Pathogenesis, immunology, and immune-targeted management of the multisystem inflammatory syndrome in children (MIS-C) or pediatric inflammatory multisystem syndrome (PIMS) EAACI Position Paper

Feleszko, W.; Okarska-Napierala, M.; Buddingh, E.P.; Bloomfield, M.; Sediva, A.; Bautista-Rodriguez, C.; ... ; Immunology Sect Working

Received: 4 December 2022 | Accepted: 5 December 2022

DOI: 10.1111/pai.13900

POSITION PAPER

WILEY

Pathogenesis, immunology, and immune-targeted management of the multisystem inflammatory syndrome in children (MIS-C) or pediatric inflammatory multisystem syndrome (PIMS): EAACI Position Paper

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Editor: Ömer Kalayci

Abstract

Multisystem inflammatory syndrome in children (MIS-C) is a rare, but severe complication of coronavirus disease 2019 (COVID-19). It develops approximately 4 weeks after severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and involves hyperinflammation with multisystem injury, commonly progressing to shock. The exact pathomechanism of MIS-C is not known, but immunological dysregulation leading to cytokine storm plays a central role. In response to the emergence of MIS-C, the European Academy of Allergy and Clinical Immunology (EAACI) established a task force (TF) within the Immunology Section in May 2021. With the use of an online Delphi process, TF formulated clinical statements regarding immunological background of MIS-C, diagnosis, treatment, follow-up, and the role of COVID-19 vaccinations. MIS-C case definition is broad, and diagnosis is made based on clinical presentation. The immunological mechanism leading to MIS-C is unclear and depends on activating multiple pathways leading to hyperinflammation. Current management of MIS-C relies on supportive care in combination with immunosuppressive and/or immunomodulatory agents. The most frequently used agents are systemic steroids and intravenous immunoglobulin. Despite good overall short-term outcome, MIS-C patients should be followed-up at regular intervals after discharge, focusing on cardiac disease, organ damage, and inflammatory activity. COVID-19 vaccination is a safe and effective measure to prevent MIS-C. In anticipation of further research, we propose a convenient and clinically practical algorithm for managing MIS-C developed by the Immunology Section of the EAACI.

KEYWORDS
children, clinical algorithm, clinical guidance, Delphi, hyperinflammation, intravenous immunoglobulin, management, MIS-C, SARS-CoV-2, steroids

1 | INTRODUCTION

Since the beginning of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic, children have been relatively spared from severe coronavirus disease 2019 (COVID-19). In children, COVID-19 is usually asymptomatic or shows a mild disease course. Interestingly, despite growing COVID-19 incidence among children due to the emergence of new, more contagious SARS-CoV-2 variants, severe disease develops in a minority of children, mostly those with chronic medical conditions.[1–4]

However, in mid-March 2020, physicians in the countries particularly hit by the first COVID-19 pandemic wave noticed a sudden rise in the number of children with fever and hyperinflammatory multisystem injury quickly progressing to shock.[5–9] This new

pediatric entity appeared to develop approximately 4 weeks after SARS-CoV-2 infection.[7,10,11] It was named pediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 (PIMS-TS)[12] or multisystem inflammatory syndrome in children (MIS-C).[13,14] Most children with MIS-C demonstrate anti-SARS-CoV-2 antibodies,[11,15–21] which were found to be higher compared to pediatric patients with acute COVID-19.[22] Delayed symptom onset and high antibody titers suggest that MIS-C is a late immunological hyperactivation in response to SARS-CoV-2 rather than a severe presentation of an acute infection.

The clinical and laboratory picture of MIS-C resembles Kawasaki disease (KD), toxic shock syndrome (TSS), and macrophage activation syndrome (MAS) despite some significant differences from those three entities.[23,24] Thus, KD, TSS, and MAS may be seen as essential points of reference when investigating the pathomechanism of MIS-C, its differential diagnosis or treatment.

In response to the emergence of MIS-C, the European Academy of Allergy and Clinical Immunology (EAACI) established a task force (TF) within the Immunology Section in May 2021. The goal of this TF was to describe state-of-the-art immune phenomena in MIS-C and provide guidance to clinicians in the evaluation and management of MIS-C. An international multidisciplinary group was mandated to propose a unified clinical management algorithm to diagnose and treat children with MIS-C.

Clinical guidance generated from this effort is intended to aid in the care of individual patients, without supplanting clinical decision-making. Modifications to treatment plans, particularly in patients with complex conditions, are highly disease-, patient-, geography-, and time-specific, and therefore, these must be individualized as part of a shared decision-making process.

2 | METHODOLOGY

TF members were selected by the TF leadership (WF, GTS) based on their expertise in basic and clinical immunology, infectious diseases, cardiology, pediatrics, dermatology, and rheumatology, as well as their experience in managing MIS-C and hyperinflammation in acute SARS-CoV-2 infection. The multidisciplinary TF was composed of basic researchers and clinicians from 10 European Countries (A, BE, CH, CZ, D, DK, ES, NL, PL, UK), Canada, and Singapore. All specialists who were approached to develop this position paper agreed to participate. Initially, nine work groups were created to address the full spectrum of topics related to MIS-C. These topics included definition, clinical description, differential diagnosis, the role of the virus, immunology (including the role of innate and adaptive immunology), diagnostic evaluation, and treatment with a special focus on immunomodulation and management of hyperinflammation.

A preliminary guidance document was generated, and the entire TF was given an opportunity to review and edit the guidance document. Individual approval of the final document was obtained from each member on 07 July 2022.

3 | CLINICAL STATEMENTS. DELPHI METHODOLOGY

After approval of the final document, an online, 2-round Delphi survey was conducted among members of the TF. The aim was to receive comments for each Clinical Statement (D-level recommendation) and achieve consensus among the panel of experts (Figure 1). The TF voted anonymously using a Google Form tool. Panelists used a 9-point scale to rate the appropriateness of each of the statements. Before voting, median scores of 1–3 were defined as insufficient evident, 4–6 as uncertain, and 7–9 as completely appropriate. The consensus would be considered high if all votes coalesced within the same tercile. In a feedback process, input from the initial voting was incorporated (by WF and MON) into the draft guidance statements, and the document was redistributed to the entire TF for the second round of voting. Voting in this phase was conducted in the same manner as described above. The panel approved guidance statements that earned a median score of 7–9 with high levels of consensus. The final approval was obtained from each panelist on 25 June 2022 and by the EAACI Executive Committee on 30 November 2022.

4 | CASE DEFINITION

Several MIS-C case definitions have been published in May 2020[12–14] and are presented in Table 1. As the disease was new and potentially dangerous, the definitions were relatively broad. The World Health Organization (WHO) and Centers for Disease Control and Prevention (CDC) definitions are commonly used in the studies concerning MIS-C. Despite some differences, all published definitions involve six major categories: (i) young age, (ii) fever, (iii) high inflammatory markers, (iv) multisystem injury, (v) exclusion of other plausible diagnoses, and (vi) SARS-CoV-2 exposure. Considering that definitions are broad and SARS-CoV-2 seropositivity is becoming universal, cautious differential diagnosis is crucial in children suspected to have MIS-C.

5 | CLINICAL DESCRIPTION

The first reports about MIS-C came from the United Kingdom (UK)[5] and Italy,[6] though the largest cohorts published thus far are from the United States of America (US),[11,25,26] where 7880 cases have been registered, as of March 2022.[27] Since then, hundreds of MIS-C patients have been reported worldwide. Intriguingly, there are no MIS-C reports from China, and only five cases were published from Japan.[28] This might mean that the risk of developing MIS-C depends on genetic factors associated with ethnicity. Noteworthy, MIS-C closely resembles a particularly severe clinical presentation of KD: Kawasaki disease shock syndrome (KDSS). Despite the highest prevalence of KD in Japan, KDSS is more common among KD patients from Europe and the US (5%–7% vs.

