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Heterogeneity in the evaluation of suspected MIS-C: a cross-sectional vignette-based survey

Claudia A. Rosu^{1†}, Anna M. Martens^{2,3†}, Jeffrey Sumner^{2,3}, Eva J. Farkas^{3,4}, Puneeta Arya^{2,3}, Alexy Boudreau Arauz^{2,3}, Vandana L. Madhavan^{2,3}, Hector Chavez⁵, Shawn D. Larson⁶, Oluwakemi Badaki-Makun⁷, Daniel Irimia^{2,8,9} and Lael M. Yonker^{2,3*}

Abstract

Background and Objectives: Multisystem Inflammatory Syndrome in Children (MIS-C) is an emerging complication of COVID-19 which lacks a definitive diagnostic test and evidence-based guidelines for workup. We sought to assess practitioners' preferences when initiating a workup for pediatric patients presenting with symptoms concerning for MIS-C.

Methods: In a cross-sectional vignette-based survey, providers were presented with clinical vignettes of a patient presenting with 24 h of fever from a community with high rates of COVID-19. Respondents were asked about their general practices in pursuing a workup for potential MIS-C including testing obtained, criteria for diagnosis, and timing to confirm or rule out the diagnosis.

Results: Most of the 174 respondents were physicians from the United States at academic medical centers. The majority of providers would not initiate MIS-C workup for fever and non-specific symptoms unless the fever lasted more than 72 h. Skin rash, abdominal pain, and shortness of breath were symptoms that raised greatest concern for MIS-C. Most providers would obtain COVID-19 PCR or antigen testing, plus blood work, in the initial workup. The list of laboratory studies providers would obtain is extensive. Providers primarily rely on cardiac involvement to confirm a MIS-C diagnosis, and establishing a diagnosis takes 24–48 h.

Conclusions: Significant heterogeneity exists amongst providers as to when to initiate the MIS-C workup, the order and content of the workup, and how to definitively diagnose MIS-C. A diagnostic test with high sensitivity and specificity for MIS-C and refined evidence-based guidelines are needed to expedite diagnosis and treatment.

Keywords: Pediatric COVID-19, Multisystem inflammatory syndrome in children

Background

Multisystem Inflammatory Syndrome in Children (MIS-C) is an emerging, rare but severe complication of COVID-19 that can result in life-threatening multi-system organ failure and death. MIS-C develops weeks to months following infection with SARS-CoV-2 and presents with unremitting fever and a constellation of symptoms including rash, gastrointestinal symptoms, edema of the hands/feet, oral mucosal changes,

[†]Claudia A. Rosu and Anna M. Martens contributed equally as co-first authors.

*Correspondence: lyonker@mgh.harvard.edu

² Harvard Medical School, Boston, MA, USA

Full list of author information is available at the end of the article



conjunctivitis, lymphadenopathy, and neurological symptoms [1, 2]. Cardiac involvement is common; almost half of patients require vasopressor support and 80% require intensive care [3]. Because of the range of clinical presentations and risk for rapid progression, early diagnosis and treatment are key [1, 2]. The pathophysiology of MIS-C is not well understood, but SARS-CoV-2 antigenemia from gastric sources triggering a superantigen-like hyperinflammation post-viral inflammatory process is suggested [4–6]. The criteria for MIS-C diagnosis established by the Center for Disease Control include patients less than 21 years old presenting with fever ($>38.0^{\circ}\text{C}$) for more than 24 h, laboratory evidence of inflammation and multisystem involvement, who require hospitalization, without an alternative diagnosis, and with known infection or exposure to COVID-19 within the four weeks prior to the onset of symptoms [1]. Currently, no definitive diagnostic test for MIS-C exists.

Guidelines have evolved to aid in the diagnosis of MIS-C, but existing laboratory tests lack specificity. Several professional associations have put forward guidelines for a MIS-C diagnostic approach, including the American College of Rheumatology [7] and the American Academy of Pediatrics [8]. From these guidelines, it is recommended that patients with persistent fever and other accompanying symptoms have lab work performed to look for evidence of inflammation and assess cardiac, renal, hematologic, and hepatic function. Given the potential for rapid progression, there is a low threshold to initiate this workup. These guidelines have significantly changed the standard of care and shifted the paradigm for children who present with 1–2 days of fever. If there is no evidence of bacterial infection, providers would routinely send febrile children home with a diagnosis of a viral illness prior to the COVID-19 pandemic; however, with the current guidelines, many of these patients now have labs drawn, imaging done, and are admitted to the hospital for monitoring. The laboratory tests obtained are non-specific and difficult to interpret. While certain findings may increase a clinician's suspicion for MIS-C, such as elevated inflammatory or cardiac markers, diagnosis remains challenging, and practitioners face variable degrees of uncertainty.

Given the lack of a definitive diagnostic test for MIS-C, the spectrum of clinical features associated with the disease, and the lack of evidence-based guidelines for evaluation, we sought to understand practitioners' preferences for workup in a pediatric patient presenting with possible MIS-C through a vignette-based survey.

