MultiInflammatory Syndrome in Children: A View into Immune Pathogenesis from a Laboratory Perspective

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Background: Multiinflammatory syndrome in children (MIS-C) is a novel and rare inflammatory disorder associated with severe acute respiratory syndrome coronavirus 2 infection in school-age children. Reports in the past year have suggested a multisystem pathophysiology characterized by hyperinflammation, gastrointestinal distress, and cardiovascular complications. Clinical laboratory investigations, including routine blood testing for inflammatory (e.g., C-reactive protein, ferritin) and cardiac (e.g., troponin, brain natriuretic peptides) markers have provided insight into potential drivers of disease pathogenesis, highlighting the role of the laboratory in the differential diagnosis of patients presenting with similar conditions (e.g., Kawasaki disease, macrophage activating syndrome).

Content: While few studies have applied high-dimensional immune profiling to further characterize underlying MIS-C pathophysiology, much remains unknown regarding predisposing risk factors, etiology, and long-term impact of disease onset. The extent of autoimmune involvement is also unclear. In the current review, we summarize and critically evaluate available literature on potential pathogenic mechanisms underlying MIS-C onset and discuss the current and anticipated value of various laboratory testing paradigms in MIS-C diagnosis and monitoring.

Summary: From initial reports, it is clear that MIS-C has unique inflammatory signatures involving both adaptive and innate systems. Certain cytokines, inflammatory markers, and cardiac markers assist in the differentiation of MIS-C from other hyperinflammatory conditions. However, there are still major gaps in our understanding of MIS-C pathogenesis, including T cell, B cell, and innate response. It is essential that researchers not only continue to decipher initial pathogenesis but also monitor long-term health outcomes, particularly given observed presence of circulating autoantibodies with unknown impact.

BACKGROUND

Severe coronavirus disease 2019 (COVID-19), caused by the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has primarily been viewed as an adult disease. However, rare but clinically distinct phenotypes associated with pediatric SARS-CoV-2 infection exist. More than 3.9 million children in the United States have tested positive for SARS-CoV-2, representing

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Received June 3, 2021; accepted August 16, 2021.
DOI: 10.1093/jalm/jfab114

IMPACT STATEMENT

Multiinflammatory syndrome in children (MIS-C) is a novel and rare inflammatory disorder associated with severe acute respiratory syndrome coronavirus 2 infection in school-age children. While the underlying drivers of MIS-C pathophysiology are unknown, delayed onset presentation suggests autoimmune involvement. Clinical laboratory investigations are integral to MIS-C diagnosis and prognostication, including in the assessment of hyperinflammation and gastrointestinal and cardiac distress. Herein, we provide a view into the immune pathogenesis of MIS-C from a laboratory perspective, including autoimmune response, and highlight key areas of consideration in the management, treatment, and follow-up of patients with MIS-C.

14.1% of all cases (1). Children with SARS-CoV-2 infection have been reported to present with minimal symptoms, suggesting pediatric SARS-CoV-2 incidence is underestimated globally. Relative to adults, the development of severe pediatric COVID-19 with acute respiratory distress syndrome is rare with estimated hospitalization and mortality rates of <1.9% and <0.03%, respectively (1). However, some children appear to develop a delayed immune-related complication known as multisystem inflammatory syndrome in children (MIS-C) or pediatric inflammatory multisystem syndrome (2–5). This syndrome is thought to be temporally associated with SARS-CoV-2 infection and resembles Kawasaki disease (KD), a multisystem inflammatory vasculitis of unknown etiology but suspected autoimmune involvement (2, 4–7). Pediatric clinical laboratories have supported the management of patients with MIS-C through the provision of routine and specialized immunology testing, providing initial insight into pathophysiological factors driving disease (6). However, our current understanding of MIS-C disease onset, progression, and long-term patient outcomes is incomplete. This review summarizes and critically evaluates the current literature regarding potential pathogenic mechanisms underlying MIS-C onset, including extent of autoimmune response, and discusses the current and evolving value of various laboratory testing paradigms in patient diagnosis and monitoring.

MIS-C CLINICAL PRESENTATION AND LABORATORY PROFILE

MIS-C was first recognized in April 2020 by a group of clinicians who reported an unusual cluster of 8 previously healthy children presenting with hyperinflammatory shock that resembled atypical KD, KD shock syndrome, or toxic shock syndrome; these children had either tested positive for active or recent SARS-CoV-2 infection or had an epidemiologic connection to a SARS-CoV-2 case (2). Reported patient characteristics at presentation included prolonged fever; gastrointestinal symptoms such as abdominal pain, vomiting, or diarrhea; and conjunctivitis with skin rash (6). Clinical laboratory testing also revealed hyperinflammation, including elevated C-reactive protein, procalcitonin, ferritin, and erythrocyte sedimentation rate as well as evidence of cellular abnormalities and electrolytes disturbances, including neutrophilia, lymphopenia, thrombocytopenia, hyponatremia, and hypoalbuminemia (6). Prominent cardiac involvement was also observed, including elevated troponin and brain natriuretic peptide (BNP), left ventricular

dysfunction, coronary artery aneurysm, and electrical conduction abnormalities (6).