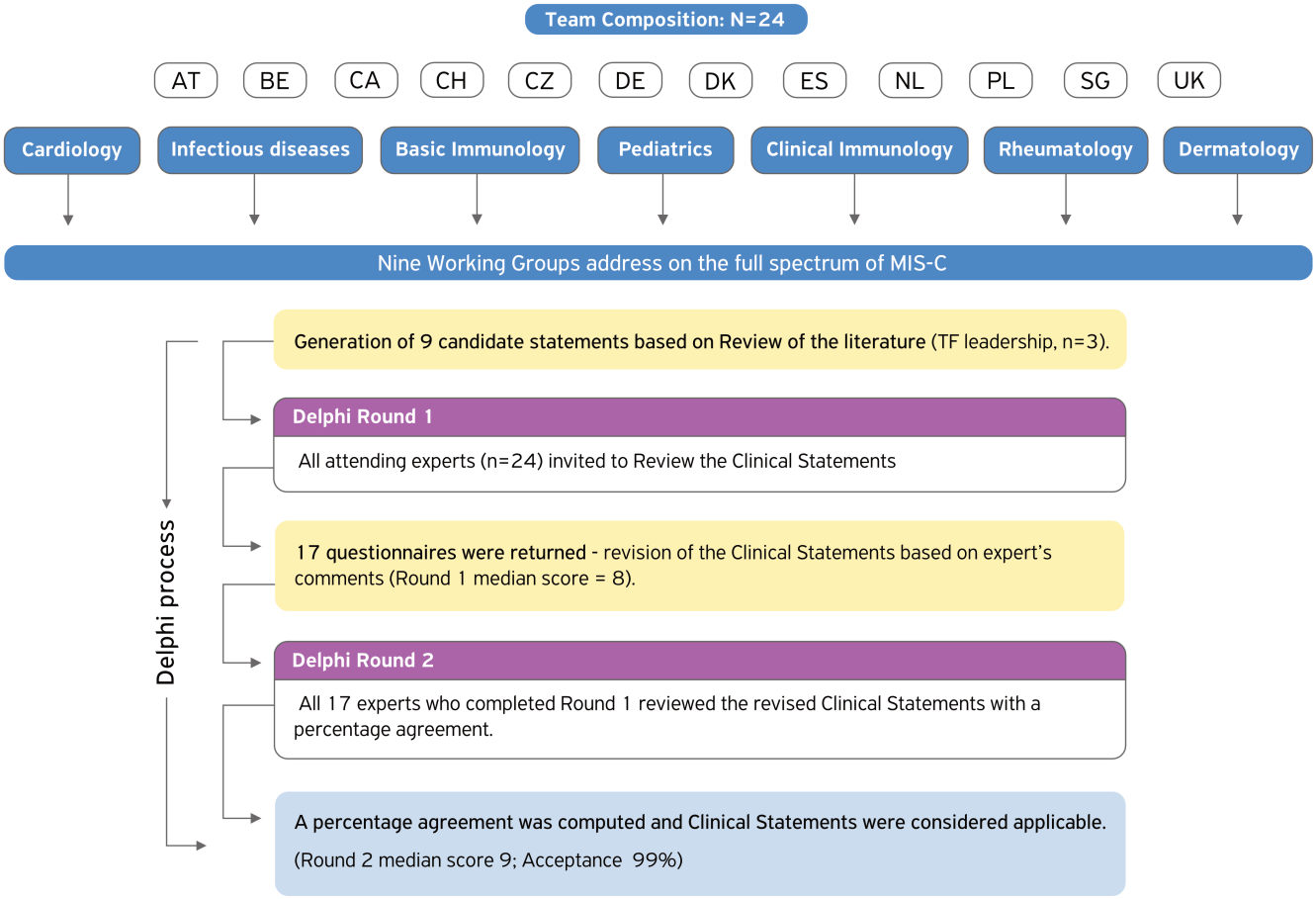

FIGURE 1 The methodology of developing the European Academy of Allergy and Clinical Immunology Statement on the Diagnostic Workup and the immune-targeted management and the Treatment Algorithm of the Multisystem Inflammatory Syndrome in Children or Pediatric Inflammatory Multisystem Syndrome. The Clinical Statements were proposed by nine working groups and subsequently accepted in the Two-round Delphi process, as described in detail in the Methods. AT, Austria; BE, Belgium; CA, Canada; CH, Switzerland; CZ, Czech Republic; DE, Germany; DK, Denmark; ES, Spain; NL, The Netherlands; PL, Poland; SG, Singapore; TF, Task Force.

1%).[29] Similarly, children from East Asia could be less susceptible to developing MIS-C. On the other hand, it is possible that the risk of MIS-C is dependent on a SARS-CoV-2 strain, which had evolved when spreading from Asia to Europe and the US, and this could have resulted in such an unequal MIS-C prevalence in different countries.

Published cohorts of MIS-C are heterogenous and challenging to compare due to varying definitions of the disease and its complications, different inclusion criteria, and incomplete data. However, the clinical picture and laboratory findings of MIS-C, emerging from those publications, are relatively reproducible (Tables 2 and 3).

MIS-C presents with fever and multisystem injury, with predominant gastrointestinal and mucocutaneous involvement, and laboratory markers of severe inflammation (Figure 2).

Table 4 summarizes the clinical features and laboratory hallmarks of MIS-C, KD, TSS, sepsis, appendicitis, and MAS for differential diagnosis. Despite clinical resemblance to KD, TSS or MAS, MIS-C remains a distinct, unique entity[23,24] (for more details see chapter VI – The role of the virus in the context of other hyperinflammatory diseases).

Some children with MIS-C develop life-threatening complications, mostly related to cardiovascular failure, with hypotension and decreased left ventricle contractility.[5,6,17,21,23–25,33,34] Older age, black race and ethnicity, higher inflammatory markers, and lower lymphocyte and platelet counts correlate with clinical deterioration and the need for intensive care treatment.[25,33,35,36] Despite the severe clinical course in a substantial proportion of MIS-C patients, immunosuppressive and/or immunomodulatory treatment is highly effective; most children recover within a week, and the mortality rate is relatively low (Table 3). Coronary artery dilations and aneurysms comprise another significant MIS-C complication, though their prevalence and persistence are difficult to establish. Fortunately, coronary arteries abnormalities seem to resolve in most patients, too.[19,24,26] This may result from transient coronary dilation due to inflammation and/or histamine release.[37] According to international study of 55 patients, the cardiac features of MIS-C involved decreased left ventricular function (64%), valvulitis (31%), pericardial effusion (22%) and coronary abnormalities (20%).[38]

Apart from particularly common mucocutaneous, gastrointestinal, and cardiovascular involvement, any tissue and organ may be

TABLE 1 Multisystem inflammatory syndrome in children (MIS-C) definitions according to the Royal College of Pediatrics and Child Health (RCPCH), the Centers for Disease Control and Prevention (CDC), and the World Health Organization (WHO).

	RCPCH (01.05.2020)	CDC (14.05.2020)	WHO (15.05.2020)
1. Age	<18 years	<21 years	<19 years
2. Fever	Persistent	Fever >38.0°C for ≥24 h	≥3 days
3. Inflammation	↑ CRP, neutrophils and ↓ lymphocytes	≥1: ↑ CRP, PCT, ESR, fibrinogen, D-dimer, ferritin, LDH, IL-6, neutrophils ↓ lymphocytes, albumin	↑ ESR, CRP, PCT
4. Multi- (single-) system involvement	≥1: shock, cardiac, respiratory, renal, gastrointestinal, or neurological disorder	≥2: cardiac, renal, respiratory, hematologic, gastrointestinal, dermatological, or neurological involvement	≥2: muco-cutaneous inflammation signs, hypotension or shock, cardiac involvement, coagulopathy, acute gastrointestinal problems
5. Other causes excluded	Infectious	Infectious and non-infectious	Infectious
6. COVID-19 history	Positive or negative	Positive for SARS-CoV-2 by PCR, serology, or antigen test; or exposure to a suspected or confirmed COVID-19 case within the 4 weeks prior to the onset of symptoms	Evidence of COVID-19 (PCR, antigen test or serology positive), or likely contact with COVID-19 patients
Additional comments	This may include children fulfilling full or partial criteria for Kawasaki disease	Clinically severe illness requiring hospitalization	

Abbreviations: CDC, Centers for Disease Control and Prevention; COVID-19, coronavirus disease 2019; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; IL, interleukin; LDH, lactate dehydrogenase; PCR, polymerase chain reaction; PCT, procalcitonin; RCPCH, Royal College of Pediatrics and Child Health; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; WHO, World Health Organization.

involved in the inflammation. Most children present with progressing lethargy, and some develop more specific neurologic symptoms, too. According to Fink et al. most common neurologic manifestations of MIS-C include headache (46.5%), acute encephalopathy (22.3%) and dizziness (2.1%).[39]

Some studies on MIS-C aimed to distinguish separate disease phenotypes using latent class analysis. Godfred-Cato et al. identified three classes of patients: Class I, with multiorgan failure and shock; Class II, with predominant respiratory involvement, likely overlapping with severe COVID-19 in a fraction of older teenagers; and Class III, characterized by predominant mucocutaneous involvement in the youngest age group, suggestive of KD overlap.[8] Similarly, Flood et al. identified three subgroups of patients: Class 1 – with the most benign clinical course, and Classes 2 and 3, which matched Class III and I, respectively, as described by Godfred-Cato.[17,36] Also other research groups have described an association between the clinical picture of MIS-C and age, with mucocutaneous involvement more common in younger children and myocarditis more prevalent in the older age group.[10,30,40] On the other hand, Belay et al. found the clinical presentation of MIS-C may depend on the symptomatic course of the preceding SARS-CoV-2 infection. Cardiovascular complications were more common in children who had asymptomatic COVID-19 before developing MIS-C in their cohort.[11]

Although the multisystem inflammatory syndrome is mainly observed in children, adults also might suffer from this condition (MIS-A). Scarcely described in case reports, MIS-A specifically affects young adults and resembles the childhood condition with a hyperinflammation and extra-pulmonary organ dysfunction. The overlapping symptoms of acute COVID-19 and MIS-A make differentiation of the two diagnoses challenging.[41,42]

6 | ASSOCIATION WITH SARS-COV-2 AND COVID-19

MIS-C develops 3–6 weeks after SARS-CoV-2 infection. Waves of MIS-C usually emerge approximately 4 weeks after the COVID-19 waves observed in the general population (Figure 3). According to Belay et al., 95% of those children who develop MIS-C will generate symptoms within 60 days after having had a SARS-CoV-2 infection.[11] The preceding infection may be symptomatic or asymptomatic. The risk of developing MIS-C following SARS-CoV-2 exposure is estimated to be 1:3000–4000 based on studies from Denmark,[43] Germany,[44] and the US.[45] The incidence of MIS-C is higher in Black, Hispanic or Latino, and Asian or Pacific Islander children as compared to Caucasians.[45] Interestingly, MIS-C incidence decreases in consecutive COVID-19 waves, possibly due to changing predominant SARS-CoV-2 variants together with growing immunity in the society.[46]

Some children (up to 50%) with MIS-C have positive nasopharyngeal polymerase chain reaction (PCR) test results for SARS-CoV-2 (Table 2), whereas the majority (60%–95%) have anti-SARS-CoV-2 antibodies. PCR-positive children with MIS-C had significantly higher cycle threshold (C_t) values than patients with acute COVID-19, suggestive of past rather than ongoing infection.[22,47,48] Importantly, MIS-C and severe acute COVID-19 share some clinical and laboratory characteristics[49] and some children may present with overlapping

TABLE 2 Clinical characteristics of MIS-C children from the largest cohorts published worldwide.

