PEDIATRICS PERSPECTIVES

A New Definition for Multisystem Inflammatory Syndrome in Children

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In Spring 2020, public health agencies worldwide rapidly issued alerts about a rare, hyperinflammatory illness in children, presumed to be a postinfectious immune response to coronavirus disease 2019 (COVID-19), using somewhat different diagnostic criteria and nomenclature. In the United States, the Centers for Disease Control and Disease Prevention (CDC) termed it the multisystem inflammatory syndrome in children (MIS-C) associated with COVID-19.

Much has been learned since the CDC published its first MIS-C definition in May 2020. The initial definition was intentionally broad and somewhat nonspecific. Because of the public health emergency, the 2020 definition had not been approved by the Council of State and Territorial Epidemiologists (CSTE), as would be expected for a condition reportable to CDC. Therefore, in 2021, the CDC and CSTE convened a working group to construct the CSTE/CDC MIS-C surveillance case definition[1] with the objectives of reducing (1) the risk of misclassification with other pediatric inflammatory conditions, and (2) complexity for nonclinically trained public health practitioners who perform case ascertainment. The CSTE approved this new surveillance case definition in June 2022, and it became effective for non-mandatory CDC reporting on January 1, 2023. In December 16, 2022's Morbidity and Mortality Weekly Report, Melgar et al describe the process and rationale by which the working group developed the CSTE/CDC MIS-C surveillance case definition.[2] The definition was based on 3 sources of data: a panel of experts who commented on features of MIS-C that distinguish it from other pediatric illnesses, a literature review and assessment of data from the Overcoming COVID-19 Network MIS-C Registry and the Best Available Treatment Study,[3] and the application of the new case definition to a dataset of ~8800 MIS-C cases previously reported to the CDC with the 2020 definition. Specifically, they determined the proportion of cases meeting the new definition, and the proportion of cases meeting the new definition with adjustments for clinical and laboratory features.

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TABLE 1 Side-by-Side Comparison of Criteria Included in the 2020 CDC MIS-C Case Definition and in the CSTE/CDC MIS-C Surveillance Case Definition

Criterion	2020 CDC MIS-C Case Definition	CSTE/CDC MIS-C Surveillance Case Definition
Patient age	<21 y	<21 y
Hospitalization	Clinically severe illness requiring hospitalization	Clinical severity requiring hospitalization or resulting in death
No alternative diagnosis	No alternative plausible diagnoses	Absence of a more likely alternative diagnosis
Fever	Fever ≥38.0°C for ≥24 h, or report of subjective fever lasting ≥24 h	Subjective or documented fever (temperature ≥38.0°C)
Laboratory evidence of systemic inflammation	Including, but not limited to, 1 or more of the following: an elevated C-reactive protein, erythrocyte sedimentation rate, fibrinogen, procalcitonin, d-dimer, ferritin, lactic acid dehydrogenase, or interleukin 6, elevated neutrophils, reduced lymphocytes and low albumin	C-reactive protein ≥3.0 mg/dL (30 mg/L)
Evidence of SARS-CoV-2 infection or exposure	Positive for current or recent SARS-CoV-2 infection by RT-PCR, serology, or antigen test, or exposure to a suspected or confirmed COVID-19 case within the 4 wks before the onset of symptoms	Detection of SARS-CoV-2 RNA in a clinical specimen up to 60 d before or during hospitalization, or in a postmortem specimen using a diagnostic molecular amplification test (eg, PCR), OR Detection of SARS-CoV-2-specific antigen in a clinical specimen up to 60 before or during hospitalization, or in a postmortem specimen, OR Detection of SARS-CoV-2-specific antibodies in serum, plasma, or whole blood associated with current illness resulting in or during hospitalization, OR Close contact with a confirmed or probable case of COVID-19 in the 60 d before hospitalization
Multisystem involvement	Multisystem (≥2) organ involvement:	New onset manifestations in at least 2 of the following categories:
	Cardiovascular (eg, shock, elevated troponin and/or BNP, abnormal echocardiogram, arrhythmia)	Cardiac involvement indicated by left ventricular ejection fraction <55%, OR coronary artery dilatation, aneurysm, or ectasia, OR troponin elevated to greater than laboratory normal range, or indicated as elevated in a clinical note
	Renal (eg, acute kidney injury, renal failure)	Mucocutaneous involvement indicated by rash, OR inflammation of the oral mucosa (eg, mucosal erythema or swelling, drying, or fissuring of the lips, strawberry tongue), OR conjunctivitis or conjunctival injection (redness of the eyes), OR extremity findings (eg, erythema [redness] or edema [swelling] of the hands or feet)
	Respiratory (eg, pneumonia, ARDS, pulmonary embolism)	Shock
	Hematologic (eg, elevated D-dimer, thrombophilia, thrombocytopenia)	Gastrointestinal involvement indicated by abdominal pain, OR vomiting, OR diarrhea
	Gastrointestinal (eg, abdominal pain, vomiting, diarrhea, elevated bilirubin, elevated liver enzymes)	Hematologic involvement indicated by platelet count <150 000 cells/μL, OR absolute lymphocyte count (ALC) <1000 cells/μL
	Dermatologic (eg, rash, mucocutaneous lesions)	
	Neurologic (eg, CVA, aseptic meningitis, encephalopathy, seizure)	