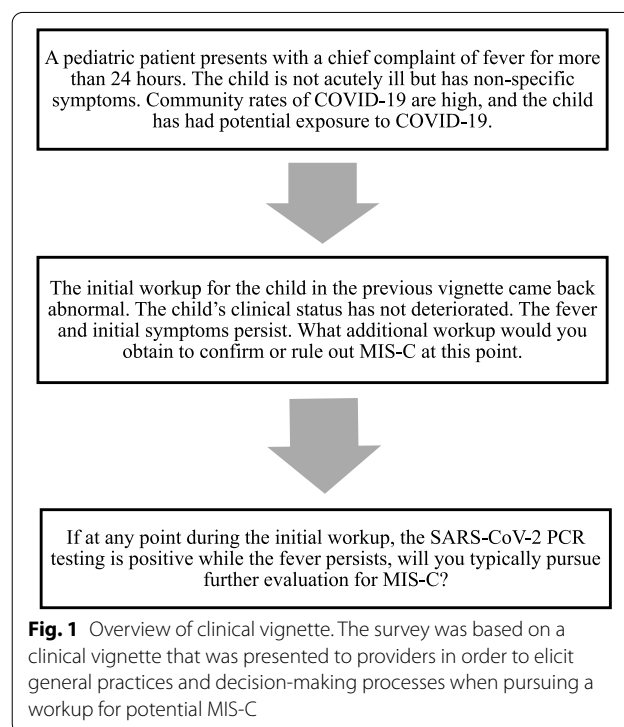
Methods

Participants

Between January–February 2021, we distributed an anonymous online survey to healthcare providers worldwide using simple random sampling to find and recruit the study participants. We recruited emergency medicine, pediatric, medicine-pediatric, family medicine, and pediatric subspecialty practitioners. Access to hospital providers' listservs from their specific departments and professional medical associations' listservs was required and granted. We invited providers to participate in the study via an email explaining the study goals. Participants were provided with an IRB-approved statement declaring that informed consent was implied by opening the survey link. The MGB Institutional Review Board approved this study (MGB IRB #2020P003972).

Study measures

The electronic survey included three clinical vignettes, which we constructed to present a pediatric patient with fever for more than 24 h from a community with high rates of COVID-19 infection followed by various potential developments in the case (Fig. 1). The focus was on the typical approach to such a case; the timing and triggers for initiating MIS-C diagnostic workup, providers' characteristics that may influence the diagnostic approach, and the spectrum of the preferred diagnostic procedures. Existing clinical literature and questionnaires



were reviewed, and expert pediatricians were consulted to support the process theoretically. This allowed the team to work backward from presenting symptoms, complaints, and practitioners' experience with suspected MIS-C cases to a controlled development of vignettes describing contextually relevant situations as the stimulus for reflection and response. Demographic items on the survey included professional role, specialty, years in practice, location, and clinical setting. Experience in treating patients with COVID-19 and MIS-C and an estimate of general patient demographics were also assessed.

Analysis

Descriptive statistics were reported for all the questionnaire items. In addition, chi-square tests and t-tests were performed to compare the responses to the clinical vignettes across several demographic characteristics like the number of years in practice (categories ranging from 0–5, 6–10, 10–25, and over 25 years), type of clinical settings (academic medical center, community hospital, and private practice), and geographic area. For the “check all that apply” survey items, we calculated the relative percentages or the prevalence of each option among the

choices selected. The data were analyzed using IBM SPSS Statistics (Version 28) predictive analytics software.

Results

Survey participants

A total of 174 health care providers completed the survey. Table 1 provides a summary of our sample characteristics of survey respondents. The majority of respondents were physicians ($n=165$, 95%) from the United States ($n=157$, 90.2%); Fig. 2 displays the distribution of respondents from the United States. Most were employed by academic medical centers ($n=115$, 66.1%), and were either general pediatricians ($n=47$, 27.0%), pediatric emergency medicine ($n=45$, 26.3%), or general emergency medicine ($n=37$, 21.3%) with a range of clinical experience and years in practice. Table 2 highlights the characteristics of the providers' patient panel. The median estimated number of pediatric COVID-19 and MIS-C patients that providers had cared for were 34.5 and 10 over a 10-month period, respectively. Providers reported that most patients evaluated for MIS-C (median 60%, interquartile range [IQR] 30) were on Medicaid, and half of the patients were from racial/ethnic minorities.

Table 1 Demographics of survey respondents

Characteristic		N(%), N = 174
Professional Role	MD/DO	165 (95%)
	Nurse Practitioner	3 (1.7%)
	Resident	2 (1.1%)
Specialty	Emergency medicine	37 (21.3%)
	Pediatrics	47 (27.0%)
	Medicine-pediatrics	4 (2.3%)
	Family medicine	1 (0.6%)
	Hospital medicine	4 (2.3%)
	Pediatric subspecialty	68 (39.1%)
	Pediatric emergency	45 (26.3%)
	Pediatric critical care	6 (3.5%)
Years in practice	Other	16 (9.6%)
	1–5 years	56 (32.2%)
	5–10 years	35 (20.1%)
	10–25 years	54 (31.0%)
Location	> 25 years	24 (13.9%)
	United States	157 (90.2%)
	DC	19 (10.9%)
	FL	47 (26.8%)
	ML	19 (10.8%)
	MA	27 (15.5%)
	Other U.S.	47 (26.8%)
Clinical settings	Outside the U.S. ^a	5 (3.0%)
	Academic medical center	115 (66.1%)
	Urban medical center	10 (5.7%)
	Private practice	12 (6.9%)
	Community hospital	26 (14.9%)
	Other	7 (4.1%)