Study ID	Belay, US[11]	Relvas-Brandt, Brasil[16]	Ciftdogan, Turkey[30]	Ludwikowska, Poland[15]	Flood, UK[17]	Kahn, Sweden[18]	Mamishi, Iran[20]	García-Salido, Spain[a21]	Tiwari, India[31]	Belhadjer, France, Switzerland[a24]	Webb, South Africa[32]
Study time	III.20-I.21	II.-XII.20	XI.20-VI.21	III.20-II.21	III.20-VI.20	XII.20-V.21	III.20-VI.20	III.20-VI.20	III.20-IV.21	III.20-IV.20	–
Case definition used	CDC	WHO	CDC/WHO	WHO	BPSU	WHO	CDC	RCPCH	CDC	[b]	–
Number of patients	1733	652	614	274	268	133	45	45	41	35	23
Age, median (IQR, if available) [years]	9 (5–13)	5	7.4 (3.9–12)	8.8 (5.2–12.1)	8.2 (4–12.1)	9.3 (4.3)[c]	7 (4–9.9)	9.4 (5.5–11.8)	6.2	10	6.6 (4.8–8.4)
Sex, % male	57.6%	57.1%	57.7%	63%	60%	61%	53%	66.7%	56%	51%	73.9%
Comorbidities, % (no.)	–	20.1% (131)	11.8% (73)	18% (38)	19% (51)	–	13% (6)	17.8% (8)	20% (8)	28% (10)	–
Clinical picture, % (no.)											
Febrile days before admission, median	–	4	4	5	–	–	–	–	–	–	–
Rash	55.6% (963)	–	54.4% (334)	83% (218)	52.6% (141)	51% (67)	–	–		57% (20)	87% (20)
Conjunctivitis	53.6% (929)	–	49.7% (305)	78% (207)	50.4% (135)	52% (69)	15.8% (12)	–	61% (25)	89% (31)	65.2% (15)
Oral inflammation	–	–	43.1% (265)	66% (173)	33.2% (89)	17% (22)	3.6% (2)	–	71% (29)	54% (19)	–
Gastrointestinal involvement (any)	–	87.6% (571)	77% (473)	93% (250)	99.3% (266)	–	–	–	27% (11)	83% (29)	–
Respiratory involvement (any)	–	66% (430)	34.6% (216)	–	17.9% (48)	–	44.7% (34)	–	78% (32)	34% (12)	43.5% (10)
Neurological involvement (any)	–	56.1% (366)	–	86% (220)	32.5% (87)	–	18.4% (14)	–	51% (21)	31% (11)	22.7% (5)
Hypotension	50.8% (880)	27.8% (181)	12.1% (74)[d]	41% (99)	42.5% (114)	–	–	84.4% (38)[d]	54% (22)[d]	–	56.5% (13)
ECHO findings, % (no.)											
Decreased myocardial contractility	31% (484)	–	–	23% (58)	38.4% (78)	19% (23)	–	48.9% (22)		100% (35)	34.8% (8)
Coronary arteries affected	16.5% (258)	–	9.9% (57)	8% (21)	26.6% (54)	16% (20)	31% (14)	6.7% (3)		17% (6)	4.3% (1)
SARS-CoV-2 status, % of tested (no.) unless otherwise											
SARS-CoV-2 PCR positive	51.1% (893)	22.2% (145)	9.4% (56)	12.6% (29)	14.8% (264)	36% (46)[e]	22% (10)	40% (18)		34% (12)	–
SARS-CoV-2 serology positive	82.6% (1432)	61.2% (399)	94.2% (520)	94.5% (241)	63.6% (75)	80% (107)	78% (35)	63% (17)[f]		86% (30)	–

Abbreviations: BPSU, British Pediatric Surveillance Unit; CDC, Centers for Disease Control and Prevention; ECHO, echocardiography; PCR, polymerase chain reaction;, SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; RCPCH, the Royal College of Pediatrics and Child Health; WHO, World Health Organization.

[a]The study involved children hospitalized in pediatric intensive care unit (PICU) only.

[b]Inclusion criteria: fever >38.5°C, cardiogenic shock or acute left ventricular dysfunction, and CRP >10 mg/dl.

[c]Mean (±SD).

[d]Reported as a shock.

[e]PCR or antigen positive.

[f]Serology reported only in a subgroup with negative PCR for SARS-CoV-2.

TABLE 3 Laboratory characteristics, treatment and outcome of MIS-C children from the largest cohorts published worldwide.

Study ID	Belay, US[11]	Relvas-Brandt, Brasil[16]	Ciftdogan, Turkey[30]	Ludwikowska, Poland[15]	Flood, UK[17]	Kahn, Sweden[18]	Mamishi, Iran[20]	Garcia-Salido, Spain[a21]	Tiwari, India[31]	Belhadjer, France, Switzerland[a24]	Webb, South Africa[32]
Laboratory results, median (IQR, if available), mean (SD) or % (no.) outside normal limit (at respective peaks)											
CRP (mg/dl)	18.1 (10.2–26.1)	–	14 (8.3–20.7)	14 (8.4–19.5)	22.3 (16.2–28.9)	–	6.7 (3–10.2)	22.6	11.9 (7.9)	24.1 (15–31.1)	30 (19.9–36.4)
Procalcitonin (μg/L)	–	–	2 (0.54–9.0)	2.5 (1.0–6.9)	4.7 (1.9–15.9)	–	–	7.5	8.9 (1.6–51)	36 (8–99)	–
D-dimers (μg/L)	2350 (1250–4380)	–	2320 (1122–4241)	2600 (1500–4600)	3400 (1757–6921)	–	3909 (848–4528)	–	2500 (1100–4300)	–	–
Ferritin (μg/L)	475.9 (243–916.3)	–	302 (147–576)	331 (197.9–622.4)	542.6 (284–1049)	–	453 (179–1450)	–	350 (170–733)	–	–
Troponin (ng/ml)	0.06 (0.01–0.3)	–	10 (4–33)	28% (62)[b]	–	–	0.6 (0.1–26)	0.06 (0.01–0.2)	50% (6)[b]	0.35 (0.19–1.27)	–
NT-proBNP (ng/L)	2789 (491–8405)	–	1420 (355–5193)	86% (171)[b]		2024 (461–5984)	–	5532 (1582–12,783)	1845 (403–6840)	41,484 (35,811–52,475)	7556 (1240–31,225)
Lymphocyte count ($\times 10^9$/L)	0.88 (0.5–1.7)	–	1.2 (0.7–2.0)	1.0 (0.7–1.8)	0.8 (0.5–1.7)	–	1.26 (0.66–2.7)	0.7	–	–	–
Platelets ($\times 10^9$/L)	134 (94–200)	–	190 (131–285)	176 (127–248)	171.5 (112–266.5)	–	167 (89–275)	119.5	–	–	–
Albumin (g/dl)	–	–	3.43 (3–3.9)	3.3 (2.8–3.7)	2.5 (2.1–3.1)	–	3.4 (3–4.2)	–	2.9 (0.7)	–	–
Treatment and outcome, % (no.) unless otherwise											
Admitted to PICU	58.2% (1009)	44.5% (290)	31.3% (192)	8% (23)	44% (118)	16% (21)	–	100% (45)	–	100% (35)	52.2% (12)
Mechanical ventilation	–	19.6% (128)	13.5% (83)	4% (10)	16.4% (44)	–	–	13.3% (6)	–	62% (22)	26.1% (6)
Inotropes/ vasopressors	–	27.8% (181)	19.1% (117)	–	29.9% (80)	–	–	66.7% (30)	–	80% (28)	39.1% (9)
IVIG	80.5% (1359)	67.9% (418)	93% (571)	93% (238)	70.5% (189)	–	48% (18)	51.1% (23)	–	71% (25)	100% (23)
Steroids	71% (1230)	62.3% (376)	83.8% (514)	67% (143)	55.6% (149)	–	60% (27)	80% (36)	–	34% (12)	65.2% (15)
Biologic agents	–	–	6.4% (39)	1% (3)	9.3% (25)	–	–	24.4% (11)	–	8.6% (3)	9.1% (2)
Median hospital stay (days)	–	9	9 (6–12)	–	8 (5–11)	–	8 (6–11)	–	–	10 (8–14)	7 (4.3–11.8)
Death	1.4% (24)	6.4% (42)	1.8% (11)	0.7% (2)	1.1% (3)	–	11% (5)	0	5% (2)	0	0

Abbreviations: CRP, C-reactive protein; IQR, interquartile range; IVIG, intravenous immunoglobulin; NT-proBNP, N-terminal prohormone of B type natriuretic peptide; PICU, pediatric intensive care unit.

