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Multisystem Inflammatory Syndrome in Infants <12 months of Age, United States, May 2020–January 2021

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Abstract

Background: Multisystem inflammatory syndrome in children (MIS-C), temporally associated with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has been identified in infants <12 months old. Clinical characteristics and follow-up data of MIS-C in infants have not been well described. We sought to describe the clinical course, laboratory findings, therapeutics and outcomes among infants diagnosed with MIS-C.

Methods: Infants of age <12 months with MIS-C were identified by reports to the CDC's MIS-C national surveillance system. Data were obtained on clinical signs and symptoms, complications,

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treatment, laboratory and imaging findings, and diagnostic SARS-CoV-2 testing. Jurisdictions that reported 2 or more infants were approached to participate in evaluation of outcomes of MIS-C.

Results: Eighty-five infants with MIS-C were identified and 83 (97.6%) tested positive for SARS-CoV-2 infection; median age was 7.7 months. Rash (62.4%), diarrhea (55.3%) and vomiting (55.3%) were the most common signs and symptoms reported. Other clinical findings included hypotension (21.2%), pneumonia (21.2%) and coronary artery dilatation or aneurysm (13.9%). Laboratory abnormalities included elevated C-reactive protein, ferritin, d-dimer and fibrinogen. Twenty-three infants had follow-up data; 3 of the 14 patients who received a follow-up echocardiogram had cardiac abnormalities during or after hospitalization. Nine infants had elevated inflammatory markers up to 98 days postdischarge. One infant (1.2%) died after experiencing multisystem organ failure secondary to MIS-C.

Conclusions: Infants appear to have a milder course of MIS-C than older children with resolution of their illness after hospital discharge. The full clinical picture of MIS-C across the pediatric age spectrum is evolving.

Keywords

multisystem inflammatory syndrome in infants; multisystem inflammatory syndrome in children (MIS-C); COVID-19; Kawasaki Disease; SARS-CoV-2

In April 2020, a cluster of children with hyperinflammatory shock and features similar to Kawasaki disease (KD) was identified in the United Kingdom.[1–3] In May 2020, patients presenting with similar manifestations were identified in New York and Bergamo, Italy among children who tested positive for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus that causes coronavirus disease 2019 (COVID-19).[4,5] The Centers for Disease Control and Prevention (CDC) established a case definition[6] for this novel illness and coined the term multisystem inflammatory syndrome in children (MIS-C). The illness is temporally associated with SARS-CoV-2 infection and is characterized by fever, multiorgan dysfunction and elevated markers of inflammation.[7] Since issuing an alert to clinicians on May 14, 2020 (HAN), CDC has received reports of more than >2000 patients meeting the case definition for MIS-C among persons <21 years of age.[3,6]

A systematic review of the literature suggested that children represent <5% of diagnosed cases of COVID-19, and usually present with milder forms of the disease.[8,9] Infants <12 months of age usually present with mild or asymptomatic COVID-19, with the most common symptoms being fever, gastrointestinal symptoms, cough or tachypnea.[10–14]

The occurrence of MIS-C in infants has been reported in aggregate with older children and adolescents.[4,15–18] Among published case reports,[19,20] no studies have focused solely on describing the clinical characteristics of MIS-C in infants <12 months of age. The aim of the present study was to describe the demographic characteristics, clinical presentation and course, laboratory findings, therapeutics and outcomes among infants diagnosed with MIS-C and to compare them with the larger MIS-C surveillance cohort of patients <21 years of age.

METHODS

Following a CDC request to report all cases of MIS-C, local, state and territorial health departments used a standardized case report form (CRF) to report patients suspected of having MIS-C to CDC during May 2020–January 2021.[21] Patients' illnesses were evaluated to ensure they met the MIS-C case definition: age <21 years, fever, laboratory evidence of inflammation, evidence of clinically severe illness requiring hospitalization with 2 or more organ system involvement, no alternative diagnosis and either laboratory testing positive for SARS-CoV-2 or exposure to a person with suspected or confirmed SARS-CoV-2 infection.[21] Infants <12 months of age at the date of MIS-C onset who met the CDC MIS-C case definition were included in the study. They represented a subset of patients identified in the surveillance system. Data described in the analysis included clinical signs and symptoms, complications, treatment, laboratory and imaging findings, and results of diagnostic testing for SARS-CoV-2.