^a Belgium N = 2; Canada N = 1; Germany N = 1; Israel N = 1

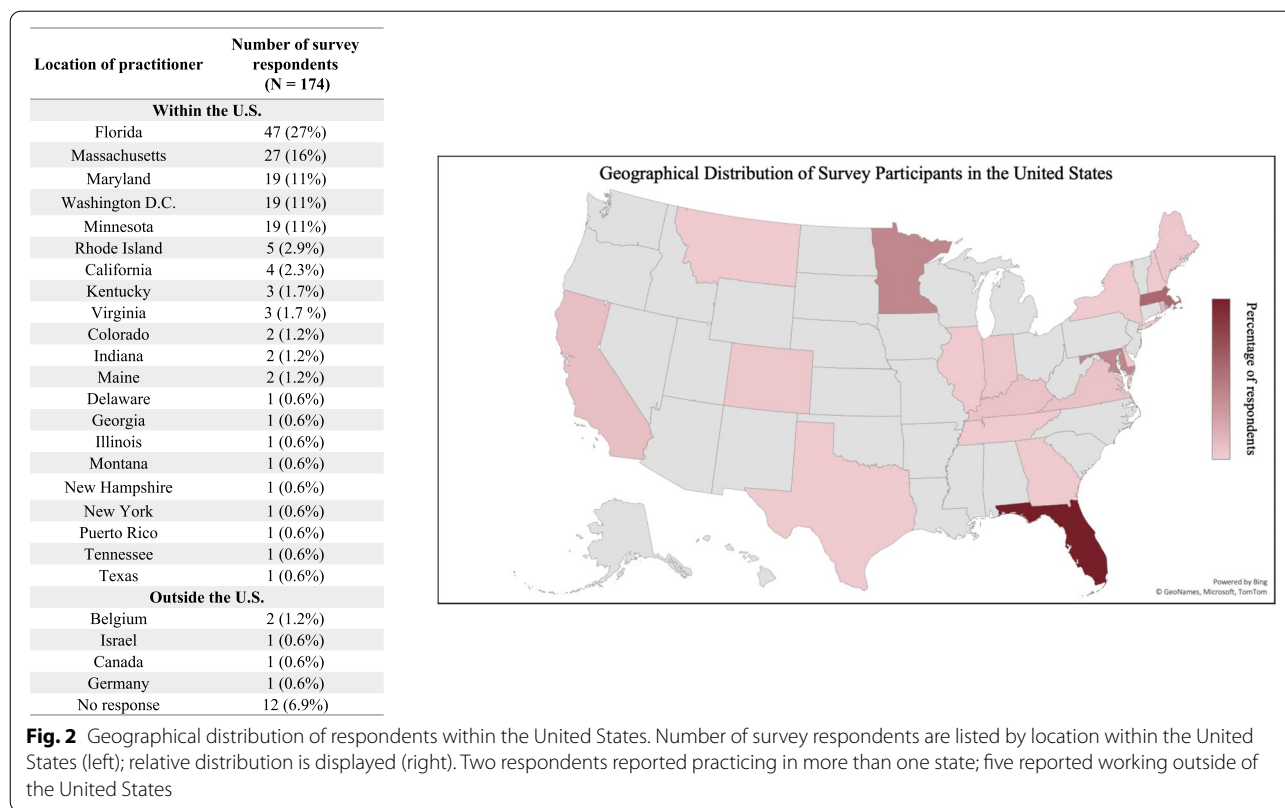


Table 2 Characteristics of providers’ patient panel

Characteristic	Median (IQR ^a)
Estimated no. of pediatric COVID-19 patients seen since March 2020	34.5 (31.25)
Estimated no. of patients evaluated for MIS-C since March 2020	10.0 (16.0)
Percentage racial/ethnic minority pediatric patients	50 (40)
Percentage pediatric patients with Medicaid	60 (30)