[a]The study involved children hospitalized in PICU only.

[b]Percentage increased.

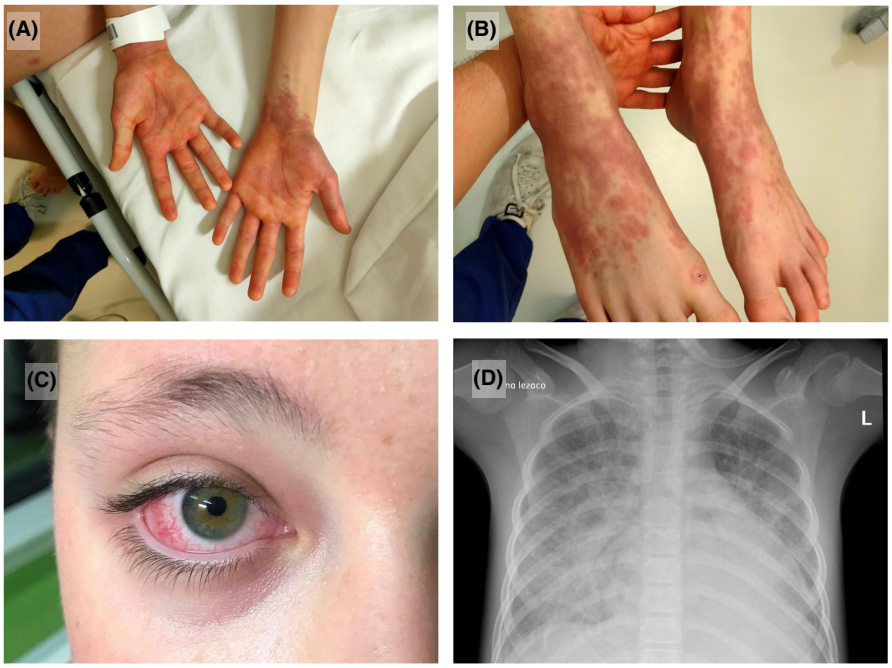

FIGURE 2 Clinical symptomatology in children with MIS-C. The pictures present the patients with MIS-C hospitalized in Pediatric Teaching Clinical Hospital of the Medical University of Warsaw, after informed consent was taken from the carer and the patient. (A, B) Typical cutaneous manifestations of MIS-C: generalized rash, dominating in extremities and acral regions. Palms and soles are involved demonstrating a polymorphic, maculopapular, and diffuse erythroderma with single "target lesions" typical for erythema multiforme. (C) Non-suppurative, limbic sparing conjunctivitis. (D) Chest radiograph of a 12-year-old girl with MIS-C demonstrates bilateral pulmonary consolidations and ground glass opacities with the predominance in the lower zone.

TABLE 4 Differential diagnosis of MIS-C.

	MIS-C	KD	TSS	Sepsis	Appendicitis	HLH/MAS
Clinical features						
Prevailing age group	School-age	Infants and toddlers	Any age	Any age	School-age, adolescents	Any age
Persistent fever	+++	+++	+++	++	+	+++
Cheilitis/red lips	++	+++	+	+	0	0
Nonexudative conjunctivitis	++	+++	+	0	0	+
Lymphadenopathy	+++	+++	0	+	0	++
GIS involvement	+++	+/−	++	+	+++	+/−
Hypotension	++	+/−	+++	++	0	+
Heart failure	++	+	+/−	+/−	0	+/−
Coronary aneurysms	+	++	0	0	0	0
Laboratory markers						
Elevated plasma CRP	+++	+++	+++	+++	+++	++
Elevated plasma Ferritin	+++	+	No data	++	+/−	+++
Lymphopenia	++	0	0	+++	0	++
Neutrophilia	++	+++	+++	+++	+++	0
Thrombocytopenia	++	+/−	+++	++	+	++
Hypertriglyceridemia	++	++	0	0	0	++

Note: Meaning of symbols: +++ typical; ++ common; + possible; +/− rare; 0 no.

Abbreviations: CRP, C-reactive protein; GIS, gastrointestinal system; HLH/MAS, hemophagocytic lymphohistiocytosis/macrophage activation syndrome; KD, Kawasaki disease; MIS-C, multisystem inflammatory syndrome in children; TSS, toxic shock syndrome.

features of both diseases.[8] Nevertheless, MIS-C differs from acute COVID-19. MIS-C develops in otherwise healthy children as opposed to severe COVID-19, which mainly affects children with chronic conditions. Children with MIS-C are more likely to have cardiovascular and mucocutaneous involvement, whereas respiratory injury is more common in severe COVID-19. Children with MIS-C more often need intensive care than children with severe COVID-19.[26]

7 | THE ROLE OF THE VIRUS IN THE CONTEXT OF OTHER HYPERINFLAMMATORY DISEASES

Many children with MIS-C fulfill KD diagnostic criteria.[6,8,15,23] KD is a vasculitis that affects mostly children under the age of 5 years.[50] KD is thought to result from a hyperinflammatory response to an

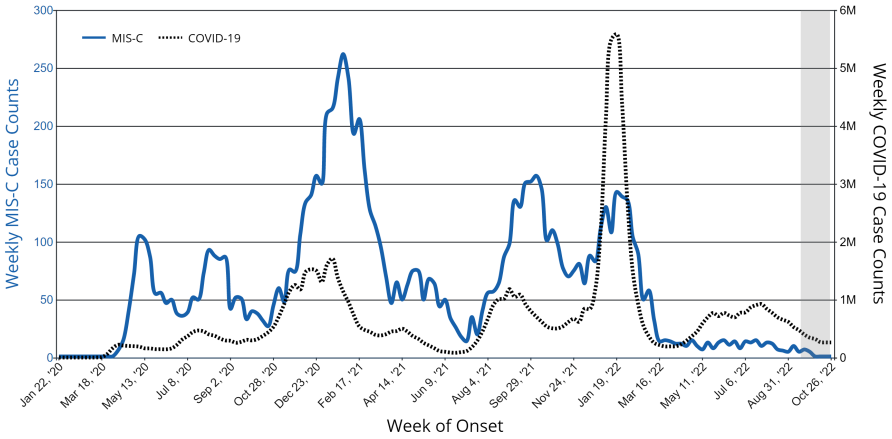

FIGURE 3 Weekly US MIS-C and COVID-19 cases reported to CDC (7-day moving average; *Source*: CDC; Materials developed by CDC; https://covid.cdc.gov/covid-data-tracker/#mis-national-surveillance. Open acess).

environmental factor in a genetically susceptible host. No single factor triggering KD has been identified till now, but an infectious agent can be a potential causative factor. With a peak in winter and early spring, the incidence of seasonal KD matches seasonal waves of viral infections. Interestingly, various undefined antigens and particles of possible viral origin have been found in the tissues of KD children.[51,52]

Similarly, SARS-CoV-2 antigens were detected in the tissues of several organs (lungs, heart, kidneys, liver, spleen, and brain) of children who died from MIS-C.[53] This surprising finding suggests a direct effect of SARS-CoV-2 on the tissues involved in the hyperinflammatory reaction. Persistent immune dysfunction or exhaustion induced by chronic antigen exposure is one of the proposed mechanisms.[54,55]

Multisystem inflammatory syndrome in children shares many clinical features with TSS, particularly highly prevalent gastrointestinal involvement, peripheral edema, hypotension, and mucocutaneous signs. TSS results from massive T-cell activation and cytokine production in response to staphylococcal or streptococcal toxins with superantigenic properties.[56] A superantigenic pathomechanism has been hypothesized in MIS-C as well. Through structure-based computational modeling, Noval-Rivas et al. identified a motif near the S1/S2 cleavage site of the SARS-CoV-2 spike protein that resembled the staphylococcal enterotoxin B of *Staphylococcus aureus*.[57] Uncontrolled cytokine production in response to SARS-CoV-2 spike protein could be involved in both severe COVID-19 and MIS-C pathogenesis. Indeed, severe COVID-19 adult patients presented a T cell receptor (TCR) β chain skewing towards fragments that can be bound by superantigens.[58] We will further discuss the possible role of superantigenic stimulation in the pathogenesis of MIS-C in section IX.

8 | VACCINATION AND MIS-C

The introduction of COVID-19 vaccinations in children did not result in rise of MIS-C cases in the US[27] and case reports of vaccine-induced MIS (called MIS-V) are only anecdotal.[59,60] Moreover, Pfizer-BioNtech vaccine was found to be 91% effective in preventing MIS-C in adolescents 12–18 years old.[61] Similar findings were observed in teenagers in France, too.[62] Interestingly, rare cases of MIS-C despite previous COVID-19 vaccination in teenagers seem to be milder, with no need for intensive care.[61] Vaccine-induced immunity may play a role in decreasing MIS-C incidence in consecutive COVID-19 waves, and some authors predict that in the future MIS-C will be a rare disease affecting only young unimmunized children, alike KD.[46]

There are many knowledge gaps though; it is still unclear whether vaccine-induced protection against MIS-C applies to younger age groups, how long it lasts and whether it is going to be as effective in newly emerging SARS-CoV-2 variants.

