronavirus disease (COVID-19). *AJR Am J Roentgenol*. 2021; 216 (2), 507-17. doi: 10.2214/AJR.20.24032.
[9] Riollano-Cruz M, Akkoyun E, Briceno-Brito E, et al. Multisystem inflammatory syndrome in children related to COVID-19: A New York City experience. *J Med Virol*. 2021; 93 (1), 424-33. doi: 10.1002/jmv.26224.
[10] American Academy Of Pediatrics, "Multisystem Inflammatory Syndrome in Children (MIS-C) Interim Guidance," 2020. https://www.aap.org/en/pages/2019-novel-coronavirus-covid-19-infections/clinical-guidance/multisystem-inflammatory-syndrome-in-children-mis-c-interim-guidance/
[11] Ziaee V, Assari R , Mamishi S, et al. An Algorithmic Approach to Multisystem Inflammatory Syndrome in Children with COVID-19: Tehran Children's Medical Center Protocol. *Iran J Pediatr.* 2020; 30 (5), e108617. doi: 10.5812/ijp.108617.
[12] Dominguez SR, Anderson MS, Glodé MP, Robinson CC, Holmes KV. Blinded case-control study of the relationship between human coronavirus NL63 and Kawasaki syndrome. *J Infect Dis*. 2006; 194 (12), 1697-701. doi: 10.1086/509509.
[13] CDC, "Health Department-Reported Cases of Multisystem Inflammatory Syndrome in Children (MIS-C) in the United States," *COVID Data Tracker*, 2020. https://covid.cdc.gov/covid-data-tracker/#mis-national-surveillance
[14] Consiglio CR, Cotugno N, Sardh F, et al. The Immunology of Multisystem Inflammatory Syndrome in Children with COVID-19. *Cell*. 2020; 183 (4), 968-981.e7. doi: 10.1016/j.cell.2020.09.016.