Following increasing reports (4), the CDC published an official health advisory regarding MIS-C associated with SARS-CoV-2 and developed a case definition that includes 4 criteria: (i) an age of <21 years; (ii) clinical presentation including fever for ≥24 h, laboratory evidence of inflammation, severe illness requiring hospitalization, and multisystem organ involvement; (iii) no alternative plausible diagnoses; and (iv) positive SARS-CoV-2 RT-PCR, serology, or antigen test or an epidemiological link to a suspected or confirmed COVID-19 case within 4 weeks of symptom onset (8). Based on this definition, reports have suggested that most children with diagnosed MIS-C are 6 to 12 years old and have no history of preexisting health conditions, with the exception of obesity (5, 9–12). Additionally, children who are Black or Hispanic appear to be disproportionately affected (5, 7, 10–13). These initial patient characteristics suggest discrepancies from similar hyperinflammatory conditions, including pediatric COVID-19 and KD. Specifically, pediatric COVID-19 patients with acute respiratory distress syndrome have shown to be older, present without gastrointestinal distress or cutaneous manifestation, and have a history of chronic illness (6). Further, unlike MIS-C, KD predominantly affects younger children <5 years of age and children who are Asian, particularly those with Japanese ancestry, and is associated with a lower incidence of cardiac involvement, particularly left ventricular dysfunction and shock (6).

While the true incidence of MIS-C is unknown, it appears to be rare. A descriptive analysis of laboratory-confirmed SARS-CoV-2 cases in New York revealed an incidence of 2 per 100 000 persons <21 years of age (11). The same study reported the incidence of laboratory-confirmed SARS-CoV-2 infection was 322 per 100 000 persons younger than 21 years of age, suggesting a small percentage of pediatric SARS-CoV-2 cases develop MIS-C (11). From initial reports of low sample size, the characteristic features of MIS-C, such as hyperinflammation and cardiogenic shock, have been defined, but the drivers underlying disease initiation, propagation, and resolution are unknown. However, several pathophysiological processes can be hypothesized by combining findings from available research studies with existent knowledge of common autoimmune mechanisms as related to infectious disease.

INSIGHTS INTO MIS-C PATHOGENESIS

Viral agents are considered an important environmental factor in eliciting autoimmune responses in genetically susceptible individuals and leading to various and diverse immune pathologies. Such autoimmune responses are not equivalent to autoimmune disease and should be considered distinct entities. Autoimmune responses to SARS-CoV-2 have been hypothesized in both children and adults. Specifically, autoimmune involvement is suspected in MIS-C pathogenesis due to timing of disease onset, with most cases presenting 3 to 6 weeks postinfection (10, 11). Children with MIS-C have been reported to have undetectable or low SARS-CoV-2 viral loads, but positive anti-SARS-CoV-2 antibody results (7). Studies assessing immunoglobulin response in MIS-C patients with different antigenic targets have shown anti-SARS-CoV-2 antibody repertoire in MIS-C resembles adult SARS-CoV-2 convalescent response with elevated antispike IgG and low antispike IgM levels (14, 15). In terms of functional response, some reports have concluded neutralization capacity of MIS-C patient sera is similar to convalescent adults (14), while others have demonstrated lower neutralization capacity relative to adults regardless of MIS-C status (15). IgG1 and IgG3 have consistently been shown to predominate among IgG responses (14, 16). Taken together, reduced viral burden and

SARS-CoV-2 antibody profile in MIS-C suggest a postacute phase onset. It is thus plausible that MIS-C could be caused by one or a combination of mechanisms known to contribute to classical viral-induced autoimmune response and tolerance breakdown, including (i) molecular mimicry wherein viral epitopes similar to self-epitopes are presented by antigen-presenting cells, activating autoreactive T cells and autoantibody production to induce tissue damage, (ii) bystander activation wherein liberation of self-antigens occurs as a result of an overreactive antiviral immune response, leading to release of inflammatory cytokines from damaged tissue, and (iii) epitope spreading caused by persistent viral infection, continued tissue damage and self-antigen release, antigen-presenting cell presentation, and nonspecific activation of autoreactive T cells (17). While the exact pathophysiological mechanism and extent of autoimmune involvement cannot yet be concluded, research findings harnessing the power of high-dimensional immunology techniques provide some clues.

Studies evaluating T-cell repertoires in patients with MIS-C have identified distinct T-cell receptor (TCR) skewing toward TRBV11-2 in both CD4+ and CD8+ memory T cells (16, 18, 19). Cheng et al. previously demonstrated through in silico analysis that SARS-CoV-2 spike protein harbors a high-affinity site for TCR β-chain binding and may serve as a superantigen (20). Superantigens are a class of bacterial or viral antigens that activate T cells in a nonspecific manner. By binding to the β-chain variable region of the TCR, they bypass conventional peptide-MHC complex recognition required for conventional antigens and result in a massive proinflammatory cytokine release. Extent of TCR skewing in MIS-C patients has been shown to correlate with cytokine levels, such as interleukin (IL)-18 (18, 19), as well as high levels of CX3CR1 (19). Vella et al. also observed activation of vascular patrolling of CX3CR1+ CD8+ T cells, which are thought to play an important role in vascular inflammation and could contribute to the endothelial disruption observed in MIS-C pathogenesis (21). Elevated soluble C5b-9, a mediator of endothelial destruction, has also been observed (16). It should be noted that all reports investigating T-cell repertoire in patients with MIS-C sampled circulating T cells as opposed to tissue-resident T cells. While tissue sampling is difficult in children, the phenotypic and functional characteristics of tissue are distinct from circulating T cells and may play both protective roles and contribute to the immunopathology observed (22). This limitation should be considered in data interpretation and warrants further study.