Despite unknown risk of either re-infection with SARS-CoV-2 or COVID-19 vaccination after MIS-C, CDC experts consider benefits from COVID-19 vaccination to outweigh its risks in children after MIS-C. The recommended interval from MIS-C diagnosis to COVID-19 vaccination is at least 3 months. A recent international survey found vaccination to be safe in children with a history of MIS-C.[63]

CLINICAL STATEMENT 1

COVID-19 vaccination is a safe and effective prophylaxis of MIS-C. Children who underwent MIS-C may be vaccinated against COVID-19 at least 3 months since MIS-C diagnosis.

9 | IMMUNOLOGY OF MIS-C

An abnormal immune response plays a central role in MIS-C. In the following section, we discuss hypotheses on MIS-C pathogenesis and the contribution of innate and adaptive immunity to inflammation. Although these three systems are deeply interrelated, for simplicity, the innate, the adaptive humoral, and cellular responses are considered separately.

9.1 | Four main hypotheses for the pathogenic etiology of MIS-C (Figure 4)

The first hypothesis is based on the above-mentioned superantigenic stimulation of T-cells.[57,58,64] Superantigen-induced generalized and polyclonal T cell activation leads to cytokine storm and multiorgan injury which clinically resembles TSS. A profound expansion of the *TRBV11-2* gene corresponding to superantigen-specific TCR skewing

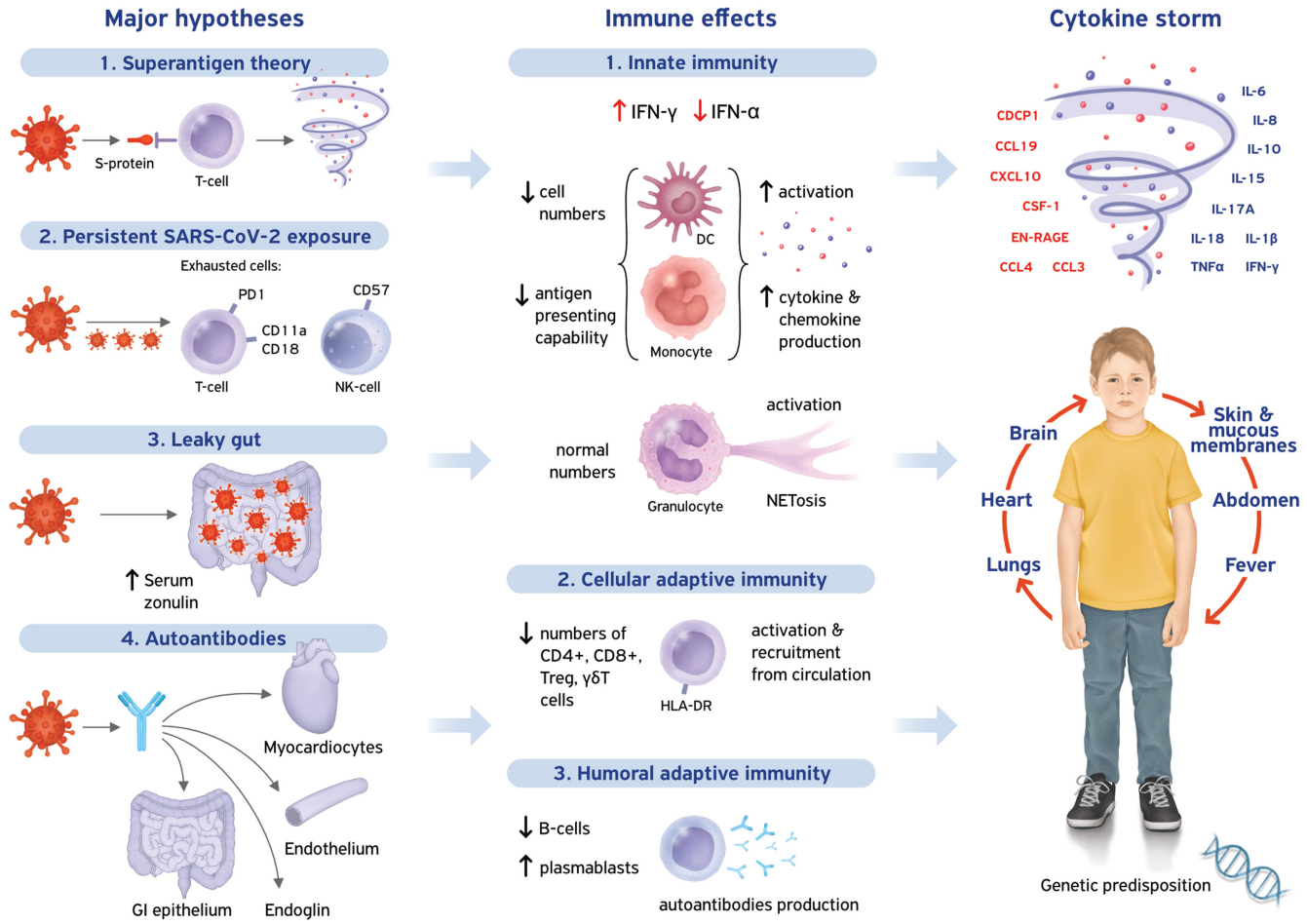

FIGURE 4 Descriptive flowchart synthesizing the hypothesized immunologic mechanisms underlying the development of multisystem inflammatory syndrome in children (MIS-C). CCL, C-C motif ligand; CD, cluster of differentiation; CDCP1, CUB domain-containing protein 1; CSF, colony stimulating factor; CXCL, C-X-C motif ligand; DC, dendritic cell; EN-RAGE, extracellular receptor for advanced glycation end products binding protein; GI, gastrointestinal tract; HLA, human leukocyte antigen; IFN, interferon; IL, interleukin, IL-1RA, interleukin-1 receptor antagonist; NETosis, neutrophil extracellular traps formation; NK, Natural Killer; PD, programmed cell death protein, SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; TNF, tumor necrosis factor.

was found in CD4(+) and CD8(+) T cells of children with MIS-C.[64–68] Moreover, polyclonal *TRBV11-2* expansion was correlated with HLA class I alleles A02, B35, C04, which may reflect genetic susceptibility to such uncontrolled immunologic response to SARS-CoV-2.[65]

The second hypothesis involves a chronic inflammatory response to continuous viral antigen exposure and subsequent T-cell exhaustion due to prolonged antigenic stimulation.[54,55,69] Both transcriptional signatures[70] and surface markers of T cell exhaustion[69] were found in children with MIS-C.

The third hypothesis regards involvement of the gastrointestinal tract. Severe gastrointestinal symptoms have been observed in 90% of MIS-C patients, possibly due to the extended presence of SARS-CoV-2 in the gastrointestinal tract,[71] which may lead to increased intestinal permeability and translocation of the virus or viral proteins (such as spike antigen) into the circulation. The leaky gut theory is supported by increased concentration of zonulin – serum marker of intestinal barrier disfunction – in children with MIS-C.[71]

Finally, the fourth plausible mechanism involves the production of autoantibodies, as indicated by several reports. Clinical data have demonstrated not only increased percentages of $CD19^{+}CD27^{+}CD38^{+}$ plasmablastic cells during the acute period of the disease,[69,72] but also elevated levels of specific target autoantibodies in patients with MIS-C. Their generation may result from the tissue damage, but also may be regarded as one of the triggers of the disease. These potential markers of an autoimmune response include autoantibodies directed against myocardial tissue, endothelium, gastrointestinal epithelium, cellular immune mediators, and endoglin, which maintains the structural integrity of arteries.[54,66,73]

One cannot exclude the notion that rare variants in genes associated with the immune system predispose children to develop MIS-C after infection with SARS-CoV-2.[74] Variants in immunological genes have been reported in 3/18 MIS-C patients (*XIAP*, *CYBB*, and *SOCS1*).[75,76] Another study found an excess of rare, deleterious heterozygous variants in immunological genes in MIS-C cases as compared to controls (64% vs. 12%).[77]

Equally plausible is the combination of these mechanisms, that is: the initial persistence of the virus in the gut, which leads to antigenemia, with the abundance of superantigens and prolonged, excessive activation of immune mechanisms with autoantibody generation, in a genetically susceptible host.

9.2 | Contribution of innate immunity to MIS-C pathology

The role of the innate immune system in MIS-C is complex. Imbalanced interferon (IFN) signaling pathways, depletion and concomitant hyperactivation of dendritic cells (DCs) and monocytes, together with activated neutrophils contribute to cytokine storm and hyperinflammation.

