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COVID-19: Important Updates and Developments
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A dermatologic perspective on multisystem inflammatory syndrome in children

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Abstract As of May 2020, an emerging immune-mediated syndrome primarily affecting children has been detected primarily in Europe and the United States. The incidence of this syndrome appears to mirror the initial infectious assault with a delay of several weeks. This syndrome has been termed “multi-system inflammatory syndrome in children” (MIS-C) and is observed in association with the coronavirus disease 2019. The phenotypes of presentation include several characteristic features, including prolonged fever, skin eruptions, neck stiffness, and gastrointestinal manifestations with pronounced abdominal pain. Shock and organ dysfunction on presentation are frequent but inconsistent, whereas respiratory distress is typically, and notably, absent. We have reviewed the recent published data aiming to better understand MIS-C, with a focus on its mucocutaneous manifestations.

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Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a novel coronavirus that originated in Wuhan, China, in December of 2019.¹ This virus causes a severe respiratory distress syndrome among several other severe manifestations.¹ Starting in early 2020, the virus spread rapidly worldwide, compelling the World Health Organization (WHO) to declare a global pandemic on March 11, 2020. To date, there are more than 15 million cases with more than half a million deaths due to coronavirus disease 2019 (COVID-19), globally. Children make up a small percentage of these cases. According to the Centers for Dis-

ease Control and Prevention (CDC) *Morbidity and Mortality Weekly Report*, published April 6, 2020, 2572 (1.7%) of roughly 150,000 known cases of COVID-19 infection in the United States were among children <18 years of age.² This is consistent with a review of more than 72,000 COVID-19 cases performed by the Chinese Center for Disease Control and Prevention, which revealed that <1% of infected patients were children under the age of 10.³ Infected children tend to be completely asymptomatic or exhibit mild clinical manifestations.^{4–8} Although the majority of children with COVID-19 are asymptomatic or have mild manifestations, a small percentage require hospitalization and intensive care for shock and multiorgan failure due to the emerging multi-system inflammatory syndrome.^{7–10} On May 14, 2020, two months after the WHO declaration of a global pandemic, the CDC released a health advisory about multisystem inflammatory syndrome in children associated with COVID-19.

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Table 1 The Centers for Disease Control and Prevention case definition for multisystem inflammatory syndrome in children

- All four diagnostic criteria must be met:
1. Age <21 years
 2. Clinical presentation should include *all* of the following:
 - a. Fever $\geq 38.0^{\circ}\text{C}$ for ≥ 24 hours or report of subjective fever lasting ≥ 24 hours.
 - b. Laboratory evidence of inflammation, including, but not limited to, one or more of the following:
 - Elevated c-reactive protein
 - Elevated erythrocyte sedimentation rate
 - Elevated fibrinogen
 - Elevated procalcitonin
 - Elevated d-dimer
 - Elevated ferritin
 - Elevated lactic acid dehydrogenase
 - Elevated interleukin 6
 - Elevated neutrophils
 - Reduced lymphocytes
 - Low albumin
 - c. Evidence of clinically severe illness requiring hospitalization.
 - d. Multisystem (≥ 2) organ involvement (cardiac, renal, respiratory, hematologic, gastrointestinal, dermatologic, or neurologic).
 3. No alternative plausible diagnoses.
 4. Positive for current or recent SARS-CoV-2 infection by RT-PCR, serology, or antigen test; or COVID-19 exposure within the 4 weeks before the onset of clinical manifestations.

Source: U.S. Centers for Disease Control and Prevention. Multisystem inflammatory syndrome in children (MIS-C) associated with coronavirus disease 2019 (COVID-19). 2020. Available at: <https://emergency.cdc.gov/han/2020/han00432.asp>

Defining MIS-C

Multisystem inflammatory syndrome in children describes an emergent childhood inflammatory disorder, with similarities to Kawasaki disease (KD), KD shock syndrome (KDSS), toxic shock syndrome (TSS), and macrophage activating syndrome (MAS). Due to its recent nascence, the constellations of manifestations defining MIS-C can be found under a number of names, such as pediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 (PIMS-TS), Kawasaki-like disease, or toxic shock-like syndrome.^{11,12} Altogether, there are now approximately 1000 cases of MIS-C documented worldwide.¹³ As the spotlight shines on this new inflammatory disease, we are beginning to have more clarification of its clinical presentation and pathogenesis.