[15] McCrindle BW, Rowley AH, Newburger JW, et al. Diagnosis, Treatment, and Long-Term Management of Kawasaki Disease: A Scientific Statement for Health Professionals From the American Heart Association [published correction appears in *Circulation*. 2019 Jul 30; 140 (5), e181-e184]. *Circulation*. 2017; 135 (17), e927-e999. doi: 10.1161/CIR.0000000000000484.
[16] Chen PS, Chi H, Huang FY, Peng CC, Chen MR, Chiu NC. Clinical manifestations of Kawasaki disease shock syndrome: a case-control study. *J Microbiol Immunol Infect*. 2015; 48 (1), 43-50. doi: 10.1016/j.jmii.2013.06.005.
[17] Zhang MM, Shi L, Li XH, Lin Y, Liu Y. Clinical Analysis of Kawasaki Disease Shock Syndrome. *Chin Med J (Engl)*. 2017; 130 (23), 2891-2892. doi: 10.4103/0366-6999.219151.
[18] Kanegaye JT, Wilder MS, Molkara D, et al. Recognition of a Kawasaki disease shock syndrome. *Pediatrics*. 2009; 123 (5), e783-e789. doi: 10.1542/peds.2008-1871.
[19] Wang W, Gong F, Zhu W, Fu S, Zhang Q. Macrophage activation syndrome in Kawasaki disease: more common than we thought? *Semin Arthritis Rheum*. 2015; 44 (4), 405-10. doi: 10.1016/j.semarthrit.2014.07.007.
[20] al-Eid W, al-Jefri A, Bahabri S, al-Mayouf S. Hemophagocytosis complicating Kawasaki disease. *Pediatr Hematol Oncol*. 2000; 17 (4), 323-9. doi: 10.1080/088800100276316.
[21] Avcin T, Tse SM, Schneider R, Ngan B, Silverman ED. Macrophage activation syndrome as the presenting manifestation of rheumatic diseases in childhood. *J Pediatr*. 2006; 148 (5), 683-6. doi: 10.1016/j.jpeds.2005.12.070.
[22] Cummings C, McCarthy P, van Hoff J, Porter G Jr. Kawasaki disease associated with reactive hemophagocytic lymphohistiocytosis. *Pediatr Infect Dis J*. 2008; 27 (12), 1116-8. doi: 10.1097/INF.0b013e31817ecb6d.
[23] Grom AA. Macrophage activation syndrome and reactive hemophagocytic lymphohistiocytosis: the same entities? *Curr Opin Rheumatol*. 2003; 15 (5), 587-90. doi: 10.1097/00002281-200309000-00011.
[24] Burnham JP, Kollef MH. Understanding toxic shock syndrome. *Intensive Care Med*. 2015; 41 (9), 1707-10. doi: 10.1007/s00134-015-3861-7.
[25] Chuang YY, Huang YC, Lin TY. Toxic shock syndrome in children: epidemiology, pathogenesis, and management. *Paediatr Drugs*. 2005; 7 (1), 11-25. doi: 10.2165/00148581-200507010-00002.
[26] Kabeerdoss J, Pilania RK, Karkhele R, Kumar TS, Danda D, Singh S. Severe COVID-19, multisystem inflammatory syndrome in children, and Kawasaki disease: immunological mechanisms, clinical manifestations and management. *Rheumatol Int*. 2021; 41 (1), 19-32. doi: 10.1007/s00296-020-04749-4.
[27] Koritala T, Pattan V, Tirupathi R, Rabaan AA et al. Infection risk with the use of interleukin inhibitors in hospitalized patients with COVID-19: A narrative review. *Infez Med*. 2021; 29 (4), 495-503. doi: 10.53854/liim-2904-1.
[28] Ahmed M, Advani S, Moreira A, et al. Multisystem inflammatory syndrome in children: A systematic review. *E Clinical Medicine*. 2020; 26, 100527. doi: 10.1016/j.eclinm.2020.100527.
[29] Rodriguez-Smith JJ, Verweyen EL, Clay GM, et al. Inflammatory biomarkers in COVID-19-associated multisystem inflammatory syndrome in children, Kawasaki disease, and macrophage activation syndrome: a cohort study. *Lancet Rheumatol*. 2021; 3 (8), e574-e584. doi: 10.1016/S2665-9913(21)00139-9.
[30] Blondiaux E, Parisot P, Redheuil A, et al. Cardiac MRI in Children with Multisystem Inflammatory Syndrome Associated with COVID-19. *Radiology*. 2020; 297 (3), E283-E288. doi: 10.1148/radiol.2020202288.
[31] Hameed S, Elbaaly H, Reid CEL, et al. Spectrum of Imaging Findings at Chest Radiography, US, CT, and MRI in Multisystem Inflammatory Syndrome in Children Associated with COVID-19. *Radiology*. 2021; 298 (1), E1-E10. doi: 10.1148/radiol.2020202543.
[32] CDC. Information for Healthcare Providers about Multisystem Inflammatory Syndrome in Children. 2020. https://www.cdc.gov/mis/misc/hcp/index.html?CDC_AA_refVal=https%3A%2F%2Fwww.cdc.gov%2Fmis%2Fhcp%2Findex.html
[33] Henderson LA, Canna SW, Friedman KG, et al. 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 (4), e13-e29. doi: 10.1002/art.41616.
[34] Davies P. Addressing fundamental questions on MIS-C. *Lancet Child Adolesc Health*. 2021; 5 (5), 310-1. doi: 10.1016/S2352-4642(21)00059-6.
[35] Emeksiz S, Çelikel Acar B, Kibar AE, et al. Algorithm for the diagnosis and management of the multisystem inflammatory syndrome in children associated with COVID-19. *Int J Clin Pract*. 2021; 75 (9), e14471. doi: 10.1111/ijcp.14471.
[36] Farooq A, Alam F, Saeed A, et al. Multisystem Inflammatory Syndrome in Children and Adolescents (MIS-C) under the Setting of COVID-19: A Review of Clinical Presentation, Workup and Management. *Infect Dis (Auckl)*. 2021; 14, 11786337211026642. Published 2021 Jun 20. doi: 1 0.1177/11786337211026642.
[37] Takia L, Angurana SK, Nallasamy K, Bansal A, Muralidharan J. Updated Management Protocol for Multisystem Inflammatory Syndrome in Children (MIS-C). *J Trop Pediatr*. 2021; 67 (3), fmab071. doi: 10.1093/tropej/fmab071.
[38] Rubens JH, Akindele NP, Tschudy MM, Sick-Samuels AC. Acute covid-19 and multisystem inflammatory syndrome in children. *BMJ*. 2021; 372, n385. Published 2021 Mar 1. doi:10.1136/bmj.n385.
[39] Zambrano LD, Newhams MM, Olson SM, et al. Effectiveness of BNT162b2 (Pfizer-BioNTech) mRNA Vaccination Against Multisystem Inflammatory Syndrome