As large-scale T-cell activation and cytokine release is not consistent with the delayed hyperinflammation observed in MIS-C, many have suggested that B-cell autoimmune reactions may play more of a causal role in pathogenesis (19). Three studies have reported presence of autoantibodies in peripheral serum/plasma of patients with MIS-C (14, 16, 23) with 2 candidates demonstrating potential pathophysiological overlap with classical autoimmune disorders: IgG reactivity to anti-Jo-1 and anti-La (14). Additional candidates identified suggest enrichment in organ systems central to MIS-C pathogenesis, primarily cardiac and endothelial tissue (e.g., endoglin, EDIL3) and correlated to disease progression (14, 16, 23). Presence of autoantibodies in MIS-C may suggest direct cross-reactivity between SARS-CoV-2 and self-antigens, causing severe disease or simply be a result of autoantigen exposure due to enhanced tissue damage. Additional immune events consistent with viral-induced autoimmune response including expansion of proliferating plasmablasts (16) and persistence of functional SARS-CoV-2 specific monocyte-activating antibodies (19, 24) have also been observed in MIS-C. The pathophysiological link between B-cell autoimmunity and TCR skewing in MIS-C is unknown. In addition to B-cell autoimmune responses, antibody-dependent enhancement (ADE) may also be a mechanistic

contributor. ADE, caused by excessive Fc-mediated effector functions and immune complex formation in an antibody-dependent manner, can exacerbate viral infection and immunopathology, as seen in respiratory syncytial virus and measles (25). It is possible that initial exposure to SARS-CoV-2 in children causes production of both neutralizing and nonneutralizing antibodies and while children with predominantly neutralizing antibodies progress to asymptomatic status, a small subset develop nonneutralizing antibody and viral antigen complexes, leading to ADE and progressing to severe MIS-C (25). However, minimal data exist to confirm the presence of ADE and prolonged viral antigen status in patients with MIS-C, with some data suggesting no significant difference between immunoglobulin response in pediatric patients with COVID-19 or MIS-C (26).

Cytokine profiles in patients with MIS-C as compared to healthy children, KD, or macrophage activation syndrome can also provide insight into disease pathogenesis, particularly propagation. In an initial report of 28 MIS-C cases by Lee et al., IL-6 and IL-10 were positively associated with disease severity (3). Other groups have also concluded patients with MIS-C have higher levels of tumor necrosis factor α (TNFα), IL-6, and IL-10 relative to severe pediatric COVID-19 (27, 28). Additional relevant findings include elevations in mediators of natural killer and T-cell recruitment [e.g., chemokine ligand (CCL)19, CSCL10, complement-dependent cell-mediated phagocytosis (CDCP) (14); neutrophil and monocyte chemotaxis (e.g., CCL3, CCL4); mucosal immunity and chemotaxis (e.g., IL-17A, CCL20, CCL28) (14); alarmins and natural killer/CD8+ T-cell cytotoxicity effectors (e.g., perforin, granzyme A, granzyme H, ENRAGE)] (16). Current interim recommendations by the Royal College of Paediatrics and Child Health and American College of Rheumatologists (6) indicate that expanded laboratory testing for monitoring inflammation (e.g., cytokine profiling) may be of diagnostic value. Clinical laboratory considerations for such testing are provided in the following sections.

Taken together, preliminary data generated by translational research studies highlight the complexity of immune involvement in MIS-C and stress the need for further studies in larger cohorts of treatment-naïve patients to delineate pathophysiological mechanisms involved and the extent of autoimmune involvement.

Is SARS-CoV-2 Autoimmune Response Limited to Children?

While MIS-C was initially thought to be limited to pediatric patients, reports have suggested similar clinical observations in adults. A CDC case series reported 27 adults with current or previous SARS-CoV-2 infection with a hyperinflammatory syndrome resembling MIS-C, termed multiinflammatory syndrome in adults (MIS-A) (29). Across case reports, patient age ranged from 21 to 50 years (7 males, 9 females), and patient ethnicity included predominantly Hispanic, Black, and Asian populations. In keeping with MIS-C, most had no underlying medical conditions, with obesity representing the most prevalent comorbidity (29). Patient clinical symptoms included lasting fever as well as presence of cardiovascular, (arrhythmias, elevated cardiac troponin, and/or left or right ventricular dysfunction), gastrointestinal (abdominal pain, vomiting, and/or diarrhea), and dermatologic (rash, mucositis) involvement without severe respiratory illness (29). Further, of the 27 patients included, 10 tested positive for SARS-CoV-2 RNA and antibodies at initial evaluation, 6 tested negative for SARS-CoV-2 RNA but positive for antibodies at initial evaluation, and remaining patients had history of positive SARS-CoV-2 RNA results (29). These initial findings suggest a similar clinical and laboratory signature to MIS-C. However, significantly less literature and clinical guidance on MIS-A is available, likely due to extremely low prevalence.