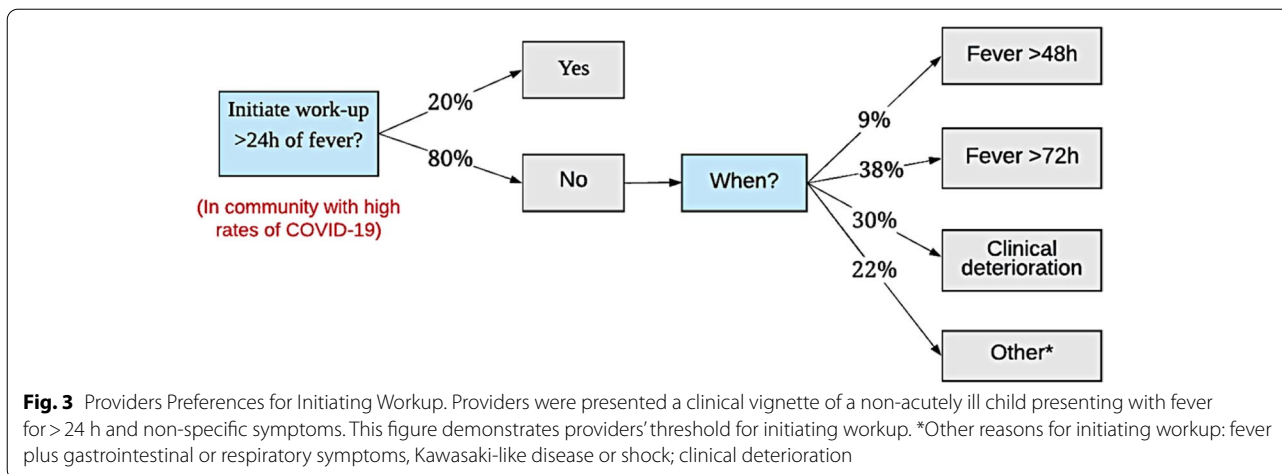
^a IQR Interquartile range

Indications for initiating MIS-C workup

Of 174 respondents, only 35 (20%) would initiate workup (blood work, imaging, or consults) for MIS-C in a non-acutely ill child presenting with fever for more than 24 h and non-specific symptoms from a community with high rates of COVID-19 (Fig. 3). Amongst the 139 providers who initially deferred a MIS-C workup, 13 (9%) would initiate a workup if the fever persisted more than 48 h, 53 (38%) would initiate the workup if the fever persisted for more than 72 h, and 42 (30%) would initiate the workup only if the child clinically deteriorates (Fig. 3).

The decision to defer MIS-C workup in a child with 24 h of fever was not associated with medical specialty (emergency medicine vs. pediatrics vs. pediatric subspecialty), years in practice (less than ten years

vs. more than ten years), or clinical settings (academic medical center vs. others) (χ^2 , not significant). On average, the practitioners who chose to defer the MIS-C workup had seen significantly more COVID-19 cases (mean=43.5, standard error of the mean [SEM]=2.67) than those who chose to initiate workup for the same child; (mean=29.4, SEM=3.37; t-test, $p=0.01$). Importantly, this finding had a large effect size ($d=0.76$) suggesting that from a population perspective, the more acute pediatric COVID-19 cases that are seen, the more likely MIS-C evaluations could be delayed. There was no statistically significant difference in initiating MIS-C workup for the child described above by the number of patients the providers had previously evaluated for MIS-C, as assessed by an independent-samples t-test.



Clinical factors impacting workup preferences for MIS-C

We then sought to determine patient-specific differences that would affect practitioners' preferences in the MIS-C workup. First, we assessed how the workup would differ based on the child's age. For younger children, practitioners were more likely to obtain blood work than older children, who were more likely to be watched clinically (Fig. 4).

Providers were then asked to rank the top three presenting features, besides fever, that would make them most concerned about MIS-C in a pediatric patient with persistent fever for more than 48 h. Skin rash ($n=61$, 35%), abdominal pain ($n=58$, 33%), and shortness of breath ($n=46$, 26%) were the most cited symptoms that raised provider concern for MIS-C (Fig. 5).

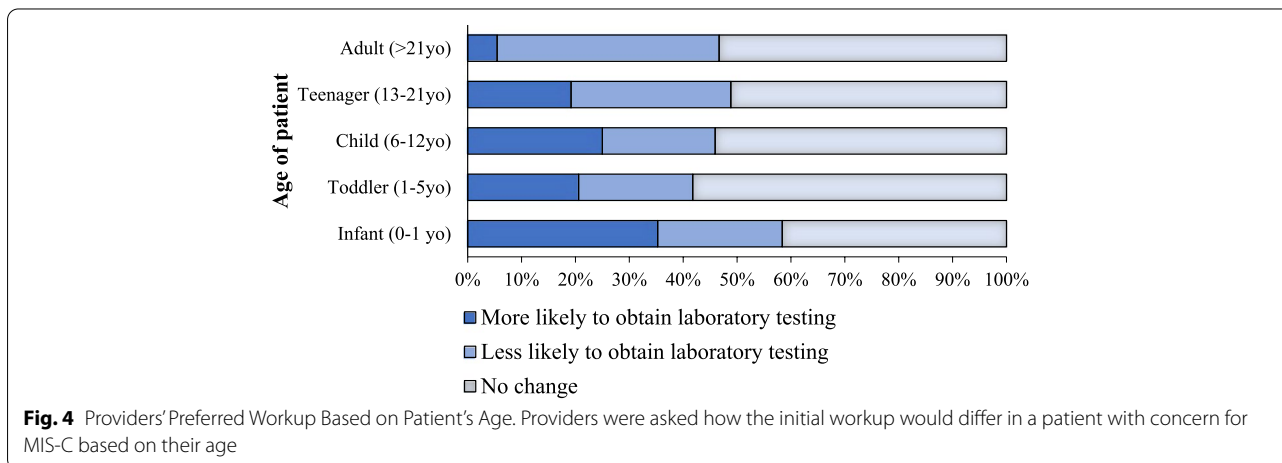
Decision-making in the evaluation of MIS-C

Providers were prompted about their preferences on the initial workup they would pursue for MIS-C in the

pediatric patient described using multiple-choice questions in which multiple answers could be selected. Ninety-three percent ($n=161$) of providers would obtain COVID-19 antigen or PCR testing, 88% ($n=153$) would obtain blood work, 47% ($n=81$) would obtain imaging, and 28% ($n=49$) would obtain subspecialty consults (Fig. 6a).