Both the CDC and the WHO have released their own MIS-C diagnostic criteria to help clinicians in making such diagnosis. Tables 1 and 2 review these criteria in detail. The main clinical manifestations that both groups focus on include fever for more than 24 hours, laboratory evidence of

Table 2 The WHO case definition of multisystem inflammatory syndrome in children

- All six diagnostic criteria must be met:
- Children and adolescents 0 to 19 years of age
 - Fever ≥ 3 days
 - At least two of the following clinical signs of multisystem involvement:
 - Rash or bilateral nonpurulent conjunctivitis or mucocutaneous inflammation signs (oral, hands, or feet)
 - Hypotension or shock
 - Features of myocardial dysfunction, pericarditis, valvulitis, or coronary abnormalities (including ECHO findings or elevated Troponin/NT-proBNP)
 - Evidence of coagulopathy (by PT, PTT, elevated d-dimers)
 - Acute gastrointestinal problems (diarrhea, vomiting, or abdominal pain)
 - Elevated markers of inflammation such as erythrocyte sedimentation rate, C-reactive protein, or procalcitonin
 - No other obvious microbial cause of inflammation, including bacterial sepsis, staphylococcal, or streptococcal shock syndromes
 - Evidence of COVID-19 (RT-PCR, antigen test or serology positive), or likely contact with patients with COVID-19

Source: World Health Organization. Multisystem inflammatory syndrome in children and adolescents with COVID-19. Available at: <https://www.who.int/publicationsdetail/multisystem-inflammatory-syndrome-in-children-and-adolescents-with-covid-19>

inflammation, two or more organ involvement (commonly gastrointestinal, followed by cardiac and renal), mucocutaneous findings, and either a positive test or exposure within 4 weeks of clinical manifestations. A negative COVID polymerase chain reaction (PCR) does not rule out this diagnosis. Because MIS-C is thought to be an immune-mediated secondary response to the virus, COVID PCRs are usually negative at the time of the illness, and antibodies are positive in the majority of cases.^{11,14-21} Importantly, diagnostic criteria for this condition are generally very broad, and thus there is significant challenge in identifying which patients falling under these diagnostic criteria are true MIS-C.^{22,2}

Demographic data of children with MIS-C from 13 recent large case series are summarized in Table 3. The size of these studies ranges from 8 to 186 children. We recap patient mean/median age, sex, cutaneous signs/clinical manifestations, SARS-CoV-2 testing method, treatments, and outcome. Fever and GI clinical manifestations were the top two most common systemic signs/clinical manifestations seen in children who met criteria for MIS-C. The majority of patients were previously healthy. The two most common comorbidities were asthma and obesity. The median age of children with MIS-C was between 8 and 12 years. Boys were equal or more prevalent in all but two publications. In the U.S. studies, the majority of the children affected were

² Table 2. ECHO, echocardiogram; PT, prothrombin time; PTT, partial thromboplastin time

Table 3 Recently published descriptive studies on multisystem inflammatory syndrome in children from the United States and Europe

Study	No. of cases	Mean/median age	Sex % male	Cutaneous signs & clinical manifestations	Positive PCR or serology	Treatment	Deaths
Riphagen et al. ¹² May 2020 UK	8	9	63	Variable eruption 50% Conjunctivitis 63%	25% PCR or Ab	IVIG 100% Steroids 63%	1
Belhadjer et al. ¹⁶ May 2020 France	35	10	51	Rash 57% Conjunctivitis 80% Red/cracked lips 54%	34% PCR 86% Ab	IVIG 100% Steroids 33%	0
Verdoni et al. ¹⁰ June 2020 Italy	10	7.5	70	Polymorphic eruption Conjunctivitis	20% PCR 80% Ab	IVIG 100% Steroids 80%	0
Toubiana et al. ¹⁸ June 2020 France	21	7.9	43	Polymorphous eruption 76% Conjunctivitis 81% Lips/oral mucosa 76%	38% PCR 90% Ab	IVIG 100% Steroids 48%	0
Dufort et al. ¹⁹ June 2020 USA	99	6-12	54	Eruption 60% Conjunctivitis 56% Oral mucosa 27%	20% PCR 99% Ab	IVIG 70% Steroids 64%	2
Feldstein et al. ²⁴ June 2020 USA	186	8.3	62	Eruption 59% Conjunctivitis 55% Oral mucosa 42% Extremity changes 37%	70% PCR or Ab	IVIG 77% Steroids 49% IL-6i or IL-1Rai 20%	4
Riollano-Cruz et al. ¹⁷ June 2020 USA	15	12	73	Eruption 47% Conjunctivitis 27% Hand/feet edema 27%	47% PCR 100% Ab	IVIG 80% IL-6i 80% Steroids 20% IL-1Rai 13% Remdesivir 13%	1
Pouletty et al. ²⁰ June 2020 France	16	10	50	Diffuse eruption 81% Conjunctivitis 93% Dry/cracked lips 87% Hands/feet eruption/edema 68%	75% PCR 50% Ab	IVIG 94% Steroids 20% IL-1Rai 6% IL-6i 6%	0
Grimaud et al. ²¹ June 2020 France	20	10	50	eruption 50% Conjunctivitis 30% Cheilitis 25%	50% PCR 75% Ab	IVIG 100% Steroids 5% IL-6i 5%	0
Kaushik et al. ¹⁵ June 2020 USA	33	10	61	<i>Authors did not comment</i>	33% PCR 81% Ab	IVIG 54% Steroids 50% IL-6i 3% Remdesivir 3%	1
Whittaker et al. ¹¹ June 2020 UK	58	9	53	Eruption 52% Conjunctivitis 45% Mucus membrane & cracked red lips 29%	26% PCR 87% Ab	IVIG 71% Steroids 64% Infliximab 14% IL-1Rai 5%	0
Ramcharan et al. ¹⁴ June 2020 UK	15	8.8	73	Eruption Conjunctivitis Swollen hands/feet Oral mucosa	13% PCR 100% Ab	IVIG 67% Steroids 33%	0
Cheung et al. ²³ July 2020 USA	17	8	47	Eruption 71% Conjunctivitis 65% Lip redness/swelling 53% Skin desquamation 18%	47% PCR 53% Ab	IVIG 76% Methylpred. 71% Hydrocortisone 21%	0