in Children Among Persons Aged 12-18 Years - United States, July-December 2021. *MMWR Morb Mortal Wkly Rep*. 2022; 71, 52-8. doi: http://dx.doi.org/10.15585/mmwr.mm7102e1external icon.
[40] Cheung EW, Zachariah P, Gorelik M, et al. Multisystem Inflammatory Syndrome Related to COVID-19 in Previously Healthy Children and Adolescents in New York City. *JAMA*. 2020; 324 (3), 294-6. doi: 10.1001/jama.2020.10374.
[41] Greene AG, Saleh M, Roseman E, Sinert R. Toxic shock-like syndrome and COVID-19: Multisystem inflammatory syndrome in children (MIS-C). *Am J Emerg Med*. 2020; 38 (11), 2492.e5-2492.e6. doi: 10.1016/j.ajem.2020.05.117.
[42] Feldstein LR, Tenforde MW, Friedman KG, et al. Characteristics and outcomes of US children and adolescents with multisystem inflammatory syndrome in children (MIS-C) compared with severe acute COVID-19. *JAMA*. 2021; 325 (11), 1074-87. doi: 10.1001/jama.2021.2091.
[43] Belay ED, Abrams J, Oster ME, et al. Trends in Geographic and Temporal Distribution of US Children With Multisystem Inflammatory Syndrome During the COVID-19 Pandemic. *JAMA Pediatr*. 2021; 175 (8), 837-45. doi: 10.1001/jamapediatrics.2021.0630.
[44] Stevens JP, Brownell JN, Freeman AJ, Bashaw H. COVID-19-associated multisystem inflammatory syndrome in children presenting as acute pancreatitis. *J Pediatr Gastroenterol Nutr*. 2020; 71 (5), 669-71. doi: 10.1097/MPG.0000000000002860.
[45] Young TK, Shaw KS, Shah JK, et al. Mucocutaneous Manifestations of Multisystem Inflammatory Syndrome in Children During the COVID-19 Pandemic. *JAMA Dermatol*. 2021; 157 (2), 207-12. doi: 10.1001/jamadermatol.2020.4779.
[46] Cirks BT, Geracht JC, Jones OY, et al. Multisystem inflammatory syndrome in children during the COVID-19 pandemic: a case report on managing the hyperinflammation [published online ahead of print, 2020 Nov 26]. *Mil Med*. 2020; usaa508. doi: 10.1093/milmed/usaa508.
[47] Ozsurekci Y, Gürlevik S, Kesici S, et al. Multisystem inflammatory syndrome in children during the COVID-19 pandemic in Turkey: first report from the Eastern Mediterranean [published correction appears in Clin Rheumatol. 2021 Mar 19]. *Clin Rheumatol*. 2021; 40 (8), 3227-3237. doi: 10.1007/s10067-021-05631-9.
[48] Valverde I, Singh Y, Sanchez-de-Toledo J, et al. Acute Cardiovascular Manifestations in 286 Children With Multisystem Inflammatory Syndrome Associated With COVID-19 Infection in Europe. *Circulation*. 2021; 143 (1), 21-32. doi: 10.1161/CIRCULATIONAHA.120.050065.
[49] Jain S, Sen S, Lakshmivenkateshiah S, et al. Multisystem Inflammatory Syndrome in Children With COVID-19 in Mumbai, India. *Indian Pediatr*. 2020; 57 (11), 1015-9. doi: 10.1007/s13312-020-2026-0.