Of the providers who would obtain blood work, a total of 8 tests were recommended on average (SD 3.7). Of these, CBC, CRP, ESR, and chemistry panel were the most commonly obtained tests (Fig. 6b). Seventy-three percent ($n=94$) of providers would obtain SARS-CoV-2 antibody. Amongst the 21 providers who would not order blood work initially, 20 practitioners felt that it had limited utility at this point, while 1 practitioner thought that the discomfort to the child involved in blood work outweighed any potential benefits.

If they opted to obtain imaging, 77% ($n=61$) of practitioners would order a chest x-ray as part of the initial



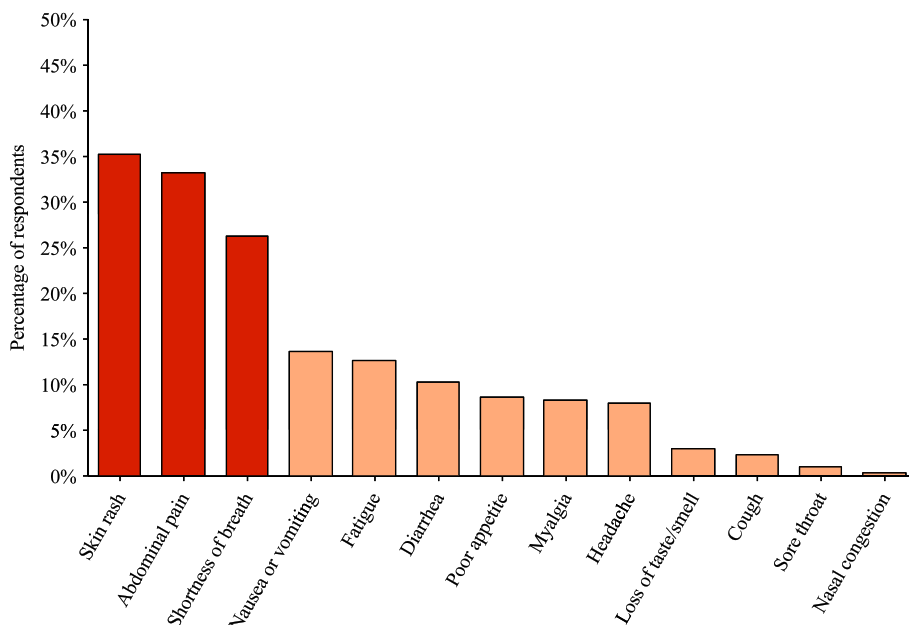


Fig. 5 Providers' perceptions of the most concerning symptoms for MIS-C. Providers ranked the top three presenting features, besides fever, that would make them most concerned about MIS-C in a pediatric patient with fever for more than 48 h. This chart demonstrates the most commonly ranked symptoms, with the top 3 highlighted in red