State, local and territorial public health jurisdictions submitting MIS-C case reports for ≥2 infants <12 months of age were invited to participate in a 3-month follow-up portion of the study. Additional data from follow-up appointments with the patient's primary care provider, specialty provider(s), imaging or laboratory data were collected using a supplemental follow-up MIS CRF, used both for initial and follow-up data submission.[21] Review of the MIS-C hospitalization data for the infants participating in the follow-up study was requested to ensure missing information was collected when available. Laboratory data from the infant's hospital admission were compared with the values found on the follow-up. For comparison, laboratory normal ranges reported in The Harriet Lane Handbook were used.[22] Coronary artery aneurysms or dilatations were reported on the basis of description or diagnosis of these conditions on echocardiograms (ECHOs) and/or reported z scores >2.0. Statistical analyses were performed using SAS version 9.4 (https://www.sas.com). This activity was determined to meet the requirements of public health surveillance as defined in 45 CFR 46.102(1)(2) (* 45 C.F.R. part 46, 21 C.F.R. part 56; 42 U.S.C. Sect. 241(d); 5 U.S.C. Sect. 552a; 44 U.S.C. Sect. 3501 et seq.).

RESULTS

During the study period, CDC received 2060 reports of persons <21 years of age who had an illness that met the case definition for MIS-C; 85 (4.1%) of these patients were <12 months of age. Race and ethnicity data were reported for 77 (90.6%) infants; 40.3% were Hispanic, 22.1% non-Hispanic Black, 26.0% non-Hispanic White, and 3.9% classified as multiple races or Other race (Table 1). The median age of the infants was 7.7 months (range, 14 days–11.96 months).

The median time from symptom onset to hospital admission for the 85 infants was 3 days (interquartile range [IQR] 1.5–5) (Table 1). Twenty-eight patients (32.9%) required ICU admission. A total of 83 of 85 infants (97.6%) tested positive for SARS-CoV-2 infection, the other 2 infants had an epidemiologic link to someone with SARS-CoV-2 infection. Fifty-one of 82 (62.2%) patients tested by polymerase chain reaction had positive results, 54 (91.5%) of 59 patients who received serology testing had positive results, and the one infant who

only received antigen testing had a positive result. Most of the infants recovered clinically after a median of 4 days in the hospital and all but 4 were discharged at the time of analysis, 3 were still admitted and one 10-month-old infant (1.2%) with a complex medical history including congenital malformations who died after experiencing multisystem organ failure secondary to MIS-C.

Common signs and symptoms in infants with MIS-C included rash 53 (62.4%), diarrhea 47 (55.3%), vomiting 47 (55.3%), conjunctival injection 37 (43.5%), cough 36 (42.4%), mucocutaneous lesions 23 (27.1%) and shortness of breath 20 (23.5%) (Table 1). Common complications included hypotension in 18 (21.2%) (11 [12.9%] with shock), pneumonia in 18 (21.2%), coronary artery dilation or aneurysm in 10 (13.9%) and cardiac dysfunction in 7 (9.7%) (Table 1).

During hospitalization, an ECHO was obtained for 72 infants (84.7%); 7 (9.7%) had some degree of ventricular dysfunction. Chest imaging was performed in 63 infants (74.1%); 36 (57.1%) were abnormal. Abnormal chest imaging results included opacities and cardiomegaly. Seventeen infants had abdominal imaging performed; 58.8% had abnormal results. Of infants with abnormal imaging, the most frequently reported findings were edema, hepatomegaly, gallbladder thickening or sludge.

Of 67 infants who received treatment, 4 (6.0%) infants were intubated and placed on mechanical ventilation. Forty-nine infants (73.1%) were treated with intravenous immunoglobulin and 45 (67.2%) with steroids (Table 1).