Table 4 Top four mucocutaneous presentations of multisystem inflammatory syndrome in children

Conjunctivitis
Diffuse, nonspecific eruption
Dry and red lips and/or other mucosal changes
Hand and feet erythema and edema

black non-Hispanic, Hispanic or Latino, and Ashkenazi Jewish.^{15,19,23,24} Most patients were treated with Intravenous Immunoglobulin (IVIG) +/- systemic steroids. Most patients had a negative COVID PCR at the time of diagnosis, likely because the disease tends to present 4 to 6 weeks after the viral infection. With the exception of one report,²⁰ all the other case series revealed that patients were more likely to have positive antibodies compared with PCR. COVID PCR positivity ranged from 13% to 50%, whereas antibody positivity ranged from 75% to 100%.^{10-12,14-21,23,24}

Mucocutaneous manifestations of MIS-C

Although mucocutaneous manifestations are not very common among children with COVID-19 at large, they are among the top clinical manifestations in children with MIS-C. Most of the clinical information to date comes from small descriptive studies, such as case series and case reports. Documented cutaneous findings reported in children with COVID-19 include a nonspecific maculopapular eruption, followed by chilblain-like or pernio-like acral lesions, urticarial lesions, livedo reticularis, papulovesicular or varicella-like lesions, petechiae or dengue-like lesions, and erythema multiforme-like lesions.²⁵⁻³³

Multiple larger case series published in the recent months^{10-12,14-21,23,24} focus on characterizing and understanding MIS-C. Each case series identified children who met criteria for MIS-C and described the cutaneous clinical manifestations that they presented. The following descriptive terminology was used to describe the skin findings: "conjunctivitis," "rash," "red/cracked lips," "lips/oral cavity changes," "cheilitis," "extremity changes," and "hand/feet edema." Most of the studies did not provide photographs of the eruption and did not attempt to describe it. Others that did used the following nondescriptive terminology: "polymorphous," "general," "variable," "skin desquamation," "diffuse," "non-specific," or simply "rash." Refer to Table 3.¹

A targeted surveillance for MIS-C at multiple pediatric health centers across the United States was conducted and identified 126 children who met criteria for MIS-C. Mucocutaneous findings were identified in 74% of children who met criteria for MIS-C. Of these, 59% had nonspecific eruption, 55% bilateral conjunctivitis, 42% oral mucosal changes,

Table 5 Comparing and contrasting multisystem inflammatory syndrome in children with Kawasaki disease

Multisystem inflammatory syndrome in children	Kawasaki disease
Mean age 8-12 years	Mean age <5 years
Non-Hispanic blacks at higher risk	Asians at higher risk
Fever >24 hours	Fever >5 days
Gastrointestinal clinical manifestations are common (severe abdominal pain)	Gastrointestinal complaints are not common
Myocarditis/myocardial dysfunction (left ventricular dysfunction)	Myocardial function normal to mildly reduced
Coronary artery aneurysms unusual	Coronary artery abnormalities such as aneurysms more common
Renal involvement more common	Renal involvement rare
Pro-inflammatory state common	Pro-inflammatory state typically less common and less severe
Lymphopenia common	Lymphopenia not common
Thrombocytopenia	Thrombocytosis