9.2.1 | The role of IFNs

Several studies underline the crucial role of IFN-γ in MIS-C pathogenesis. IFN-γ seems to be central in the communication between activated T-cells with a skewed variable region of the beta-chain (Vb) repertoire and monocytes.[68] IFN-γ concentration correlates with the disease severity[78] and IFN-γ-induced chemokines, CXCL9 and CXCL10 are disproportionately high in MIS-C patients.[64,79,80] The cytokine profiles of children with MIS-C are characterized by elevated IFN-γ, IL-18, GM-CSF, CCL5, CXCL9 and CXCL10, and inflammatory monocyte activation markers including MCP-1, IL-1α, and IL-1RA.[78,79] This cytokine profile positions an IFN-γ induced response as the main trigger of inflammation. In addition, an important negative regulator of IFN-γ mediated immunity, TWEAK (TNF-like weak inducer of apoptosis), is downregulated in acute MIS-C patients.[73]

On the other hand, MIS-C is characterized by depleted type I IFN response, possibly due to decreased frequencies of plasmacytoid dendritic cells (pDCs) which constitute the major source of IFN-α.[54,79,81] Low levels of IFN-α correlate with severe course and poor outcome of acute COVID-19 in adult patients.[82,83] Moreover, it has been observed that genetic disorders of IFN I pathway, as well as circulating antibodies against IFN I, are associated with severe COVID-19 pneumonia in children with selected inborn errors of immunity.[84,85] Interestingly, haploinsufficiency in suppressor of cytokine signaling (SOCS) 1, an essential negative regulator of type I and type II IFN signaling, was identified in some children with MIS-C.[75,76]

9.2.2 | The role of dendritic cells and monocytes

An inflammatory profile with reduced numbers of circulating myeloid (conventional) and plasmacytoid DCs, and monocytes in MIS-C patients were reported by different groups.[54,79,81] Moreover, de Cevins et al. showed significant heterogeneity in classical and intermediate monocytes in severe MIS-C cases.[81] Using multiparametric large-scale analyses, they found upregulated TNF signaling, overexpression of HIF-1α, low type I and II IFN responses, and decreased expression of NF-κB inhibitors, specifically in monocytes and DCs. Thus, it is possible that sustained NF-κB signaling leads to overexpression of monocyte and DC-derived inflammatory mediators that are crucial in the severe phase of MIS-C. In fact, classical monocytes from MIS-C patients showed increased CD64 and CD54 expression concomitant with CD14 and TLR4 downregulation, characteristic for activated cells and cytokine production.[72,81,86] Notably, MIS-C, like other cytokine storm syndromes, such as KD, is manifested with elevated levels of monocyte-derived and DC-derived inflammatory mediators, including cytokines (IL-1α, IL-6, IL-8, IL-10) and chemokines (CXCL9, CXCL10, CCL2, CCL3, CCL4, CCL19, CDCP1, and CSF-1).[54,73,79,80] Furthermore, decreased levels of costimulatory molecules and HLA-DR in monocytes and DCs indicate impaired antigen presentation capacity, which affects the development of adaptive immunity.[72]

9.2.3 | The role of natural killer cells and neutrophils

Both children with MIS-C and acute COVID-19 had reduced numbers of natural killer (NK) cells, cytolytic NK subset, and unconventional mucosal associate invariant T-cells (MAITs), whereas innate lymphoid cells frequencies are like those in healthy adults.[69] Similarly, transcriptional signatures of exhausted $CD56^{dim}CD57^{+}$ NK cells were found in MIS-C patients.[87]

Carter et al. demonstrated that absolute neutrophil counts were similar during the acute, resolution and convalescence phases of MIS-C and comparable to counts in healthy controls.[72] However, neutrophils of MIS-C patients had an increased expression of CD64 combined with a decreased expression of CD10 during the acute phase, indicating neutrophil activation and a reduction of mature neutrophils.[72] The acute pediatric COVID-19 neutrophil response is governed by a robust anti-viral interferon-stimulated gene signature.[88] However, the MIS-C neutrophils demonstrate a different phenotype. Boribong et al. found a strong granulocytic myeloid-derived suppressor cell (G-MDSC) enrichment with altered metabolism towards activation, degranulation, reactive oxygen species (ROS) generation and formation of neutrophil extracellular traps (NETosis).[79,88] NETosis, which can be stimulated by immune complexes of S protein with specific anti-S antibodies,[88] contributes to vascular damage.[79] Thus, given the possible antigenemia due to the leaky gut theory in MIS-C pathogenesis, chronic intravascular neutrophil activation and NETs formation may be directly linked to endothelial damage and cardiovascular complications. Therefore, neutrophils may play a crucial role in the pathogenesis of MIS-C.

9.2.4 | Hyperinflammation in MIS-C

Several studies investigated the plasma proteome in MIS-C patients highlighting an increase in IL-6, IL-8, IL-10, IL-15, IL-17A, IL-18, IL-1β, TNF-α and IFN-γ.[48,54,72,89] In addition, chemokines important for NK–/T-cell (CCL19, CXCL10) and monocyte/neutrophil (CCL3, CCL4) recruitment and factors for their differentiation and activation (ENRAGE, CSF-1) were enhanced.[54,73] Further, soluble programmed cell death ligand 1 (PD-L1) and IL-18R1 were increased pointing to immune exhaustion and reflecting a host-driven immune compensation.[54] Interestingly, hyperinflammation in MIS-C patients was not driven by CXCL8 as it is the case in adult COVID-19.[90] Interestingly, children with rare inborn errors of immunity who developed MIS-C, presented with decreased markers of IL-10 signaling pathway and overrepresentation

of IL-18 signaling markers, similar to acute COVID-19, but different from MIS-C without prior immunosuppression.[85]

9.3 | Humoral adaptive immunity

Pronounced lymphopenia has been consistently observed in MIS-C children.[23,73,91,92] In the acute phase of the disease, total B cell numbers are decreased.[72,93] The frequencies of naïve-, $CD27^{-}IgD^{-}$, non-switched, and switched memory B cells do not differ between active pediatric COVID-19 and MIS-C.[69,72] Although MIS-C develops late after acute infection, the frequency of plasmablasts is still as high as in the active COVID-19 patients indicating ongoing and prolonged humoral responses in MIS-C.[69,72] The frequencies of follicular T helper cells (Tfh) are unaltered. However, the expression of the Tfh homing chemokine CXCR5 is reduced on these cells, indicating potential alterations in the generation of germinal centers and subsequent humoral responses.[69]

Interestingly, several reports indicated the presence of autoantibodies in MIS-C.[54,66,73] The autoantibody profile consisted of target structures already known e.g., lupus erythematosus or Sjogren's disease (anti-La, anti-Jo-1)[54] or hereditary hemorrhagic telangiectasia (anti-endoglin)[73] and of several proteins not attributed to autoinflammation. Autoantibodies targeting myocardial and endothelial tissue, as well as gastrointestinal epithelium and cellular immune mediator targets, were also identified.[54] However, it must be determined if the occurrence of autoantibodies is a direct effect of SARS-CoV-2 infection or an epiphenomenon due to substantial tissue damage.

9.4 | Cellular adaptive immunity

In line with reduced B cell numbers in MIS-C patients, also the total number of T cells is lower than in healthy controls and is restored during clinical improvement.[54,72,93,94] Noteworthy, shifts in lymphocyte counts in MIS-C correlate with disease severity markers, particularly hypotension.[54,72,93,94] A general lymphopenia results from a decreased numbers of T helper cells ($CD4^{+}$), cytotoxic T cells ($CD8^{+}$), γδ T cells and Treg cells.[72,94] The antiviral and cytotoxic γδ T cells expressed higher HLA-DR levels in the acute phase of MIS-C, suggestive of cell activation.[54,72] Also, naïve and memory $CD4^{+}CCR7^{+}$ T cells expressed high amount of HLA-DR in the acute phase of MIS-C.[72] However, overall relative distribution of all T cell subpopulations seem to be normal in MIS-C patients. Importantly, all those subpopulations returned to control levels during clinical improvement or convalescence.[72,93] In a few MIS-C patients, increased phosphorylation of Signal Transducer and Activator of Transcription (STAT3) in naïve and memory $CD4^{+}$ and $CD8^{+}$ T cells was noted.[54] In addition, serum protein profiling revealed a profound induction of cytokines and chemokines responsible for recruiting T cells from circulation and modifying their functions, such as CCL19, CXCL10, and CDCP1, in MIS-C patients.[54,79]

CLINICAL STATEMENT 2

The immunological mechanism leading to MIS-C is unclear and depends on activating multiple pathways leading to hyperinflammation. The treatment should include immunosuppressive and/or immunomodulatory agents.

10 | DIAGNOSTIC WORKUP

Diagnosis of MIS-C is based on the characteristic constellation of clinical, laboratory, and imaging findings and exclusion of other infectious and non-infectious causes of hyperinflammation. Epidemiological context is important – diagnosis is more likely at the time of the MIS-C wave. However, as SARS-COV-2 is becoming endemic, we can expect to be finding sporadic cases of MIS-C throughout the year, particularly in the youngest children.[17,95] Diagnostic workup in MIS-C patients aims at confirming the diagnosis and assessing the extent of multiorgan involvement. Here, we propose a simple diagnostic algorithm (Figure 5). Most MIS-C patients exhibit some degree of cardiac involvement. The most severe manifestation is left ventricle systolic failure and subsequent cardiac shock.[38,91] Therefore, every patient with a high suspicion of MIS-C should have immediate (preferably within 12 hours from admission) electrocardiography (ECG) and echocardiography (ECHO) performed. The frequency of subsequent ECGs and ECHOs should be consulted closely with a pediatric cardiologist, preferably at least every 2–3 days during the acute phase of the disease. After hospital discharge, follow-up studies should be performed within 1–2 and 4–6 weeks with further monitoring for selected patients.

CLINICAL STATEMENT 3

MIS-C diagnosis is based on clinical and laboratory picture with the exclusion of other plausible diagnoses. Prompt and regular electro- and echocardiographic evaluation is important.