[50] Ionescu MD, Taras R, Dombici B, Balgradean M, Berghea EC, Nicolescu A. The challenging diagnosis of pediatric multisystem inflammatory syndrome associated with Sars-Cov-2 infection-two case reports and literature review. *J Pers Med*. 2021; 11 (4), 318. Published 2021 Apr 19. doi: 10.3390/jpm11040318 .
[51] Abel D, Shen MY, Abid Z, et al. Encephalopathy and bilateral thalamic lesions in a child with MIS-C associated with COVID-19. *Neurology*. 2020; 95 (16), 745-8. doi: 10.1212/WNL.0000000000010652.
[52] Mahajan N, Chang HT, Leeman R, Manalo R, Glaberson WR. Case of multisystem inflammatory syndrome in children presenting as fever and abdominal pain. *BMJ Case Rep*. 2020; 13 (9), e237306. doi: 10.1136/bcr-2020-237306.
[53] Torres JP, Izquierdo G, Acuña M, et al. Multisystem inflammatory syndrome in children (MIS-C): Report of the clinical and epidemiological characteristics of cases in Santiago de Chile during the SARS-CoV-2 pandemic. *Int J Infect Dis*. 2020; 100, 75-81. doi: 10.1016/j.ijid.2020.08.062.
[54] Verkuil LD, Liu GT, Brahma VL, Avery RA. Pseudotumor cerebri syndrome associated with MIS-C: a case report. *Lancet*. 2020; 396 (10250), 532. doi: 10.1016/S0140-6736(20)31725-6.
[55] Ghatasheh G, Al Dhanhani H, Goyal A, Noureddin MB, Al Awaad D, Peerwani Z. COVID-19-Related giant coronary aneurysms in an infant with multisystem inflammatory disorder in children: the first case report from the United Arab Emirates and the Arab Region. *Case Rep Infect Dis*. 2021; 2021, 8872412. doi: 10.1155/2021/8872412.
[56] Chacón-Cruz E, Correa-Bautista Y, Urrea-Sanchez G, Lopatynsky-Reyes EZ, Chan-Dzib F, and Montaño Durón J. Multisystem inflammatory syndrome in children associated with COVID-19: report of four cases in Mexico across the Mexico-US Border. *J Infecti Dis & Case Reps*. 2020; 1 (4), 1-3. doi: 10.47363/JIDSCR/2020(1)122.
[57] Clouser K, Baer A, Bhavsar S, et al. MIS-C After ARDS Associated with SARS-CoV-2. *Pediatr Infect Dis J*. 2020; 39 (11), e363-e365. doi: 10.1097/INF.0000000000002879.
[58] Tolunay O, Çelik Ü, Arslan İ , et al. Multisystem Inflammatory Syndrome in Children (MIS-C) Associated with COVID-19: A Case Series Experience in a Tertiary Care Hospital of Southern Turkey. *J Trop Pediatr*. 2021; 67 (2), fmab050. doi: 10.1093/tropej/fmab050.
[59] Kurz H, Gombala T. Multisystem inflammatory syndrome in children (MIS-C)-A case series in December 2020 in Vienna, Austria. *Front Pediatr*. 2021; 9, 656768. doi: 10.3389/fped.2021.656768.
[60] Hasan MR, Al Zubaidi K, Diab K, et al. COVID-19 related multisystem inflammatory syndrome in children (MIS-C): a case series from a tertiary care pediatric hospital in Qatar. *BMC Pediatr*. 2021; 21 (1), 267. doi: 10.1186/s12887-021-02743-8.
[61] Racko I, Smane L, Klavina L, Pucuka Z, Roge I, Pa-