In addition to MIS-A, recent data suggest the onset of a wide spectrum of autoimmune responses following SARS-CoV-2 infection in previously healthy adults with neurological, rheumatological, and hematological implications. Autoimmune-like neurologic disorders have been observed in adult COVID-19 patients, including Guillain-Barré syndrome, demyelinating lesions, encephalitis, myelitis, and myasthenia gravis. This is not surprising as SARS-CoV-2 and other coronaviruses have displayed neurotropism leading to anosmia and ageusia (30, 31). Acute arthritis has also been observed following SARS-CoV-2 infection in previously healthy patients (32, 33). Furthermore, detection of anticyclic citrullinated peptid antibodies in select patients suggests autoimmune origin (34). Few cases of autoimmune hemolytic anemia have been reported in SARS-CoV-2 patients, with 1 review notating 23 cases in available literature (31). In addition to autoimmune hemolytic anemia, 56 cases of immune thrombocytopenic purpura have been reported following SARS-CoV-2 infection in the literature (31, 35). Further, few cases of new onset of systemic lupus erythematosus or systemic lupus erythematosus–like syndrome associated with COVID-19 have been observed (31, 35). Additional autoimmune-like clinical manifestations associated with SARS-CoV-2 infection include interstitial lung disease, antineutrophil cytoplasmic antibodies (ANCA) -associated vasculitis, and lesions resembling livedo reticularis, Raynaud phenomenon, chilblain, petechiae, and purpura, as reviewed elsewhere (31, 35). Similar findings in children has not yet been described.

Circulating autoantibodies have also been detected in adult COVID-19 patients, including antinuclear antibodies (ANA), antiphospholipid antibodies, anticyclic citrullinated peptide, c-ANCA, p-ANCA, anti-SSA/Ro antibodies, anti-Scl-70 antibodies, and rheumatoid factor (34, 36, 37). The pathophysiological significance of circulating autoantibodies as well as their longevity is unknown. Age appears to be a covariate in autoantibody presence in COVID-19 patients. This is not surprising given known relationship of ANA positivity with age. In addition, some autoantibodies, including antiphospholipid antibodies, should be interpreted in the context of thrombotic events and may be transient in nature. Due to low prevalence of autoimmune manifestations following adult COVID-19, it is difficult to conclude pathogenesis and the risk factors that may contribute to triggering an autoimmune reaction as well as the role of the clinical laboratory in patient monitoring, warranting further consideration as more cases become available. In addition, recent literature suggests that, when compared to a more appropriate control group of patients admitted to the intensive care unit, there is no significant enhancement of autoimmune responses induced by SARS-CoV-2 infection ($n = 20$), as determined by circulating autoantibodies (38).

MIS-C/A PATIENT MONITORING—CHALLENGES AND CONSIDERATIONS FOR THE CLINICAL LABORATORY

Routine Laboratory Testing

Despite evidence gaps in our knowledge of MIS-C pathophysiological progression, we do know that clinical laboratory testing for routine biochemical and hematological parameters is essential in patient diagnosis and monitoring. The American College of Rheumatology recently released updated guidance on MIS-C diagnosis, treatment, and monitoring, adopting a tiered clinical laboratory testing approach at presentation. Tier 1 includes initial screening parameters to assess extent of inflammation (ferritin, erythrocyte sedimentation rate, complete blood count, procalcitonin) and SARS-CoV-2 exposure (RT-PCR or serology) (6). If initial laboratory test results suggest evidence of hyperinflammation or if the patient presents with shock of unclear etiology, additional

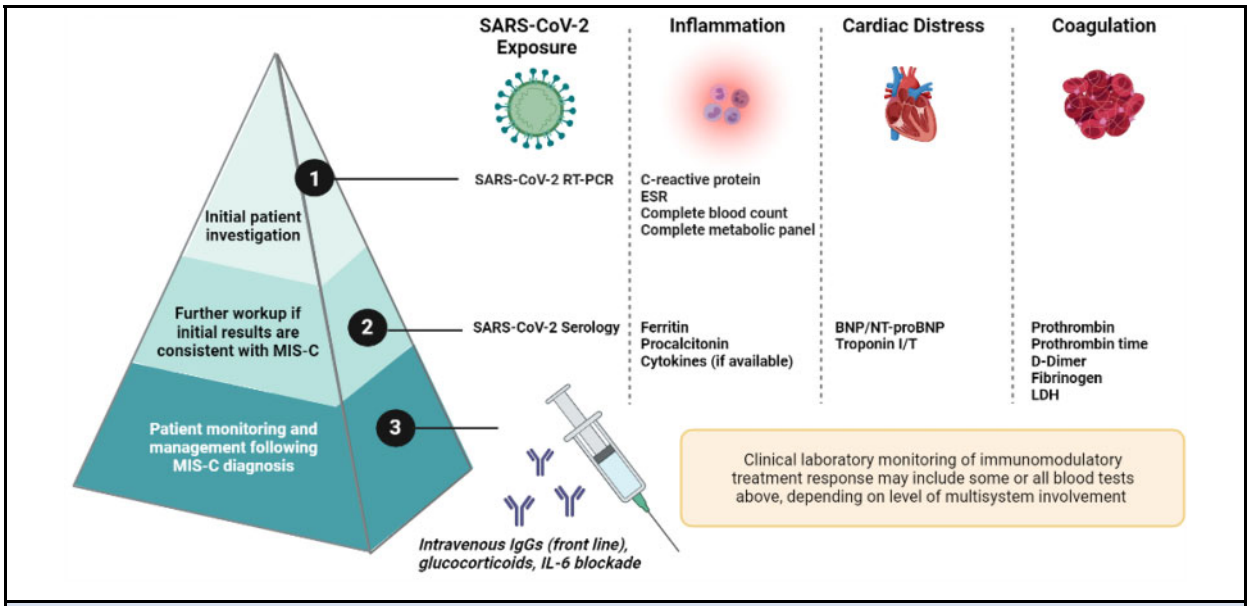

Fig. 1. Tiered approach to laboratory investigation of MIS-C at presentation as per American College of Rheumatology guidance (6). Tier 2 should also be completed if the patient presents with hypovolemic shock, regardless of Tier 1 outcome. NT-proBNP: N-terminal pro-type brain natriuretic peptide; LDH: lactate dehydrogenase.