and 37% peripheral extremity changes.²⁴ A review of more than 191 potential MIS-C cases of hospitalized children reported to the New York State Department of Health indicated that 95 met criteria for MIS-C. Of the children who met criteria for MIS-C, 60% had a diffuse nonspecific eruption, whereas 56% had conjunctivitis and 27% oral mucosal changes.¹⁹ Looking at all the 13 case series presented in Table 3, the percentage of children diagnosed with MIS-C who developed mucocutaneous findings were conjunctivitis 27%-93%, oral mucosal changes 25%-87%, rash 47%-81%, and hand/feet erythema and edema 27%-68%. Table 4 summarizes the top mucocutaneous manifestations of children with MIS-C.^{10-12,14-21,23,24} The skin findings associated with MIS-C tend to be more common in younger children and decrease with age. Of the children between 0 and 5 years old, 87% had mucocutaneous findings, compared with only 61.5% of those 13-20 years old.¹⁹

Similarities and differences with Kawasaki disease

As we discuss the various mucocutaneous manifestations associated with MIS-C, many sound similar to other diseases, specifically KD (both typical and atypical). The differential diagnosis of a child presenting with a mucocutaneous eruption includes the following: Stevens Johnson syndrome/toxic epidermal necrolysis (SJS/TEN), drug reaction with eosinophilia and systemic symptoms (DRESS), mycoplasma-induced rash and mucositis / reactive infectious mucocutaneous eruption (MIRM/RIME), and toxic shock

¹ Table 3. Ab, antibodies; IL-6i, Interleukin-6 inhibitors; IL-1Ra, Interleukin-1Ra inhibitor; IVIG, Intravenous Immunoglobulin



Fig. 1 A 7-year-old girl diagnosed with multisystem inflammatory syndrome in children, presented with erythematous urticarial-appearing plaques on the neck overlying lymphadenopathy.



Fig. 2 A 12-year-old boy diagnosed with multisystem inflammatory syndrome in children, presented with erythematous macules and papules coalescing into patches and plaques, respectively, on the trunk and extremities. This patient also presented with palmar erythema (Figure 3).



Fig. 3 The same patient as in Figure 2. Patient presented with bilateral palmar erythema.

syndrome, as well as other viral or postviral etiologies. Identifying the similarities and differences between these entities is crucial in distinguishing them and making the correct diagnosis.

From a clinical perspective, a subset of patients with MIS-C show features that are similar to KD, including mucocutaneous findings. The question arises as to whether these two syndromes represent a single entity, rather than completely separate conditions. Kawasaki shock syndrome, which is a known variant of KD, as well as severe KD both recapitulate many of the more common features found in MIS-C, such as shock, pro-inflammatory state and pathology, and some of the hematologic disturbances, such as thrombocytopenia, which at first glance appear unique to MIS-C. A reasonable argument can be made that MIS-C represents a severe Kawasaki spectrum.

Many of the demographic features of the disease differ, such as age (mean age 8-12 years in MIS-C versus the rarity of Kawasaki cases in children older than 5 years). The absence of predilection for Asian populations being affected in MIS-C is also contrary to what one might see in KD.³⁴ For instance, only 1 of 17 children diagnosed with MIS-C in New York City was of Asian descent.²³ The most common cardiac abnormality associated with MIS-C is left ventricular dysfunction/myocarditis, unlike coronary artery abnormalities in KD.¹⁶ Of the children who met criteria for MIS-C at Columbia University Irving Medical Center/New York-Presbyterian Morgan Stanley Children's Hospital in New York City, 35% had moderate left ventricular dysfunction, whereas only one child developed a medium-sized aneurysm.²³ Coronary aneurysms are observed in other vasculitis syndromes, such as Takayasu arteritis and polyarteritis nodosa,³⁵ but rarely are they seen in association with other vi-

ral and infectious conditions.³⁶ The presence of an aneurysm itself is not a defining feature that would necessitate relating the two syndromes. Table 5 further compares and contrasts clinical manifestations of MIS-C and KD.

Conclusions

MIS-C is a recently recognized childhood inflammatory disorder seen in patients with confirmed or suspected COVID-19. The increasing incidence 3 to 4 weeks after COVID-19 infection suggests a postinfectious phenomenon occurring in susceptible individuals. We have reviewed recently published large case series on MIS-C in an effort to identify and characterize the mucocutaneous manifestations of MIS-C and conclude that the vast majority of MIS-C cases present with mucocutaneous manifestations, including conjunctivitis, diffuse eruptions, and oral mucosal changes, represent MIS-C. The eruption of MIS-C is typically diffuse and nonspecific, whereas mucocutaneous manifestations of MIS-C are more common in younger children with the prevalence decreasing with age. Although the mucocutaneous findings of MIS-C may resemble those of KD, the two conditions differ widely for the mean age of onset, race predilection, and the associated findings Fig. 1, 2 and 3.

Declaration of Competing Interest

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

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