Hematologic abnormalities included elevated C-reactive protein (CRP), ferritin, d-dimer and fibrinogen. Among 76 infants with reported CRP levels, 74 (97.4%) had elevated levels. Ferritin was elevated in 39 (58.2%) of 67 infants, D-dimers were elevated in 60 (98.4%) out of 61 infants tested, and 33 (58.9%) of 56 had elevated fibrinogen. Evidence of cardiac abnormalities were defined as elevated levels of troponin, proBNP and brain natriuretic peptide (BNP). Elevation of troponin occurred in 21 (30.4%) of 69 infants with testing performed, proBNP was elevated in 23 (76.7%) of 30 infants and 25 (75.8%) of 33 infants had elevated BNP (Table 2).

Twenty-three (27.1%) of the 85 infants with MIS-C, had follow-up records available from a variety of sources (Table 3). Eight patients (34.8%) were evaluated by a primary care provider, 8 (34.8%) by a cardiologist, and 4 (25.0%) patients by a rheumatologist. For 9 (39.1%) infants, follow-up information was obtained for MIS-C discharge visits from “other” providers (emergency department, follow-up MIS-C imaging appointments, and infectious disease providers). Of those evaluated by a primary care provider, physical examination identified fever and periorbital edema in one patient. Four patients (17.4%) had laboratory data without provider notes. Nine patients (39.1%) had only one follow-up visit recorded, 7 (30.4%) had 2, and 7 (30.4%) ≥3 follow-up visits recorded. The median length of time between hospital discharge and first follow-up visit was 16 (IQR 4–43) days. Of the 14 patients (60.9%) who received a follow-up ECHO, most had normal results: 11 infants had either a normal ECHO or had unknown ECHO data during MIS-C hospitalization. Three infants had an abnormal ECHO. One patient had conjunctival injection on follow-up. Eleven

patients (47.8%) who were discharged home on medication(s) were still on medication at the time of follow-up; the medications included aspirin and steroids.

Among the 23 infants with follow-up data, 15 (65.2%) had follow-up laboratory tests performed; for 14 infants with complete reported date information, laboratory tests were performed a median of 16 days (IQR 6–43 days) after hospital discharge. Nine infants had elevated inflammatory markers. Tests included CRP, ferritin and d-dimer. CRP was evaluated in 11 infants with 4 patients reporting continued elevated values (36.4%), median 0.45 mg/dL. D-dimer was elevated in 6 of 8 infants (75.0%), median 0.51 mg/L. Ferritin level was normal in all 6 (0.0%) of the infants tested, median 92.5 ng/mL and one patient had thrombocytosis and elevated liver enzymes (Table 2).

DISCUSSION

Infants accounted for about 4% of the MIS-C patients reported to CDC's national surveillance system during May 2020–January 2021, and they appear to have a milder course of MIS-C than older children. Outcome data were compared with previously described MIS-C patients <21 years of age reported to the MIS-C surveillance system,[23] a lower proportion of infants <12 months of age had shock, hypotension, cardiac manifestations and admission for intensive care (Table 4). Shock was reported in 12.9% versus 36.8% and hypotension in 21.2% versus 50.8% of infants and all MIS-C patients, respectively (Table 4). Most cardiac complications were less common in infants than the MIS-C cohort in all ages, including coronary artery dilatation or aneurysms (13.9% vs. 16.5%), cardiac dysfunction (9.7% vs. 31.0%), and myocarditis (4.7% vs. 17.3%) (Table 4). Infants had lower ICU admission rates; one-third of infants required care in the ICU compared with 58.2% for all MIS-C patients <21 years of age (Table 4).