laboratory testing is recommended, including markers of cardiac distress (BNP, troponin), coagulation (D-dimer, prothrombin, prothrombin time), and cytokines when available (Fig. 1) (6). While recommendations were based on available studies as previously described, limitations in these initial studies pose challenges for clinical laboratories in the interpretation and reporting of test results in patients with suspected MIS-C. Four main considerations of note are discussed next.

First, studies reporting biomarker trends in children with suspected MIS-C often include statistical comparison to a control group without sufficient consideration of age and sex. Importantly, appropriate reference standards and analytical information in available clinical reports are not provided. Biochemical and hematological parameters are known to vary significantly with growth and development in pediatrics, requiring age- and sex-specific interpretation to account for such variation (39). It is likely that standards based on adult reference values were used for test interpretation in MIS-C, complicating translation of study findings. Further, available studies do not provide an assessment of clinical significance of biomarker elevations in the appropriate context. It is critical to consider the magnitude of elevations in laboratory test result values in the appropriate clinical context relative to differential diagnoses. For example, ferritin is reported to be elevated in MIS-C relative to healthy children, but concentrations are significantly less elevated when compared to patients with other hyperinflammatory conditions such as macrophage activation syndrome (3). Low sample sizes and the rare nature of disease onset have limited the ability to characterize laboratory profile at presentation in a translatable way. In addition, the cutoffs used in many guidelines are often arbitrary or based on limited data in poorly characterized populations. Further work is needed to better characterize routine laboratory profile at MIS-C presentation in comparison to

differential diagnoses. Further, while autoantibodies have been observed in patients with severe MIS-C and in adult patients with COVID-19, their causal role in pathogenesis is unclear, and ANA profile is not expected to hold high clinical specificity and value in the diagnosis of SARS-CoV-2–related autoimmune response in children and adults. However, it is essential to continue to reassess the value of laboratory testing for common autoantibodies in patients with suspected SARS-CoV-2–related autoimmune response particularly as their longitudinal impact on health outcome is unknown.

Second, serology assays for the detection of antibodies against SARS-CoV-2 are an important component of patient diagnosis, as many present later in disease course when SARS-CoV-2 RNA is no longer detectable (7). There are limited data available on the performance of commercially available SARS-CoV-2 antibody assays in children and adolescents. Most manufacturers and peer-reviewed data report characteristics in specimens collected from adults. Children have been shown to have distinct antibody responses, regardless of MIS-C status, emphasizing that pediatric-focused assay evaluations are needed prior to test implementation (26).

Third, cytokine testing has been proposed as useful in MIS-C patient prognostication as IL-6, IL-10, and TNFα are often increased and may be helpful in monitoring response to treatment (e.g., corticosteroids, intravenous immunoglobulins, cytokine-blocking agents). However, it is challenging to provide access to cytokine testing in acute clinical care. These methods are often very costly, labor-intensive, and not well standardized. A recent report assessing variability in clinical laboratory measurement of cytokines (i.e., IL-1, Il-6, IL-10, TNFα), through a College of American Pathologists survey demonstrated significant variability between methodologies assessed (e.g., ELISA, chemiluminescence, magnetic bead–based multiplex immunoassay) (40). Due to poor standardization and availability in test measurement, results from research findings are not easily translatable to clinical practice. In addition, while cytokine testing can provide a window into inflammatory response in MIS-C patients, elevations can be nonspecific and need to be considered in the context of differential diagnoses. For example, while IL-6 and IL-17A have been shown to be elevated in MIS-C relative to healthy controls, some reports demonstrate significantly lower levels as compared to patients with KD (23). Currently, the American College of Rheumatology recommends the use of cytokines in MIS-C diagnostic evaluation, when available, but cautions use for guiding treatment due to known variability as well as minimal evidence to suggest value in this context (6).

Finally, most studies support the utility of routine laboratory testing in the context of patient diagnosis. However, minimal data exist on longitudinal clinical laboratory monitoring in MIS-C. Although intravenous immunoglobulin treatment has been shown to quickly resolve clinical symptoms, the long-term impacts of MIS-C are unknown. Future studies should continue to unravel pathogenic factors driving MIS-C as well as complete longitudinal follow-up of patients with severe MIS-C to assist in the diagnosis, prognosis, and monitoring of these patients.