vare J. Case Series of Multisystem Inflammatory Syndrome (MIS-C) in Children during the SARS-CoV-2 Pandemic in Latvia. *Clin Pract*. 2021; 11 (2), 363-73. doi: 10.3390/clinpract11020051.
[62] Asseri AA, AlHelali I, Elbastawisi E, et al. Multi-system inflammatory syndrome in children during the coronavirus disease 2019 in Saudi Arabia: Clinical perspective from a case series. *Medicine (Baltimore)*. 2021; 100 (22), e25919. doi: 10.1097/MD.0000000000025919.
[63] Nelson C, Ishimine P, Hayden SR, Correia M, Wardi G. Multisystem Inflammatory Syndrome in Children (MIS-C) in an Adolescent that Developed Coronary Aneurysms: A Case Report and Review of the Literature. *J Emerg Med*. 2020; 59 (5), 699-704. doi: 10.1016/j.jemermed.2020.09.008.
[64] Deza Leon MP, Redzepi A, McGrath E, et al. COVID-19-associated pediatric multisystem inflammatory syndrome. *J Pediatric Infect Dis Soc*. 2020; 9 (3), 407-8. doi: 10.1093/jpids/piaa061.
[65] Greene AG, Saleh M, Roseman E, Sinert R. Toxic shock-like syndrome and COVID-19: Multisystem inflammatory syndrome in children (MIS-C). *Am J Emerg Med*. 2020; 38 (11), 2492.e5-2492.e6. doi: 10.1016/j.ajem.2020.05.117.
[66] Rodriguez-Smith JJ, Verweyen EL, Clay GM, et al. Inflammatory biomarkers in COVID-19-associated multisystem inflammatory syndrome in children, Kawasaki disease, and macrophage activation syndrome: a cohort study. *Lancet Rheumatol*. 2021; 3 (8), e574-e584. doi: 10.1016/S2665-9913(21)00139-9.
[67] Domico M, McCanta AC, Hunt JL, Ashouri N, Nugent D, Kelly RB. High-grade heart block requiring transvenous pacing associated with multisystem inflammatory syndrome in children during the COVID-19 pandemic. *HeartRhythm Case Rep*. 2020; 6 (11), 811-4. doi: 10.1016/j.hrcr.2020.08.015.
[68] Lee M, Hilado M, Sotelo S, Opas LM, Im DD. acute kidney injury in multisystem inflammatory syndrome in children (MIS-C): a case report. *SN Compr Clin Med*. 2020; 2 (12): 2899-2. doi: 10.1007/s42399-020-00647-9.
[69] Navaeifar MR, Shahbaznejad L, Sadeghi Lotfabadi A, Rezai MS. COVID-19-Associated Multisystem Inflammatory Syndrome Complicated with Giant Coronary Artery Aneurysm. *Case Rep Pediatr*. 2021; 2021, 8836403. doi: 10.1155/2021/8836403.
[70] Dolinger MT, Person H, Smith R, et al. Pediatric Crohn disease and multisystem inflammatory syndrome in children (MIS-C) and COVID-19 treated with infliximab. *J Pediatr Gastroenterol Nutr*. 2020; 71 (2), 153-5. doi: 10.1097/MPG.0000000000002809.
[71] Racko I, Smane L, Klavina L, Pucuka Z, Roge I, Pavare J. Case series of multisystem inflammatory syndrome (MIS-C) in children during the SARS-CoV-2 pandemic in Latvia. *Clin Pract*. 2021; 11 (2), 363-373. doi: 10.3390/clinpract11020051.
[72] LaRovere KL, Riggs BJ, Poussaint TY, et al. Neurologic Involvement in children and adolescents hospitalized in the United States for COVID-19 or multisystem inflammatory syndrome. *JAMA Neurol*. 2021; 78 (5), 536-547. doi: 10.1001/jamaneurol.2021.0504
[73] Choi NH, Fremed M, Starc T, et al. MIS-C and Cardiac Conduction Abnormalities. *Pediatrics*. 2020; 146 (6), e2020009738. doi: 10.1542/peds.2020-009738.
[74] Kest H, Kaushik A, DeBruin W, Colletti M, Goldberg D. Multisystem Inflammatory Syndrome in Children (MIS-C) Associated with 2019 Novel Coronavirus (SARS-CoV-2) Infection. *Case Rep Pediatr*. 2020; 2020, 8875987. doi: 10.1155/2020/8875987.
[75] Esteve-Sole A, Anton J, Pino-Ramirez RM, et al. Similarities and differences between the immunopathogenesis of COVID-19-related pediatric multisystem inflammatory syndrome and Kawasaki disease. *J Clin Invest*. 2021; 131 (6), e144554. doi: 10.1172/JCI144554.
[76] Suratannon N, Dik WA, Chatchatee P, Hagen PMV. COVID-19 in children: Heterogeneity within the disease and hypothetical pathogenesis. *Asian Pac J Allergy Immunol*. 2020; 38 (3), 170-7. doi: 10.12932/AP-170720-0920.