11 | MIS-C TREATMENT

Immunosuppressants and/or immunomodulators have been the mainstay of MIS-C treatment since the first reports concerning the disease.[5,17,23,26] However, MIS-C therapy is complex and involves anti-thrombotic therapies, anti-microbials in the suspicion of sepsis, and all sorts of organ dysfunction support. There are several published guidelines on MIS-C patients management, though all of them are based on observational studies.[92,96–98] Here, we focus on immunosuppressive and immunomodulatory therapies, as well as anti-thrombotic treatment in MIS-C.

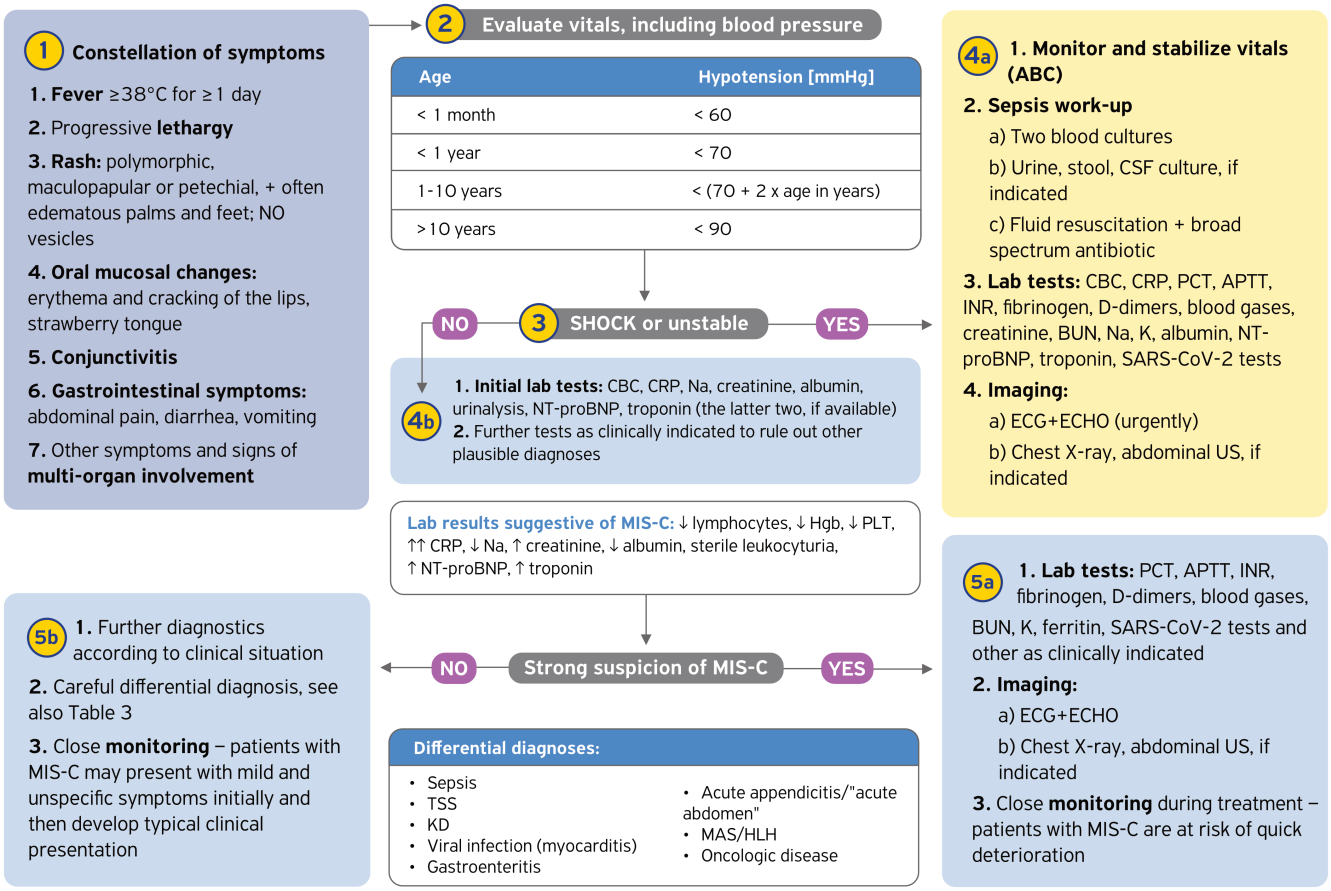

FIGURE 5 Diagnostic workup in patients suspected for MIS-C. APTT, activated partial thromboplastin time; BUN, blood urea nitrogen; CBC, complete blood count; CRP, C-reactive protein; CSF, cerebrospinal fluid; ECG, electrocardiogram; ECHO, echocardiogram; Hgb, hemoglobin; INR, international normalized ratio; K, potassium; KD, Kawasaki disease; MAS/HLH, macrophage activation syndrome/hemophagocytic lymphohistiocytosis; MIS-C, multisystem inflammatory syndrome in children; Na, sodium; NT-proBNP, N-terminal prohormone of natriuretic peptide type B; PCT, procalcitonin; PLT, platelets; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; TSS, toxic shock syndrome; US, ultrasonography.

11.1 | Immunosuppression and immunomodulation

The post-infectious, immunological nature of MIS-C, its hyperinflammatory character, and close clinical resemblance to KD formed the basis for MIS-C treatment with intravenous immunoglobulin (IVIG) and/or glucocorticosteroids (GCS).

11.1.1 | IVIG

Intravenous immunoglobulin in a dose ranging from 1 to 2 g/kg and, according to some sources not exceeding 100 g, has been used in most MIS-C patients (Table 3). On the one hand, coronary arteries aneurysms (CAAs) have been reported as a complication of MIS-C[17,23,26,35,36] and, on the other, IVIG has a well-documented efficacy in reducing the risk of CAAs in KD.[99] However, neither the exact risk of CAAs in MIS-C is known nor IVIG efficacy in this indication. Unlike in KD, most patients with MIS-C receive GCS (Table 3), which could be partially due to unsatisfactory response to IVIG alone. Nevertheless, IVIG is included in most recommendations as a first-line treatment (Figure 6).[92,96–98]

11.1.2 | GCS

Glucocorticosteroids administered either as prednisolone (2 mg/kg/day) or pulsed methylprednisolone (10–30 mg/kg/day for 1–3 days), are used as a first-line treatment in patients with shock or particularly severe disease and as a second line in non-responders to IVIG.[92,96–98] Interestingly, in an Italian study, GCS were used as a single first-line treatment in MIS-C, and 74% of patients needed no step-up therapy.[100] The optimal GCS treatment length is also debatable. Whereas some of the guidelines recommend stepwise dose reduction within 2–3 weeks,[74–77] in a study by Ouldali, most patients received 5 days of therapy, which appeared effective, too.[101]

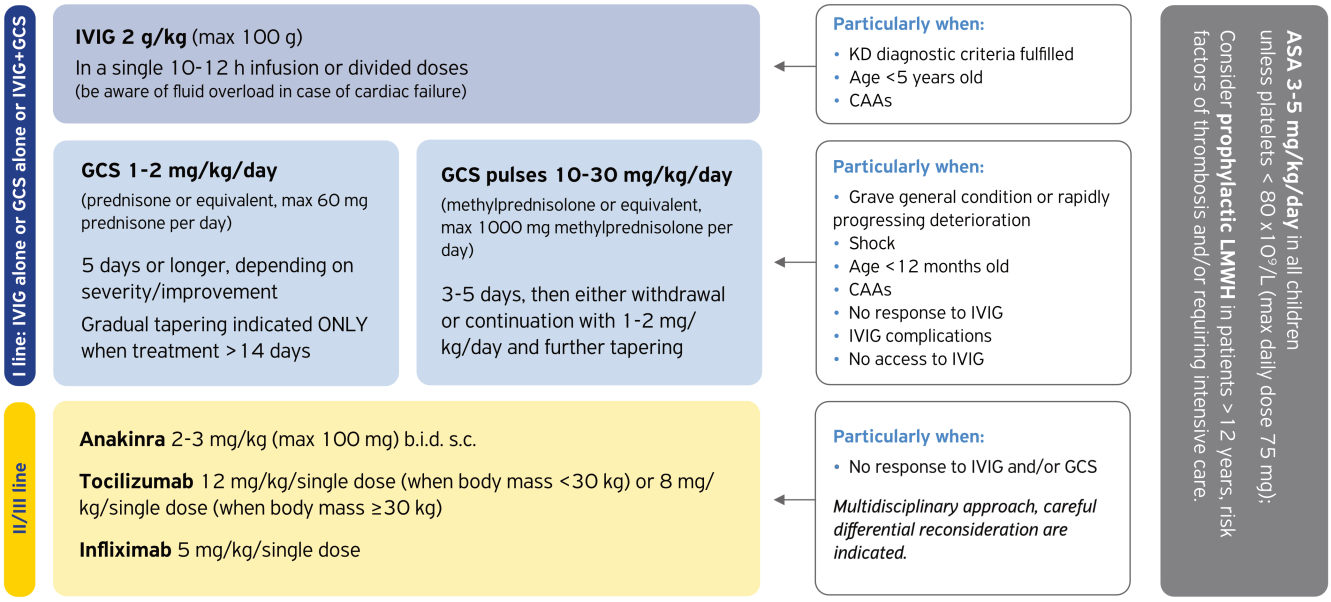

FIGURE 6 Treatment algorithm for MIS-C. ASA, acetylsalicylic acid; B.i.d., twice a day; CAAs, coronary arteries aneurysms; GCS, glucocorticosteroids; IVIG, intravenous immunoglobulins; LMWH, low molecular weight heparin; MIS-C, multisystem inflammatory syndrome in children; KD, Kawasaki disease; PLT, platelets; s.c., subcutaneous.