We summarize the differences between the definitions in Table 1. In the CSTE/CDC MIS-C surveillance case definition, fever of any duration is sufficient to meet that criterion, whereas fever lasting ≥24 hours was previously required. The criterion of systemic inflammation is now met solely with a C-reactive protein ≥3mg/dL, instead of via a myriad of acute phase reactants. Multisystem involvement is now met with ≥2 of 5 organ systems, instead of ≥2 out of 7, because renal, respiratory, and neurologic categories were eliminated, and the cardiac category is now split into 2 criteria: (1) shock and (2) cardiac involvement, as evidenced by low ventricular ejection fraction (≤55%), coronary artery abnormalities, or elevated troponin. The dermatologic category is now mucocutaneous involvement, including rash, inflammation of the oral mucosa, conjunctival injection, or extremity findings. These criteria are strongly reminiscent of classic Kawasaki disease (KD) stigmata but without unilateral lymphadenopathy. Gastrointestinal involvement now specifies abdominal pain, vomiting, or diarrhea. Lastly, hematologic involvement was simplified to require the presence of thrombocytopenia (<150 000 cells/μL) or a low absolute lymphocyte count (<1000 cells/μL). Age <21 years, severe illness requiring hospitalization, and absence of a more likely alternative diagnosis remain criteria for MIS-C in the new case definition. Notably, KD is now considered an alternative diagnosis. Laboratory criteria for confirmed MIS-C cases require a positive severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) RNA polymerase chain reaction (PCR) or specific antigen test result within 60 days of illness or positive SARS-CoV-2 serology result (antigen-specificity not required), if associated with the current illness. In the absence of a positive laboratory test result for SARS-CoV-2, the definition of a probable MIS-C case is met with an epidemiologic link, defined as close contact with a probable or confirmed COVID-19 case within 60 days of illness, plus the required clinical criteria. When the CSTE/CDC MIS-C surveillance case definition for confirmed and probable cases was applied to MIS-C cases with an available quantitative C-reactive protein who were reported to the CDC using the 2020 definition, 87% (6158/7081) met the new case definition.

Many of the new features of the CSTE/CDC MIS-C surveillance case definition, such as simpler requirements for fever, systemic inflammation, organ involvement, and the identification of any positive serology result (not antigen specific), were instituted to improve the feasibility of data collection by jurisdictional health department staff, 1 of the 2 goals of the CDC/CSTE working group. In regard to the other goal (ie, decreasing the misclassification of MIS-C cases), the working group primarily focused on distinguishing MIS-C from severe COVID-19, KD, and toxic shock syndrome. It is well documented that severe acute COVID-19 has significant overlap with MIS-C, and removing the respiratory category from the MIS-C case definition is expected to decrease the misclassification of severe COVID-19 as MIS-C.[4] The CDC has also published diagnostic scores to distinguish MIS-C, COVID-19, KD, and toxic shock syndrome.[5] It is unknown how many children hospitalized with other febrile illnesses would meet the new MIS-C definition given widespread seropositivity, COVID-19 exposure, and nonspecific features overlapping with acute infectious illnesses and other hyperinflammatory conditions. As such, the definition's specificity and false positive rates as a tool in the real world of clinical practice cannot be estimated.

In addition, the CSTE/CDC MIS-C surveillance case definition was explicitly developed for MIS-C passive surveillance, not for diagnosis, and the CDC authors distinguish between the use of the definition for reporting purposes versus clinical purposes. Specifically, they emphasize that clinicians should use all available data to consider alternative diagnoses and determine treatment on the basis of clinical judgment. We agree that the use of the new case definition as a clinical instrument in isolation poses important challenges. First, the new definition was developed by using a dataset that included MIS-C cases from earlier in the pandemic when SARS- CoV-2 variants were more likely to cause MIS-C and more severe illness, many children were less exposed to usual childhood viruses, and fewer children had been vaccinated and, hence, protected against MIS-C. Moreover, seropositivity in the pediatric population has become widespread since MIS-C's first description; by August 2022, almost 62 million children, or 86% of the pediatric population, had had at least 1 SARS-CoV-2 infection. It is, thus, difficult to interpret if positive serology results are associated with the MIS-C illness in question, if there is not a history of positive SARS-CoV-2 RNA PCR or antigen test results in the preceding 2 to 8 weeks. However, negative antigen, PCR, and serology test results against SARS-CoV-2 likely exclude a diagnosis of MIS-C. Lastly, if new SARS-Co-V2 variants continue to be associated with milder MIS-C,[6] overlap with other viral illnesses will increase. Taken together, these considerations emphasize the importance of clinical judgment in considering the broad array of alternative diagnoses that may masquerade as MIS-C.

Given increasing challenges to the diagnosis of MIS-C, readily accessible diagnostic tools, such as machine learning physician support tools,[7] T cell receptor repertoire skewing (ie, the expansion of TRβV11-2), or a more specific cytokine fingerprint[8] are needed to provide rapid, accurate results to differentiate MIS-C from other febrile conditions of childhood and to determine a temporal link to SARS-CoV-2 infection. Accurate diagnostic tests may also facilitate the diagnosis of milder forms of MIS-C that present without life-threatening involvement. However, in the absence of such tools, clinicians will need to use clinical judgment, in collaboration with subspecialty experts, to accurately diagnose and treat MIS-C. Fortunately, the CSTE/CDC MIS-C surveillance case definition will facilitate research by aligning with a common set of manifestations in the World Health Organization's MIS-C definition, thereby enhancing critical international collaborations for our understanding of MIS-C biology, diagnosis, and treatment.

ABBREVIATIONS

CDC: Centers for Disease Control and Prevention
COVID-19: coronavirus disease 2019
CSTE: Council of State and Territorial Epidemiologists
KD: Kawasaki disease
MIS-C: multisystem inflammatory syndrome in children
SARS-CoV-2: severe acute respiratory syndrome coronavirus 2

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