We found a high proportion of Hispanic and non-Hispanic Black infants disproportionately affected by MIS-C. In the follow-up portion of the study, non-Hispanic White patients were more likely to receive follow-up care than non-Hispanic Black patients. Reasons for this are thought to be multifactorial and, for this age group in particular, exposure to COVID-19 was likely from a caregiver.[24,25]

MIS-C diagnosis in some infants could have been confused with acute COVID-19 or KD. However, the infant MIS-C patients tested positive for SARS-CoV-2 and had illness manifestations more severe than that of KD. KD more commonly affects Asian/Pacific Islander children. Estimates vary by study, but approximately 17% of KD cases in the United States occur in Asian/Pacific Islanders,[26] and in our study, only 2 (2.6%) of MIS-C patients <12 months of age were Asian/Pacific Islanders. Less than 4% of KD patients require ICU admission, whereas 33% of the infants in this MIS-C study required ICU care.[27]

Our study is subject to several limitations. First, MIS-C in infants could have been reported at a lower rate than in older children perhaps due to either a lower incidence or less awareness of MIS-C in this population and, therefore, decreased diagnosis and reporting. Second, because infants seem to have a less severe clinical picture of MIS-C, fewer follow-up visits might have been scheduled. In addition, the records of some follow-up

evaluations, particularly by primary care providers, might not have been captured by the health department. It is also possible that some of the patients may have attended less follow-up visits. It was challenging to gather follow-up records, especially from primary care providers who might not have been within the original hospital system. Third, selection bias might have played a role in the follow-up portion of the study because only jurisdictions that reported ≥2 infant cases were included.

CONCLUSION

The full clinical picture of MIS-C across the pediatric age spectrum is evolving. The present study is the first to examine both the clinical manifestation of MIS-C and outcomes among US infants <12 months of age. Improving consistent access for follow-up primary and specialty care is critical to addressing health disparities, particularly among Hispanic and non-Hispanic Black infants. More patient follow-up data will inform medical and public health providers about potential long-term complications of MIS-C in infants. A standardized approach is needed to evaluate any long-term complications to help ensure provision of comprehensive care.

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TABLE 1.

Clinical Characteristics of Infants (N = 85) With Multisystem Inflammatory Syndrome in Children (MIS-C)—United States, May 2020–January 2021

Characteristic	No. (%)
Sex	
Female	36 (42.4)
Male	49 (57.6)
Age (months), median (range)	7.7 (14 days–11.96 months)
Race/ethnicity	
Hispanic	31 (40.3)
Black, non-Hispanic	17 (22.1)
White, non-Hispanic	20 (26.0)
Other	3 (3.9)
Multiple	3 (3.9)
Asian	2 (2.6)
American Indian/Alaskan Native	1 (1.3)
Native Hawaiian/Pacific Islander	0 (0.0)
Unknown	8 (−)
Outcome	
Died	1 (1.3)
Discharged	73 (94.8)
Still Admitted	3 (3.9)
Missing	8 (−)
Days between symptom onset and hospital admission, median (IQR)	3 (1.5–5)
Days in hospital, median (IQR)	4 (2–6)
1	4 (5.6)
2–7	59 (81.9)
8–14	7 (9.7)
≥15	2 (2.8)
Missing	13 (−)
ICU admission	28 (32.9)
Days in ICU, median (IQR)	3 (1.5–5)
Underlying medical conditions	10 (11.8)
Seizures	1 (1.2)
Congenital heart disease	3 (3.5)
Chronic lung disease	4 (4.7)
Other congenital malformations *	4 (4.7)
Clinical characteristic	
No. organ systems involved	
2–3	22 (25.9)
4–5	55 (64.7)
≥6	8 (9.4)