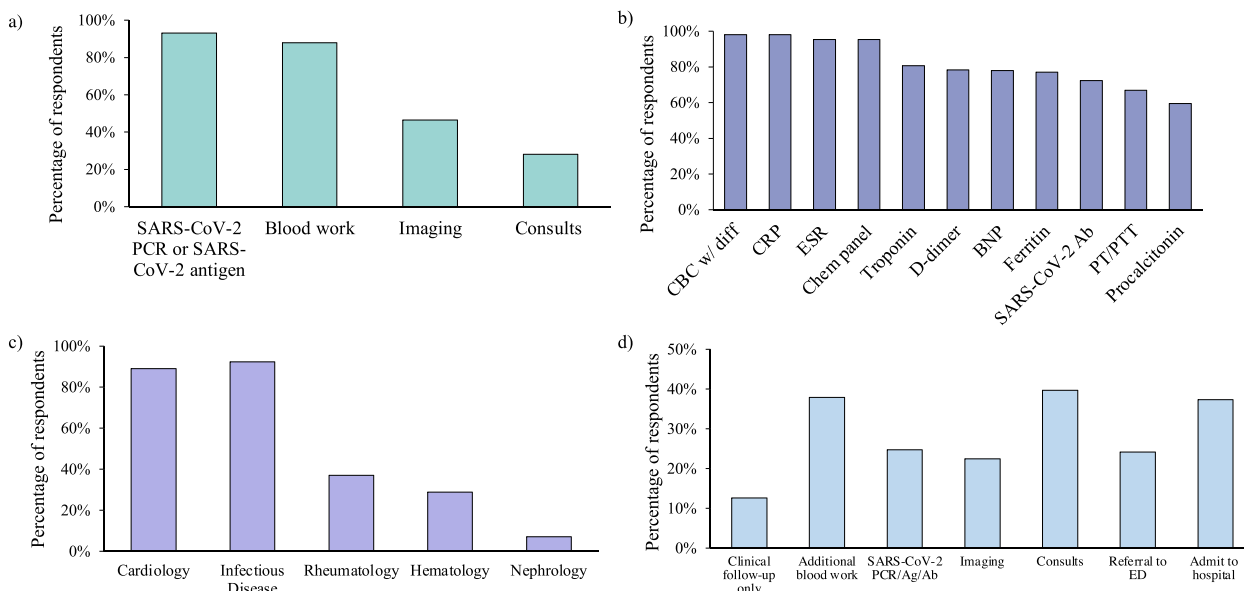


Fig. 6 Characteristics of initial workup. **a** Initial components of workup obtained **b** Most frequently obtained laboratory tests **c** Most frequently obtained consults **d** Next steps if initial workup was abnormal. Providers were allowed to select more than one answer within each respected question

evaluation of the child in our original vignette, while 88% ($n=65$) would order ECG and 70% ($n=60$) would order echocardiography. Nineteen percent ($n=14$) of providers obtaining imaging would order an abdominal

ultrasound, while 16% ($n=12$) would prefer a chest CT and 15% ($n=11$) an abdominal CT.

Of the providers who would seek out additional subspecialty consultation, the most requested consultants

were infectious disease ($n=48$, 92%) and cardiology ($n=49$, 89%) (Fig. 6c).

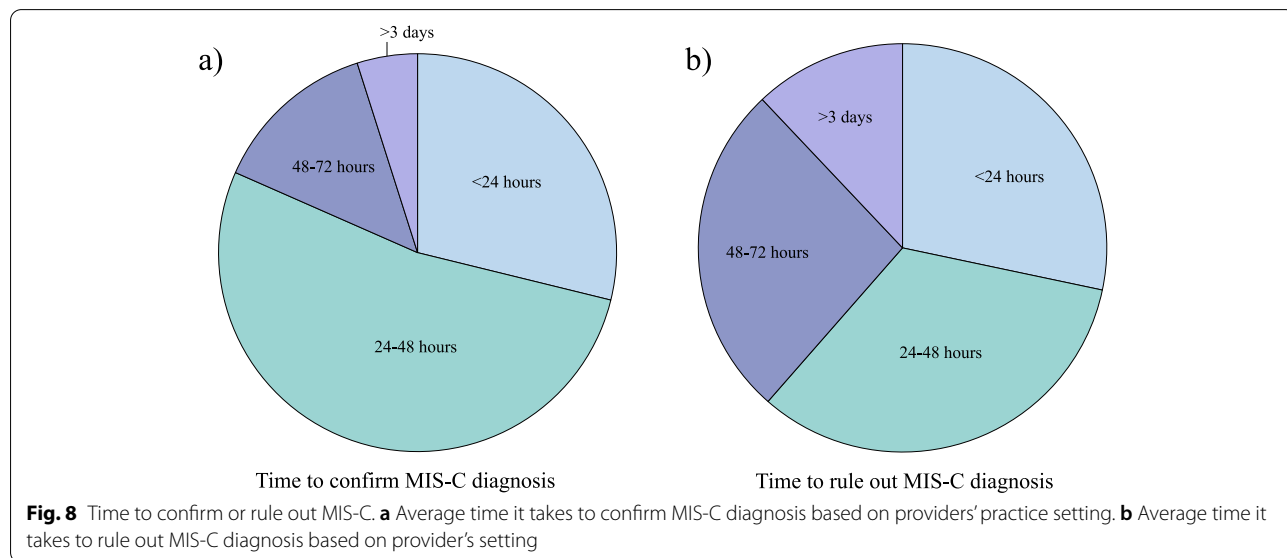
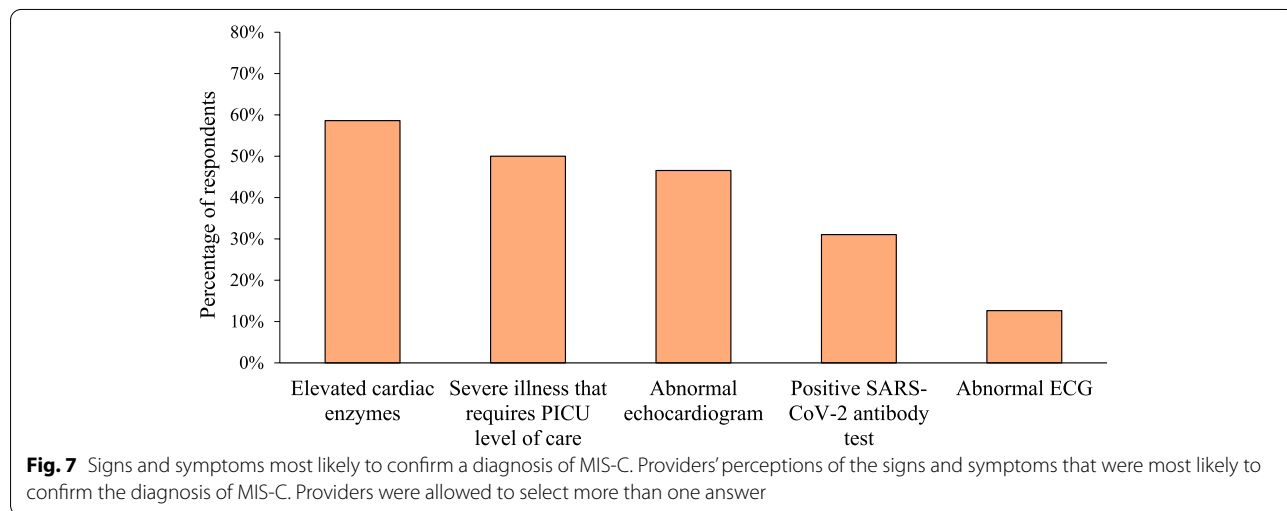
The next steps that providers would take if the initial workup returned abnormal varied, but most commonly providers would obtain consults ($n=69$, 40%), admit to the hospital ($n=65$, 37%), and obtain additional lab work ($n=66$, 38%) (Fig. 6d).