CONCLUSION

In the current review, we have discussed studies characterizing MIS-C, suggesting autoimmune involvement in pathogenesis. We have also reviewed literature regarding similar multiinflammatory syndromes as well as new onset classical autoimmune disorders in adults following SARS-CoV-2 infection. From initial data, it is clear that MIS-C and, theoretically, MIS-A have unique inflammatory signatures involving both adaptive and innate systems (Fig. 2). Certain cytokines (IL-6, IL-17A), inflammatory markers (ferritin), and cardiac markers (troponin, N-terminal pro-type BNP) assist in the differentiation of MIS-C from other hyperinflammatory

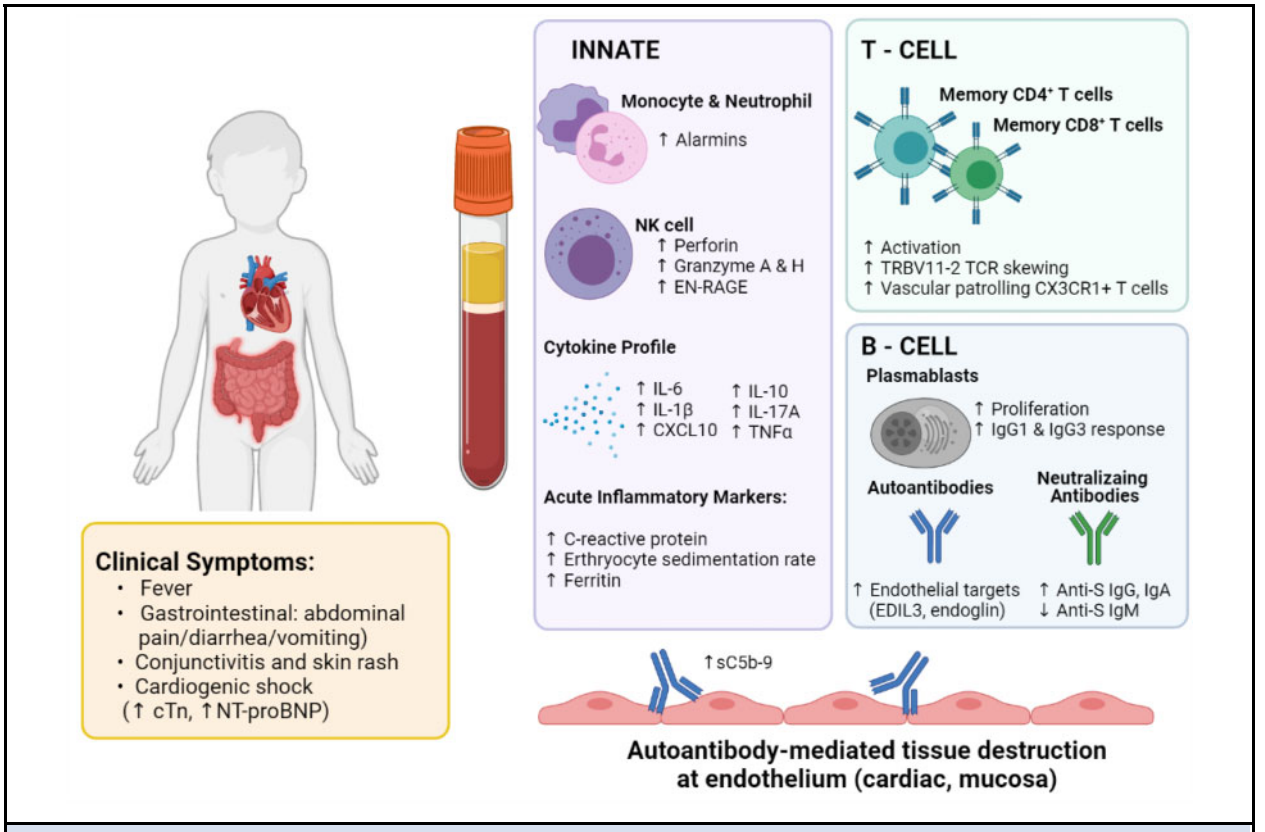

Fig. 2. Innate and adaptive immune signatures observed in patients with MIS-C. cTn: cardiac troponin; NT-proBNP: N-terminal pro-type brain natriuretic peptide; sC5b-9: soluble C5b-9; EDIL3: EGF-like repeats and discoidin domains 3; Anti-S: antispike. Made with BioRender. Adapted from Moreews et al. (19) and Szabo et al. (22).

conditions, emphasizing the role of the clinical laboratory in patient diagnosis and management. However, there are still major gaps in our understanding of MIS-C pathogenesis, including T-cell, B-cell, and innate response. Further work, particularly in clinical laboratory investigations, is needed to better elucidate pathogenesis and potential factors that predispose individuals to develop MIS-C/MIS-A. While individuals with MIS-C appear to only have transient hyperinflammation that can be quickly resolved with administration of intravenous immunoglobulins, it is essential that researchers not only continue to decipher initial pathogenesis but also monitor long-term health outcomes, particularly given observed presence of circulating autoantibodies with unknown impact.

Nonstandard Abbreviations: COVID-19, coronavirus disease 2019; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; MIS-C, multisystem inflammatory syndrome in children; KD, Kawasaki disease; BNP, brain natriuretic peptide; TCR, T-cell receptor; IL, interleukin; ADE, antibody-dependent enhancement; TNFα, tumor necrosis factor α; CCL, chemokine ligand; MIS-A, multisystem inflammatory syndrome in adults; ANCA, antineutrophil cytoplasmic antibodies; ANA, antinuclear antibodies.