Characteristic	No. (%)
Missing	0 (−)
Days with fever, median (IQR)	5 (4–6)
Kawasaki disease[†]	4 (4.7)
Signs and symptoms	
Rash	53 (62.4)
Diarrhea	47 (55.3)
Vomiting	47 (55.3)
Conjunctival injection	37 (43.5)
Cough	36 (42.4)
Mucocutaneous lesions	23 (27.1)
Shortness of breath	20 (23.5)
Periorbital edema	13 (15.3)
Cervical lymphadenopathy >1.5 cm diameter	7 (8.2)
Complications	
Hypotension	18 (21.2)
Pneumonia[§]	18 (21.2)
Coronary artery dilatation or aneurysm[¶]	10 (13.9)
Shock	11(12.9)
Mitral regurgitation[¶,**]	7 (9.7)
Cardiac dysfunction[¶]	7 (9.7)
Acute kidney injury	5 (5.9)
Myocarditis	4 (5.6)
Encephalopathy	2 (2.4)
Renal failure	0 (0.0)
Abdominal imaging	
Imaging done	17 (20.0)
Normal[††]	7 (41.2)
Other[††,§§]	4 (23.5)
Chest imaging	
Imaging done	63 (74.1)
Normal[††]	27 (42.9)
Other[††,¶¶]	16 (25.4)
SARS-CoV-2 testing	
Any laboratory test done	85 (100.0)
Any positive laboratory test[***]	83 (97.6)
PCR positive/serology negative, not done, or missing[†††]	28 (32.9)
Serology positive/PCR negative, not done[§§§]	31 (36.5)
PCR positive/serology positive	23 (27.1)
Epidemiologic link only, with no testing	2 (2.4)

Characteristic	No. (%)
Treatment[¶¶¶]	
IVIG[****]	49 (73.1)
Steroids	45 (67.2)
Antiplatelet medication	51 (76.1)
Anticoagulation medication	21 (31.3)
Vasoactive medications	16 (23.9)
Respiratory support, any	16 (23.9)
Intubation and mechanical ventilation	4 (6.0)
Immune modulators	9 (13.4)
Dialysis	0 (0.0)

[*] Other congenital malformations include chromosomal abnormality, congenital brain and heart defects, seizure disorder, and growth hormone deficiency.

[†] Patient had fever, rash, conjunctival injection, cervical lymphadenopathy >1.5 cm diameter, and mucocutaneous lesions or provider indicated the infant had Kawasaki disease (KD). If including suspect KD cases, defined as having at least 3 of the 4 symptoms (rash, conjunctival injection, cervical lymphadenopathy >1.5 cm diameter and mucocutaneous lesions), and including incomplete KD cases, defined as having fewer than 4 of these symptoms plus either having evidence of either coronary artery aneurysms or coronary artery dilatation, then the number of suspect KD cases increases from 4 to 10 of the 85 infants.

[§] Information about pneumonia was collected on the case report form under signs and symptoms, complications, or chest imaging.

[¶] Percentages calculated among 72 persons with an echocardiogram performed.

[**] 3 (4.2%) mild, 2 (2.8%) moderate, 0 (0%) severe gradings, 2 unspecified.

[††] Percentages calculated among persons with imaging performed.

[§§] Other abdominal imaging results include edema and hepatomegaly.

[¶¶] Other chest imaging results include opacities and cardiomegaly.

[***] Antigen-positive result only in 1 infant, out of 1 infant tested by antigen. 82 had a PCR test performed; 59 had a serology test performed.

[†††] Five serology-negative and for 23 infants, serology not done.

[§§§] 29 PCR negative and for 2 infants, PCR was not done.

[¶¶¶] Percentages calculated among 67 persons who received treatment.

[****] Ten patients had a second IVIG treatment.

SARS-CoV-2 indicates severe acute respiratory syndrome coronavirus 2; IQR, interquartile range; IVIG, intravenous immunoglobulin; PCR, polymerase chain reaction.

TABLE 2.

Laboratory Values for Infants with Multisystem Inflammatory Syndrome in Children (MIS-C) During Hospitalization and Follow-Up Evaluation—United States, May 2020–January 2021