SUPPLEMENTARY MATERIAL

Studies that met the inclusion criteria were selected and summarized as follows:

Demographics
A total of 5822 patients were included in this review, ranging from a single case per study to 1733 patients in another (mean, 153.21; median, 7), across 38 studies, with a male to female ratio of 2919 to 2257, and a mean age of 8.73 years.

Signs, Symptoms and Physical Examination
A wide array of symptoms was seen in MIS-C cases studied, involving almost all organ systems. Majority patients had milder clinical course or features of KD [6]. Symptoms usually began with prodromal illness, with complaints of sore throat, fever [8, 9, 30, 40-63], reduced appetite [41, 64]. Physical examination revealed pharyngeal erythema [41, 46], tonsillar exudates [46]. Mucocutaneous findings were observed, including a blanchable maculopapular rash on palms and soles [6, 8, 9, 30, 40, 41, 43, 45, 47-51, 54-56, 58, 60, 61, 63, 66, 67], conjunctivitis [8, 9, 29, 30, 40, 43-50, 56, 58, 60, 63, 67], mucositis [49, 56, 66], lip swelling [30, 40, 50, 56], strawberry tongue [45], periungal peeling [42], swelling of hands, feet, [9, 29, 44, 47, 49-50, 56] and eyelids (periorbital edema) [44, 45] and pain in the extremities [41, 44, 47, 63], these being consistent with features of KD. Prominent GI symptoms were seen, such as vomiting [8-9, 30, 40, 42-44, 49-51, 56, 59, 60, 62, 63], abdominal pain [6, 8, 9, 30, 40, 41-44, 46-49, 52, 53, 56, 58-60, 62, 63, 68], diarrhea [8, 9, 30, 40, 42-44, 46, 48, 49, 53, 56, 59, 60, 62, 63], mild abdominal distension [69], and anorexia [44]. A patient with newly diagnosed Crohn's was found to have MIS-C [70], presenting with fever, abdominal pain, with physical exam showing tachycardia, a facial maculopapular rash, and perianal abscess with drainage. Respiratory symptoms were rare, usually presenting with cough or dyspnea [8, 9, 42, 43, 46, 47, 49, 51, 54, 57, 60, 62, 69], or rhinorrhea [42]. Cardiac dysfunction [6, 29, 43, 71] was seen, with chest pain [9, 50] on presentation, myocarditis [8, 43], and coronary artery dilatation/aneurysm [43]. Ophthalmic examination described by Verkuil et al. [54] showed right-eye abduction deficit, consistent with abducens palsy. A study by LaRovere et al. [72] studied the neurological manifestations of severe COVID-19 illness in patients presenting with anosmia, ageusia, headache, fatigue, and seizures. Studies by Feldstein et al. [42], and Verkuil et al. [54] also showed headache and altered mental status. 22% patients in the LaRovere study showed CNS involvement, with a majority likely to have an underlying neurological disorder. Among this cohort, 43 had life-threatening neurological symptoms, such as severe encephalopathy, stroke (ischemic or hemorrhagic), acute CNS infection, acute edema, or GBS, and 20 of those met the MIS-C criteria. Mortality was seen in 14 patients with COVID-19 related neurological involvement [72]. Many of the cases studied took a turn for the worse, with signs and symptoms of prolonged inflammation [40], tachycardia [9, 30, 44, 46, 47, 50, 57, 63], bradycardia [67] with conduction abnormalities [67, 73], hypotension [9, 43, 44, 64, 67], somnolence [50, 51], hypotonia [51], hypoxia [48, 67], respiratory failure [54] and shock [6, 30, 40, 43, 48, 54, 56], with admission to the intensive unit care [48, 50].
In many, the symptoms were very similar to those of KD [6, 29, 30, 41, 44-46, 48-50, 52, 54, 55, 67, 69, 70], making it a viable differential diagnosis. Other differentials included MIS-C [8, 9, 40, 42-47, 51, 52, 56-60, 63, 68, 70, 72-74], severe COVID-19 illness [42, 43, 47, 72], TSS [41, 49, 67, 68], cytokine storm, HLH, [41] septic shock [41, 68], cardiogenic shock secondary to myocarditis [41, 48, 52], pulmonary embolism [41], acute pancreatitis [44], drug-hypersensitivity rewaction [70], immune-mediated vasculitis [70], viral infection [59, 62, 67, 70], bacterial pneumonia [59, 67], systemic juvenile idiopathic arthritis, MAS [29], early Stevens-Johnson syndrome [67], typhoid infection, rickettsial infection [68], acute abdomen and acute appendicitis [71].

Laboratory Testing
Primary laboratory tests included positive COVID RT-PCR test [6, 8, 9, 40, 41, 48, 51, 53, 56-58, 70], and positive SARS-CoV-2 antibody test [30, 44, 48, 50, 51, 53, 55, 58, 59, 60, 68, 69, 73]. Cases also involved

elevated markers of inflammation such as high C-Reactive Protein [6, 8, 9, 29, 30, 41-43, 45-54, 57-64, 67-70, 72, 74], Ferritin [6, 9, 41, 44, 46-50, 58-64, 67, 70, 74], LDH [41, 45, 46, 52, 61, 64], procalcitonin [9, 41, 44, 48, 50, 51, 58, 60], D-Dimer [8, 9, 41, 43-53, 57-59, 61, 64, 67, 70, 72, 74], fibrinogen [9, 29, 41, 43-46, 50, 54, 61, 64, 74] and ESR [9, 29, 44, 46, 50, 55, 56, 58, 59, 61, 62, 67, 69, 70, 74]. Cytokine profile showed elevated IL-6 [9, 40, 43-46, 48-50, 59-61, 63, 67, 70], IL-2R [40,46,67], IL-18 [40, 46, 75], CXCL 9 [40], IFN-γ [40, 75], TNF-α [9, 70] and IL-8 [9, 40, 46, 70].