Diagnosing MIS-C

We then assessed the diagnostic findings that would help providers confirm the diagnosis of MIS-C using a multiple-choice question in which multiple answers could be selected. Of the 174 respondents, the most common findings that providers felt would confirm MIS-C diagnosis were elevated cardiac enzymes ($n=102$, 59%), severe illness requiring admission to a pediatric intensive care

unit ($n=87$, 50%), or abnormal echocardiogram ($n=81$, 47%) (Fig. 7).

We also assessed participants' perceptions about the role of a positive COVID-19 PCR test in evaluation for MIS-C diagnosis in a child with persistent fever. One hundred and twenty-four respondents (73%) would further evaluate for MIS-C, while 46 (27%) would only follow the child clinically. In this question, providers were asked to select one option. Reasons given for opting to follow the child clinically without further workup in the setting of a positive COVID-19 PCR included the perception that a diagnosis of acute COVID-19 infection is more likely ($n=31$, 67%), the need for additional criteria to be met, including positive SARS-CoV-2 serology



($n=9$, 10%), or a decline in child's clinical status ($n=25$, 54%) (providers were allowed to select multiple options).

Time to diagnosis

Finally, we wanted to ascertain how long it typically takes to confirm or exclude a MIS-C diagnosis based on our study respondents' experience at their workplace. The majority of participants reported that it took 24–48 h to confirm or rule out MIS-C (Fig. 8a and b, respectively). There was no statistically significant association between the time to confirm or exclude a diagnosis of MIS-C and the type of clinical setting (academic medical center vs. urban medical center/community hospital vs. private practice/other settings), highlighting the high degree of ambiguity in current diagnostic guidelines, the high costs associated with evaluating MIS-C, and urgent need to establish improved diagnostic criteria for MIS-C across a range of clinical settings.

Discussion

MIS-C is a rare but severe sequela of COVID-19 in children; early diagnosis and treatment are critical to reduce or avoid MIS-C morbidity and mortality. Unfortunately, the number of pediatric illnesses that present with similar symptoms is broad, making it challenging to differentiate MIS-C from other more benign childhood illnesses, as well as distinguish it from bacterial infections and Kawasaki disease. Because of the non-specific presenting symptoms, potential for rapid progression, and the life-threatening nature of MIS-C, there is a low threshold for initiating workup. Our study shows significant heterogeneity amongst providers as to when they initiate MIS-C workup, components of the workup, and how to confirm MIS-C diagnosis.

Given how extensive the MIS-C workup is, it is important to carefully consider which patients warrant an evaluation. Current guidelines, however, lack explicit screening criteria. While the CDC case definition of MIS-C includes fever for at least 24 h, guidelines are unclear on the duration of fever that should generate a workup. This lack of clarity is reflected in our study, where providers were divided when asked about the duration of fever that would prompt them to initiate workup. Additional thought also must be put into excluding other febrile illnesses, such as viral illnesses, bacterial infections, or Kawasaki disease, which can be particularly challenging given the overlapping clinical features [11].

Providers who had seen more COVID-19 cases were more likely to initiate MIS-C workup, suggesting that the more exposure providers have to COVID-19, the more likely they are to consider MIS-C. Our study also shows that providers are more likely to initiate a workup in younger children than in older children; however, current

guidelines do not differ based on age. Such heterogeneity could lead to missed or delayed diagnosis.

Once it is determined that a child warrants workup for MIS-C, there is a recommended set of "Tier 1" screening labs, which if abnormal, prompt additional evaluation, including "Tier 2" labs, EKG, and echocardiogram [7]. Both tiers of labs are non-specific and their ability to distinguish MIS-C from other causes of acute febrile illnesses. Our study shows that providers often do obtain lab work, which is consistent with the existing guidelines, but it is unclear how these results help guide diagnosis. For example, the majority of providers would obtain SARS-CoV-2 serology. However, with over 13 million children under 18 years old testing positive for COVID-19 thus far in the pandemic in the United States alone, we can expect that most children will develop post-vaccination and/or post-infectious antibodies at some point. Thus, relying on serology as a laboratory marker will become even less specific [9]. Additional workup that providers obtained beyond laboratory work, including consults and imaging, was largely heterogeneous and inconsistent.