Laboratory Test	No. With Values* Reported	Median (IQR)	No. Tested	No. With Elevated Levels† Reported (%)
CRP, peak (mg/dL)	74	8.65 (2.5–15.8)	76	74 (97.4)
Ferritin, peak (ng/mL)	67	224 (135–412)	67	39 (58.2)
Troponin, peak (ng/mL)	61	0.01 (0.01–0.05)	69	21 (30.4)
D-dimer, peak (mg/L)	57	1.38 (0.75–2.15)	61	60 (98.4)
Fibrinogen, peak (mg/dL)	54	456 (293–566)	56	33 (58.9)
proBNP, peak (ng/L)	27	1030 (311–2684)	30	23 (76.7)
BNP, peak (pg/mL)	32	365.5 (119–822.6)	33	25 (75.8)
IL-6, peak (pg/mL)	7	13.2 (9–41.2)	8	8 (100.0)
Follow-up data				
Laboratory test¶				
CRP, peak (mg/dL)	10	0.45 (0.4–1.1)	11	4 (36.4)
Ferritin, peak (ng/mL)	6	92.5 (82.0–101.0)	6	0 (0.0)
D-dimer, peak (mg/L)	6	0.51 (0.125–0.650)	8	6 (75.0)

*Values reported: infants with quantitative values reported. This did not include qualitative results that indicated only “elevated” levels.

†Elevated levels: infants that had either laboratory values reported that were elevated or the laboratory values were not reported but were marked as elevated on the case report form checkbox.

¶Nine infants had elevated laboratories.

CRP indicates C-reactive protein; IQR, interquartile range..

TABLE 3.

Follow-Up Findings for Infants (N = 23) with Multisystem Inflammatory Syndrome in Children (MIS-C)

Characteristic, N = 23	No.
Sex	
Female	6 (26.1)
Male	8 (34.8)
Race/ethnicity	
Hispanic	12 (52.2)
Black, non-Hispanic	3 (13.0)
White, non-Hispanic	4 (17.4)
Multiple	3 (13.0)
Missing	1 (4.3)
Patient outcome from initial hospital admission	
Died	0 (0.0)
Discharged	21 (91.3)
Missing	2 (8.7)
Provider type for follow-up [*]	
Primary care provider	8 (34.8)
Cardiology	8 (34.8)
Rheumatology	4 (17.4)
Laboratory tests only	4 (17.4)
Other [†]	9 (39.1)
No. follow-up visits	
1	9 (39.1)
2	7 (30.4)
≥3	7 (30.4)
Days between hospital discharge and first follow-up visit, median (IQR)	16 (4-43)
Normal ECHO [§]	11 (78.6)
Still on discharge medication	11 (47.8)
Aspirin	10 (43.5)
Steroids	2 (8.7)

Eleven infants that had normal ECHOs on follow-up had initial normal or unknown ECHO data. Three infants with abnormal ECHOs had evidence of the following: coronary artery aneurysms, coronary artery dilatation, and/or max coronary artery Z-score. One infant with abnormal ECHO had the following: trivial tricuspid valve insufficiency, trivial pulmonic valve insufficiency, possible right ventricular hypertrophy.

[*] Since some patients had multiple follow-up visits, provider type is not mutually exclusive.

[†] Other includes emergency department, imaging, infectious disease, vaccinations or unspecified.

[§] Percentage calculated among 14 patients with ECHO data.

ECHO indicates echocardiograms.

TABLE 4.

Clinical characteristics of infants (N = 85) with multisystem inflammatory syndrome in children (MIS-C) compared with a previously published cohort[23] of MIS-C cases (N = 1733)

Characteristic	Infant MIS-C cases, n = 85 No. (%)	All MIS-C cases, n = 1733 No. (%)
ICU admission	28 (32.9)	1009 (58.2)
Complications		
Hypotension	18 (21.2)	880 (50.8)
Pneumonia *	18 (21.2)	330 (19)
Coronary artery dilatation or aneurysm †,§	10 (13.9)	258 (16.5)
Shock	11(12.9)	638 (36.8)
Cardiac dysfunction †,§	7 (9.7)	484 (31.0)
Myocarditis	4 (4.7)	300 (17.3)

* Information about pneumonia was collected on the case report form under signs and symptoms, complications, or chest imaging.

† For the infant cohort percentages calculated among 72 persons with an echocardiogram performed.

§ For all MIS-C cases, cohort percentages were calculated among 1563 persons with an echocardiogram performed.

MIS-C, multisystem inflammatory syndrome in children.