Abnormal cardiac profile was seen, with elevations in troponins [6, 28, 40, 44-46, 48, 58-60, 63, 67, 73, 75], BNP [6, 28, 29, 40, 44, 46, 73] or pro-BNP [6, 28, 45, 47, 48, 51, 54, 58, 59, 60, 67]. Renal function abnormalities were observed in with azotemia [8,63] (elevated BUN [40, 49, 67], creatinine [40, 43, 49, 67], hyperammonemia [50]). Lee et al. also found elevated creatine kinase in a patient of MIS-C [67]. Ionescu et al. found proteinuria in a 10 y/o male with MIS-C [49]. Hypoalbuminemia was found in many studies [8, 9, 43, 45, 56, 57, 58, 60, 69, 73]. Liver function tests were abnormal with elevated alanine aminotransferase [9, 28, 43, 49, 54, 55, 67-69], aspartate aminotransferase [9, 28, 43, 49, 54, 55, 67-69, 72], gamma glutamyl transferase [69, 49] and alkaline phosphatase [69].

Blood investigations revealed mild anemia [55], leukocytosis [9, 40, 45, 46, 55, 58, 62, 63, 68, 73], lymphopenia [9, 29, 40, 42, 45, 49, 52, 56-60, 66, 73], neutrophilia [45, 55, 58, 66, 68, 73], bandemia [67], thrombocytopenia [9, 42, 49, 50, 55, 58-60, 73]/thrombocytosis [41]. Electrolyte profile showed hyponatremia [45, 46, 57, 58, 60, 62, 63, 67], hypochloremia [62], hyperkalemia [63]/hypokalemia [67], hypophosphatemia [57], hypomagnesemia [57] and elevated anion gap [62]. Coagulation studies showed elevated PT/INR [40, 51, 67] and prolonged PTT [49, 51].

Radiological Findings

Initial chest radiograph showed prominent cardiac silhouette [63] (cardiomegaly [8, 43]) with clear lung fields [63]; bilateral interstitial opacities [8, 9, 43, 45, 46, 59]; peri-hilar infiltrates, with peri-bronchial thickening [59]; ground-glass opacities [9, 46] with central bronchial cuffing [45] and patchy shadowing [46]; signs of dependent or compressive atelectasis [8, 43, 45]; signs of restrictive airway diseases [9]; pleural effusions [8, 9, 43, 45, 46, 50, 59, 60]; signs of congestive heart failure [8] or pulmonary edema [8, 43, 59], and changes of multifocal pneumonia [66]. Chest CT revealed typical COVID-19 opacities- peripheral, posterior, multilobar, and bilateral distribution of ground-glass opacities and consolidations, especially in lower lobes [29, 68]; diffuse opacities with subpleural sparing [53]; pulmonary edema [49]; bilateral pleural effusion, pericardial effusion, cardiomegaly [49]. In the case of MIS-C with Crohn's disease, described by Doline et al, CT (chest, abdomen, and pelvis) showed mediastinal lymphadenopathy and hepatosplenomegaly, and Magnetic Resonance Enterography revealed perianal abscess, fistula, and ileitis [69]. ECG manifested with ST-segment depression and decreased T-wave amplitude in inferior leads [29], sinus tachycardia [40, 45, 50, 51] and S1Q3T3 without acute ischemia [40], QTc prolongation [45], biphasic inverted T waves [45], tachy/brady arrhythmias and intraventricular conduction defects [60]. In one study [49], ECG showed atrial flutter (atrial rate of 300 beats/min, ventricular rate of 100-150 bpm, 3:1-2:1 atrioventricular conduction). Echocardiography revealed decreased left ventricular (LV) function [9, 29, 41, 43-45, 47, 50, 52, 57-61, 63, 67, 72, 73], depressed biventricular function [9,49], systolic myocardial dysfunction [8, 29, 40, 42, 46, 48, 52], myocarditis [42], pericarditis, global/septal hypokinesia [29], and reduced peak global longitudinal strain [51]. It also showed valvular abnormalities such as mitral [29, 43, 44, 49, 58, 60, 61] and tricuspid regurgitation [43, 49, 58, 60], and coronary dilation [9, 44, 46, 48, 53, 58, 61, 62]/aneurysms [41, 42, 45, 54, 59, 68] or ectasia [8, 9, 51, 66], in addition to pericardial effusion [8, 41, 42, 49, 52, 57], intra-cardiac thrombus [57]. Cardiac MRI showed signs suggestive of interstitial edema [29], and myocarditis [60]. Brain MRI revealed diffuse T2 prolongation and reduced diffusivity in bilateral periventricular white matter, with involvement of splenium and genu of corpus callosum; prolonged encephalopathy showed multifocal areas of restricted diffusion and hemorrhage throughout the posterior white matter and brainstem [71], restricted diffusion in bilateral lateral thalamic nuclei without T2/fluid-attenuated inversion recovery changes [50], signs consistent with increased