Once a patient is diagnosed with MIS-C, they are usually treated with IVIG and/or systemic steroids, which are thought to improve clinical outcomes. The most common findings that our respondents perceived to confirm MIS-C diagnosis were elevated cardiac enzymes, abnormal echocardiogram, or severe illness requiring admission to a pediatric intensive care unit. While cardiac involvement is one of the most feared complications of MIS-C and is present in up to 80% of cases, it is not necessary to diagnose MIS-C [10]. Therefore, heavy reliance on cardiac findings to confirm MIS-C diagnosis could mean that providers are missing or under-reporting cases of MIS-C. This highlights the need for more clear diagnostic criteria.

Limitations of this study include it being a cross-sectional survey of self-reported preferences in providers, with potential for sampling and response biases. We did not examine the medical records to compare with real observed cases to ascertain accuracy. Our sample was skewed toward providers from academic medical centers where access to laboratory tests, imaging, and specialized consultants is readily available. Further research is needed to assess what happens in other clinical settings (e.g., rural primary care offices) where access to testing, imaging, and specialized consultants would be limited. Identifying MIS-C and differentiating it from other illness is an important step in the diagnostic process. While our study focused on the process of identifying MIS-C, we did not ask providers to specify how they would exclude other illnesses, such as bacterial infections. However, this study highlights the need to better understand

the initial presentation that should prompt further diagnosis, as well as a simplified diagnostic test that is more specific and widely accessible to help facilitate timely diagnosis and treatment.

Conclusion

Our study illustrates significant heterogeneity among healthcare providers as to when to initiate MIS-C workup, the order and context of the workup, and the criteria for MIS-C diagnosis. The current guidelines are designed to be sensitive as to minimize missed or delayed diagnoses. However, this subsequently results in high healthcare resource utilization. A diagnostic test is needed that is highly sensitive and specific in order to expedite diagnosis and treatment. With the United States in its fourth wave of the COVID-19 pandemic, it is evident that SARS-CoV-2 and MIS-C will likely remain a threat for the foreseeable future. The scientific community therefore needs to urgently build on existing research and refine clinical guidelines to minimize pediatric MIS-C morbidity and mortality.

Abbreviations

MIS-C: Multisystem inflammatory syndrome in children; SEM: Standard error of the mean; IQR: Interquartile range.

Acknowledgements

The authors would like to thank Dr. Lyle Moldawer PhD for his contributions as well as the medical community who participated in this survey.

Authors' contributions

Drs. Rosu, Irimia, and Yonker designed the initial draft of the survey. All authors provided edits to the survey and assisted in survey distribution. Drs. Arya, Madhavan, and Boudreau Arauz provided intellectual contributions. Drs. Rosu, Martens, Irimia, and Yonker analyzed and interpreted the data. Drs. Rosu, Martens, Sumner, and Yonker drafted the initial manuscript. All authors critically reviewed the manuscript. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

Funding

This research was supported in part with Federal funds from the Department of Health and Human Services, including the National Heart Lung and Blood Institute (5K08HL143183 to LY), the National Institute of General Medical Sciences and the National Institute of Child Health and Human Development (GM092804 and HD089939 to DI, GM139690 to LLM), and the Office of the Assistant Secretary for Preparedness and Response: Biomedical Advanced Research and Development Authority, under Contract No 75A0120C00189.

Availability of data and materials

The datasets generated and/or analyzed during the current study are not publicly available due Mass General Brigham policies. However, data used in this study may become available to other researchers upon reasonable request to the corresponding author and in compliance with the Mass General Brigham Innovations Office.

Declarations

Ethics approval and consent to participate

Providers were invited via email to anonymously participate in an on-line survey. Participation in the survey was voluntary. Participants were provided with an IRB-approved statement declaring that informed consent was implied by opening the survey link. The Mass General Brigham Institutional Review Board

approved this study (MGB IRB #2020P003972). All methods were performed in accordance with the relevant guidelines and regulations.

Consent for publication

Not applicable.

Competing interests

The authors have no conflicts of interest to disclose.

Author details

¹Massachusetts General Hospital, Institute of Health Professionals, Boston, MA, USA. ²Harvard Medical School, Boston, MA, USA. ³Massachusetts General Hospital, 55 Fruit Street, Boston, MA 02114, USA. ⁴Massachusetts General Hospital, Mucosal Immunology and Biology Research Center, Boston, MA, USA. ⁵Department of Pediatric Emergency Medicine, Holtz's Children's Hospital, Miami, FL, USA. ⁶Department of Surgery, University of Florida, Gainesville, FL, USA. ⁷Department of Pediatrics, Johns Hopkins Hospital, Baltimore, MD, USA. ⁸Department of Surgery, Massachusetts General Hospital, Center for Engineering in Medicine, Boston, MA, USA. ⁹Shriners Burn Hospital, Boston, MA, USA.

Received: 2 March 2022 Accepted: 20 June 2022

Published online: 04 July 2022

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