Author Contributions: *All authors confirmed they have contributed to the intellectual content of this paper and have met the following 4 requirements: (a) significant contributions to the conception and design, acquisition of data, or analysis and interpretation of data; (b) drafting or revising the article for intellectual content; (c) final approval of the published article; and (d) agreement to be accountable for all aspects of the article thus ensuring that questions related to the accuracy or integrity of any part of the article are appropriately investigated and resolved.*

Authors' Disclosures or Potential Conflicts of Interest: *No authors declared any potential conflicts of interest.*

REFERENCES

1. American Academy of Pediatrics and Children's Hospital Association. Children and COVID-19: state data report (version 4/29/21). https://downloads.aap.org/AAP/PDF/AAP%20and%20CHA%20-%20Children%20and%20COVID-19%20State%20Data%20Report%202.4.21%20FINAL.pdf (Accessed April 2021).
2. Riphagen S, Gomez X, Gonzalez-Martinez C, Wilkinson N, Theocharis P. Hyperinflammatory shock in children during COVID-19 pandemic. Lancet 2020;395:1607–8.
3. Lee PY, Day-Lewis M, Henderson LA, Friedman KG, Lo J, Roberts JE, et al. Distinct clinical and immunological features of SARS-CoV-2-induced multisystem inflammatory syndrome in children. J Clin Invest 2020;130:5942–50.
4. Verdoni L, Mazza A, Gervasoni A, Martelli L, Ruggeri M, Ciuffreda M, et al. An outbreak of severe Kawasaki-like disease at the Italian epicentre of the SARS-CoV-2 epidemic: an observational cohort study. Lancet 2020;395:1771–8.
5. Toubiana J, Poirault C, Corsia A, Bajolle F, Fourgeaud J, Angoulvant F, et al. Kawasaki-like multisystem inflammatory syndrome in children during the covid-19 pandemic in Paris, France: prospective observational study. BMJ 2020;369:m2094.
6. Henderson LA, Canna SW, Friedman KG, Gorelik M, Lapidus SK, Bassiri H, 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:e13–29.
7. Godfred-Cato S, Bryant B, Leung J, Oster ME, Conklin L, Abrams J, et al.; California MIS-C Response Team. COVID-19-associated multisystem inflammatory syndrome in childre—United States, March-July 2020. MMWR Morb Mortal Wkly Rep 2020;69:1074–80.
8. Centers for Disease Control and Prevention. Information for healthcare providers about multisystem inflammatory syndrome in children (MIS-C). https://www.cdc.gov/mis-c/hcp/ (Accessed April 2021).
9. Whittaker E, Bamford A, Kenny J, Kaforou M, Jones CE, Shah P, et al.; PIMS-TS Study Group and EUCLIDS and PERFORM Consortia. Clinical characteristics of 58 children with a pediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2. JAMA 2020;324:259–69.
10. Feldstein LR, Rose EB, Horwitz SM, Collins JP, Newhams MM, Son MBF, et al.; CDC COVID-19 Response Team. Multisystem inflammatory syndrome in U.S. children and adolescents. N Engl J Med 2020;383:334–46.
11. Dufort EM, Koumans EH, Chow EJ, Rosenthal EM, Muse A, Rowlands J, et al.; New York State and Centers for Disease Control and Prevention Multisystem Inflammatory Syndrome in Children Investigation Team. Multisystem inflammatory syndrome in children in New York State. N Engl J Med 2020;383:347–58.
12. Swann OV, Holden KA, Turtle L, Pollock L, Fairfield CJ, Drake TM, et al. Clinical characteristics of children and young people admitted to hospital with covid-19 in United Kingdom: Prospective multicentre observational cohort study. BMJ 2020;370:m3249.
13. Davies P, Evans C, Kanthimathinathan HK, Lillie J, Brierley J, Waters G, et al. Intensive care admissions of children with paediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 (PIMS-TS) in the UK: a multicentre observational study. Lancet Child Adolesc Health 2020;4:669–77.
14. Gruber CN, Patel RS, Trachtman R, Lepow L, Amanat F, Krammer F, et al. Mapping systemic inflammation and antibody responses in multisystem inflammatory syndrome in children (MIS-C). Cell 2020;183:982–95.e14.
15. Weisberg SP, Connors TJ, Zhu Y, Baldwin MR, Lin WH, Wontakal S, et al. Distinct antibody responses to SARS-CoV-2 in children and adults across the COVID-19 clinical spectrum. Nat Immunol 2021;22:25–31.
16. Ramaswamy A, Brodsky NN, Sumida TS, Comi M, Asashima H, Hoehn KB, et al. Immune dysregulation and autoreactivity correlate with disease severity in SARS-CoV-2-associated multisystem inflammatory syndrome in children. Immunity 2021;54:1083–95. e7.
17. Smatti MK, Cyprian FS, Nasrallah GK, Al Thani AA, Almishal RO, Yassine HM. Viruses and autoimmunity: a review on the potential interaction and molecular mechanisms. Viruses 2019;11:762.
18. Porritt RA, Paschold L, Noval Rivas M, Cheng MH, Yonker LM, Chandnani H, et al. HLA class I-associated expansion of TRBV11-2 T cells in multisystem inflammatory syndrome in children. J Clin Invest 2021;131:e146614.
19. Moreews M, Le Gouge K, Khaldi-Plassart S, Pescarmona R, Mathieu A-L, Malcus C, et al. Polyclonal expansion of TCR Vbeta 21.3 + CD4 + and CD8 + T cells is a hallmark of multisystem inflammatory syndrome in children. Sci Immunol 2021;6:eabh1516.
20. Cheng MH, Zhang S, Porritt RA, Rivas MN, Paschold L, Willscher E, et al. Superantigenic character of an insert unique to SARS-CoV-2 spike supported by skewed TCR repertoire in patients with hyperinflammation. Proc Natl Acad Sci USA 2020;117:25254–62.