Several retrospective studies comparing different treatment strategies with IVIG, and GCS were published in 2021. Ouldali et al.[101] compared IVIG alone to combined IVIG and GCS as first-line therapy. They found that IVIG alone was associated with a higher risk of treatment failure and progression to cardiovascular complications. Similar results were revealed by the Overcoming COVID-19 Investigators group. They observed that initial IVIG and GCS treatment was associated with a lower risk of new or persistent cardiovascular dysfunction than with IVIG alone.[102] In contrast, the British Best Available Treatment Study group (BATS) found no significant difference between three primary treatment options: IVIG alone, GCS alone, or combined IVIG and GCS, in terms of recovery from the disease.[103] These discrepancies may be due to different inclusion criteria, different disease severity (with a milder course in patients included in the BATS), and different outcomes measured. What is particularly interesting is that in a smaller study from the UK involving pediatric intensive care unit (PICU) patients only, no short-term benefit from any kind of treatment was found compared to supportive treatment only.[104] It must be emphasized that MIS-C severity may vary in different populations, as was found by Polish authors.[35] Thus, the immunosuppressive and immunomodulatory treatment strategy may need to be adjusted to a specific population.

CLINICAL STATEMENT 4

In the light of current knowledge, either intravenous immunoglobulin (IVIG) alone, glucocorticosteroids (GCS) alone, or both IVIG and GCS, are acceptable first-line therapy in children with MIS-C. There is insufficient evidence to determine if IVIG alone, GCS alone, or both IVIG and GCS are the best first-line treatment for MIS-C.

CLINICAL STATEMENT 5

IVIG is particularly indicated in young children with Kawasaki disease phenotype and cases of coronary artery aneurysms. GCS are particularly indicated in children with the severe illness, rapidly progressing deterioration, and shock. A combination of the above clinical presentations might be an indication for both IVIG and GCS.

11.2 | Biological treatment

A minority of patients with MIS-C do not respond to IVIG and GCS and receive immunomodulatory biological agents (e.g., human interleukin-1 receptor antagonist (anakinra), humanized monoclonal antibody against the interleukin-6 receptor (tocilizumab), a chimeric monoclonal antibody that blocks TNF-α (infliximab)). Importantly, before initiating such treatment, a multidisciplinary consultation should take place to rule out other possible diagnoses that may underlie such an unusual clinical presentation.[97] Anakinra appears to have an advantage over other alternatives due to its shorter half-life and upstream effects. For this reason, its use may be preferable to other biologics, particularly in an off-label situation and due to the safety reasons of using biologicals in young children.

CLINICAL STATEMENT 6

Biological treatment is the II/III-line treatment in MIS-C. It should always be preceded by careful differential re-evaluation and multidisciplinary consultation. There is insufficient evidence to recommend one biological agent above another.

11.3 | Anti-thrombotic treatment

Thrombotic complications have been observed since the earliest reports about MIS-C,[5,17,105] and laboratory markers of coagulopathy (high D-dimers and fibrinogen, low platelets) are typical for this hyperinflammatory disease.[17,23,26] Whitworth et al. found that age ≥12 years, cancer, central venous catheter, and MIS-C were independent risk factors for thrombosis in children hospitalized for COVID-19 and/or MIS-C.[105] According to the guidelines, anticoagulation prophylaxis with low molecular weight or unfractionated heparin should be administered based on individual risk profiles (including obesity, immobility, history of thrombo-embolism and other known risk factors), with patients hospitalized in intensive care units considered the most vulnerable.[92,96–98]

On the other hand, due to similarities to KD mentioned above, anti-platelet low-dose aspirin (3–5 mg/kg/day, maximum dose of 75 mg) is recommended in all children with MIS-C unless they have active bleeding or their platelet level falls <80.000/μl.[92,97,98]

CLINICAL STATEMENT 7

Anti-thrombotic prophylaxis involves routine acetylsalicylic acid (ASA) in a low dose unless contraindicated. Low molecular weight or unfractionated heparin might be indicated in selected cases with an elevated risk of thrombotic complications.

12 | FOLLOW UP

Despite MIS-C being a life-threatening condition, the overall outcome appears to be good across the reported cohorts (Table 3). However, long-term data are scarce. While a substantial proportion of children need intensive care and at least several days of PICU management, the overall mortality is low,[9,11,15,17,36] even among the youngest infants[106] and those with organ failures. The most common direct causes of death are cardiac dysfunction, shock, or multiorgan failure.

Mid- and long-term outcomes are unknown. The cardiac dysfunction and the CAAs appear to be the most severe sequelae of MIS-C. However, the emerging evidence shows a very high CAAs' early resolution rate, ranging from 80% to 90%, within weeks from MIS-C.[26] Follow up studies assessing myocardial function with cardiac MRI found that myocardial deformation indices measured by CMR are within normal range in the vast majority of the patients within a few weeks after the onset of MIS-C.[107,108] The disease heterogeneity and, consequently, the multitude of specialties involved in managing MIS-C patients present a challenge in establishing a unified follow-up protocol. To date, no universal consensus exists, and much of the post-discharge care is practiced according to institutional or regional recommendations. Cardiovascular pathology appears to be the main determinator of individual follow-up scheduling, along with the markers of inflammatory activity, which are monitored variedly by rheumatologists, immunologists, or infectious diseases specialists.

CLINICAL STATEMENT 8

The overall short-term outcome of MIS-C is good. Most children recover without clinical or laboratory sequalae within weeks post-discharge. There is insufficient data on long-term outcomes.

CLINICAL STATEMENT 9

MIS-C patients should be followed-up at regular intervals after discharge, focusing on cardiac disease, organ damage, and inflammatory activity.

13 | FUTURE DIRECTIONS

Given the significant advances in research over the past year, we believe that there is sufficient evidence to support the current therapeutic options. Nevertheless, there is still a need for further research. The following research gaps are of importance:

Immunology and diagnostics:

- Identification of a sensitive and specific panel biomarkers.
- Identification of risk factors that predict clinical deterioration.
- Revealing the genetic basis of the disease.
- Identification of the superantigens responsible for skewing of the T-cell receptor Vb repertoire in patients with MIS-C.
- Evaluation of incidence and extinction of MIS-C with subsequent SARS-CoV-2 virus variants.

Management and treatment:

- Identification of new treatment strategies.
- Mechanisms of response or non-response to treatment.
- Verification of the optimal therapeutic option in prospective, preferably randomized, controlled trials.
- Further evaluation of the role of vaccination in the prevention of MIS-C.

14 | CONCLUSIONS

MIS-C is a new and rare manifestation of SARS-CoV-2 infection in children, that is clinically distinct to COVID-19 but shares features with other severe pediatric diseases, e.g., KD, TSS, and MAS. Case definition is broad and necessitates careful differential diagnosis. The exact pathomechanism of the disease is unknown, but the immune system dysregulation affecting both innate and adaptive immunity plays a central role. Current management of MIS-C relies on supportive care in combination with immunosuppressive and/or immunomodulatory agents. The most frequently used agents are systemic steroids and IVIG. Intensive studies in recent months

have provided sufficient data to elaborate on the origins of the disease; however, mechanistic studies are still lacking. In anticipation of further research, we also propose a convenient and clinically practical algorithm for managing MIS-C developed by the Immunology Section of the EAACI.

CONFLICT OF INTEREST

WF, MON, EPB, MB, AS, CBR, PAE, TE, AE, SE, CGC, AF, JJ, RJS, TK, IKK, CGM, CR, JS, ZS, EU, GTS have no specific conflict of interest to report. HB reports speaker honoraria from DBV Technologies, Sanofi and GSK and research grants from NIH, Aimmune and DBV Technologies. MS reported research grants from Swiss National Science Foundation, Novartis and GSK and speaker's fee from AstraZeneca and a leadership in the European Academy of Allergy and Clinical Immunology: Secretary of the Board of the Basic and Clinical Immunology Section. TE reports to act as local PI for company sponsored trials by DBV and sub-investigator for Regeneron, holds grants from Innovation Fund Denmark, CIHR outside the submitted work. He is Co-investigator or scientific lead in three investigator-initiated oral immunotherapy trials supported by the Food Allergy and Anaphylaxis Program SickKids and serves as an associate editor for Allergy. He/his lab received unconditional/in-kind contributions from Macro Array Diagnostics and an unrestricted grant from ALK. He holds advisory board roles for ALK, Nutricia/Danone and Aimmune. RJS acknowledges the support received from the FSE/FEDER through the Instituto de Salud Carlos III (ISCIII; CP20/00043).

PEER REVIEW

The peer review history for this article is available at https://publons.com/publon/10.1111/pai.13900.

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How to cite this article: Feleszko W, Okarska-Napierała M, Buddingh EP, et al. Pathogenesis, immunology, and immune-targeted management of the multisystem inflammatory syndrome in children (MIS-C) or pediatric inflammatory multisystem syndrome (PIMS): EAACI Position Paper. *Pediatr Allergy Immunol*. 2023;34:e13900. doi:10.1111/pai.13900