intracranial pressure [53]. In a case described by Abel et al, EEG done showed moderate background slowing [50]. USG Abdomen showed mesenteric lymph nodes with maximum diameter of 23/14 mm and 5 mm of free fluid in recto-vesical pouch [49], edema and thickening of gallbladder wall, mesenteric lymphadenitis [5-59], hepatosplenomegaly, hyperemia of testicles and epididymis [58], abdominal aortic aneurysm, increased echogenicity of the liver, and bulky and echogenic kidneys and ascites [59]. CT Abdomen/Pelvis revealed inflammatory change within peripancreatic fat, with prominent pancreas, suggestive of acute pancreatitis [43].

Diagnoses

After extensive lab and radiological investigations, a final diagnosis was made, which included MIS-C [6, 29, 40-42, 44-52, 54-62, 66-68, 72] in the majority of the articles reviewed. In addition, diagnoses of severe COVID-19 illness [46], incomplete Kawasaki [9,53,63], MIS-C with features of acute pancreatitis [43], and suspected MIS-C in newly diagnosed patients of Crohn's disease [69], were also made.

Treatments

Among those receiving treatment, the patients were given broad-spectrum antibiotics [9, 45, 46, 52, 60, 69], such as piperacillin-tazobactum, ciprofloxacin [69], metronidazole [59, 69], ceftriaxone [45, 49, 59], clindamycin [45], meropenem [49, 59], teicoplanin [49], doxycycline [53], cefepime and vancomycin [59]. Major treatment modalities were IVIG [6, 8, 28, 29, 40-46, 48-50, 52, 53, 55-63, 66-69, 72, 73], steroids [6, 8, 28, 29, 40-42, 44, 48, 49, 52, 59-61, 72, 73] like prednisolone [53, 62], methylprednisolone [45, 46, 50, 56, 57, 60, 66, 67], hydrocortisone [53, 58], or dexamethasone [55], antiplatelet medications [6, 41, 54] such as aspirin [43-45, 55, 58-61, 63, 66], and clopidogrel [45], and anticoagulation medications [6, 41, 50, 60] like enoxaparin [9, 41, 47, 50, 56, 58, 67, 70]. Vasoactive [6, 9, 40, 47, 54] and ionotropic agents [30, 45, 56, 61] such as norepinephrine [41], dopamine [64, 74], and milrinone [41, 44, 74] were added to treatment regimens when indicated. In a study by Greene A.G. et al., vitamin K [41] was indicated as well. Other medications which were given included volume expanders (IV fluids) [30, 50, 70], diuretics [61] such as furosemide [41], IV albumin [44], hydroxychloroquine [56, 58, 62, 70], blood transfusion for anemia [69], anti-arrhythmic therapy, such as amiodarone [50], anti-interleukin-6 medication tocilizumab [9, 40-42, 47, 49, 56, 70, 74], interleukin 1 receptor antagonist anakinra [8, 29, 45-47, 50, 51, 58, 60, 61, 73], SARS-CoV-2 convalescent plasma transfusion [9, 41, 42], anti-viral drugs like remdesivir [41, 42, 45, 70], and Favipiravir [47, 58], and TNF-α inhibitor infliximab [29, 49, 70].

Those with hypoxia were given supportive oxygen therapy [53, 61, 64, 74] usually with high flow nasal cannula [44, 46]. Patients progressing to respiratory distress required mechanical ventilation [9, 30, 40, 42, 49, 53, 54, 60, 64, 72] either by non-invasive positive pressure [74] or invasive methods and/or placement on ECMO [42, 47, 64, 72]. A case in a study by Riollano-Cruz et al., with cardiogenic shock was treated with an intra-aortic balloon pump [9]. Many cases warranted either ward [9] or ICU admission [9, 40, 53, 61, 62].