21. Vella LA, Giles JR, Baxter AE, Oldridge DA, Diorio C, Kuri-Cervantes L, et al.; UPenn COVID Processing Unit. Deep immune profiling of MIS-C demonstrates marked but transient immune activation compared to adult and pediatric COVID-19. Sci Immunol 2021;6:eabf7570.
22. Szabo PA, Miron M, Farber DL. Location, location, location: tissue resident memory T cells in mice and humans. Sci Immunol 2019;4(34):eaas9673.
23. Consiglio CR, Cotugno N, Sardh F, Pou C, Amodio D, Rodriguez L, et al.; CACTUS Study Team. The immunology of multisystem inflammatory syndrome in children with COVID-19. Cell 2020;183:968–81, e7.
24. Bartsch YC, Wang C, Zohar T, Fischinger S, Atyeo C, Burke JS, et al. Humoral signatures of protective and pathological SARS-CoV-2 infection in children. Nat Med 2021;27:454–62.
25. Rothan HA, Byrareddy SN. The potential threat of multisystem inflammatory syndrome in children during the COVID-19 pandemic. Pediatr Allergy Immunol 2021; 32:17–22.
26. Bohn MK, Hall A, Wilson S, Taher J, Sepiashvili L, Adeli K. Pediatric evaluation of clinical specificity and sensitivity of SARS-CoV-2 IgG and IgM serology assays. Clin Chem Lab Med 2021;59:e235–37.
27. Diorio C, Henrickson SE, Vella LA, McNerney KO, Chase J, Burudpakdee C, et al. Multisystem inflammatory syndrome in children and COVID-19 are distinct presentations of SARS–CoV-2. J Clin Invest 2020;130:5967–75.
28. Carter MJ, Fish M, Jennings A, Doores KJ, Wellman P, Seow J, et al. Peripheral immunophenotypes in children with multisystem inflammatory syndrome associated with SARS-CoV-2 infection. Nat Med 2020;26:1701–7.
29. Morris SB, Schwartz NG, Patel P, Abbo L, Beauchamps L, Balan S, et al. Case series of multisystem inflammatory syndrome in adults associated with SARS-CoV-2 infection—United Kingdom and United States, March-August 2020. MMWR Morb Mortal Wkly Rep 2020;69: 1450–6.
30. Escobar MM, Kataria S, Khan E, Subedi R, Tandon M, Peshwe K, et al. Acute transverse myelitis with dysautonomia following SARS-CoV-2 infection: a case report and review of literature. J Neuroimmunol 2021; 353:577523.
31. Novelli L, Motta F, De Santis M, Ansari AA, Gershwin ME, Selmi C. The JANUS of chronic inflammatory and autoimmune diseases onset during COVID-19—a systematic review of the literature. J Autoimmun 2021; 117:102592.
32. López-González MDC, Peral-Garrido ML, Calabuig I, Tovar-Sugrañes E, Jovani V, Bernabeu P, et al. Case series of acute arthritis during COVID-19 admission. Ann Rheum Dis 2021;80:e58.
33. Alivernini S, Cingolani A, Gessi M, Paglionico A, Pasciuto G, Tolusso B, et al. Comparative analysis of synovial inflammation after SARS-CoV-2 infection. Ann Rheum Dis 2021;80:e91.
34. Vlachoyiannopoulos PG, Magira E, Alexopoulos H, Jahaj E, Theophilopoulou K, Kotanidou A, et al. Autoantibodies related to systemic autoimmune rheumatic diseases in severely ill patients with COVID-19. Ann Rheum Dis 2020; 79:1661–3.
35. Tang KT, Hsu BC, Chen DY. Autoimmune and rheumatic manifestations associated with COVID-19 in adults: an updated systematic review. Front Immunol 2021;12: 645013.
36. Fujii H, Tsuji T, Yuba T, Tanaka S, Suga Y, Matsuyama A, et al. High levels of anti-SSA/Ro antibodies in COVID-19 patients with severe respiratory failure: A case-based review: high levels of anti-SSA/Ro antibodies in COVID-19. Clin Rheumatol 2020;39:3171–5.
37. Bowles L, Platton S, Yartey N, Dave M, Lee K, Hart DP, et al. Lupus anticoagulant and abnormal coagulation tests in patients with Covid-19. N Engl J Med 2020;383:288–90.
38. Mj F UT. COVID-19-associated autoimmunity as a feature of acute respiratory failure. Intensive Care Med 2021;47: 801–4.
39. Adeli K, Higgins V, Trajcevski K, White-Al Habeeb N. The Canadian laboratory initiative on pediatric reference intervals: a CALIPER white paper. Crit Rev Clin Lab Sci 2017;54:358–413.
40. Knight V, Long T, Meng QH, Linden MA, Rhoads DD. Variability in the laboratory measurement of CytokinesA longitudinal summary of a College of American Pathologists proficiency testing survey. Arch Pathol Lab Med 2020;144:1230–3.