Multisystem Inflammatory Syndrome in Children—United States, February 2020–July 2021

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Summary:

In 4,470 MIS-C patients reported to national surveillance with onset date through July 31, 2021, cardiovascular complications and clinical outcomes including length of hospitalization, receipt of ECMO, and death decreased over time across the first 3 pandemic waves of MIS-C.

Abstract

Background: Multisystem inflammatory syndrome in children (MIS-C) is a severe hyperinflammatory condition in persons aged <21 years associated with antecedent SARS-CoV-2 infection. Our objective was to describe MIS-C cases reported to CDC's national surveillance since the COVID-19 pandemic began.

Methods: We included patients meeting the MIS-C case definition with onset date from February 19, 2020 through July 31, 2021, using CDC's MIS-C case report form, which collects information on demographics, clinical presentation, and laboratory results. Trends over time across 3 MIS-C pandemic waves were assessed using Cochran-Armitage test for categorical and Jonckheere-Terpstra test for continuous variables.

Results: Of 4,901 reported cases, 4,470 met inclusion criteria. Median patient age increased over time (P<0.001), with a median of 9 years (interquartile range, 5–13 years) during the most recent (third) wave. Male predominance also increased (62% in third wave, P<0.001). A significant (P<0.001) increase in severe hematologic and gastrointestinal involvement was observed across the study period. Frequency of several cardiovascular complications (i.e., cardiac dysfunction, myocarditis, and shock/ vasopressor receipt) and renal failure declined (P<0.001). Provision of critical care including mechanical ventilation (P<0.001) and extracorporeal membrane oxygenation (ECMO; P=0.046) decreased, as did duration of hospitalization and mortality (each P<0.001).

Conclusions: Over the first 3 pandemic waves of MIS-C in the United States, cardiovascular complications and clinical outcomes including length of hospitalization, receipt of ECMO, and death decreased over time. These data serve as a baseline for monitoring future trends associated with SARS-CoV-2 B.1.617.2 (Delta) or other variants and increased COVID-19 vaccination among children.

Keywords: multisystem inflammatory syndrome in children, COVID-19, child, epidemiology

Background

Multisystem inflammatory syndrome in children (MIS-C) is a severe hyperinflammatory condition in children and adolescents associated with antecedent SARS-CoV-2 infection, characterized by fever, systemic inflammation, and multisystem organ involvement [1-6]. Clinicians in the United Kingdom first described severe inflammation in previously healthy children after acute SARS-CoV-2 infection in April 2020, and this illness was soon recognized elsewhere including the United States [5-10]. In May 2020, the US Centers for Disease Control and Prevention (CDC) issued a health advisory, outlined a MIS-C case definition, and asked clinicians to report suspected cases to local and state health departments [10]. The CDC established a national reporting platform to systematically collect data on suspected cases of MIS-C from health departments. MIS-C incidence in 7 jurisdictions from April to June 2020 was 1 case of MIS-C per approximately 3,200 SARS-CoV-2 infections among persons aged <21 years [11].

MIS-C represents a severe complication of COVID-19 in children, although initial SARS-CoV-2 infection in most persons with MIS-C is mild or asymptomatic [12]. MIS-C generally occurs 2–6 weeks after SARS-CoV-2 infection, and higher MIS-C incidence closely follows peaks of reported SARS-CoV-2 circulation [2, 5, 13]. Following issue of Emergency Use Authorizations for the Pfizer-BioNTech COVID-19 vaccine, the Advisory Committee on Immunization Practices issued interim recommendations for use of the vaccine in persons ≥16 years on December 12, 2020 [14]; for adolescents aged ≥12 years on May 12, 2021 [15]; and for children aged 5–11 years, the group comprising the largest burden of MIS-C, on November 2, 2021 [11, 13, 16]. Variable adherence to recommended preventive strategies, including consistent and correct mask use, physical distancing, and vaccination among eligible persons, places unvaccinated children at risk for SARS-CoV-2 infection and subsequent development of MIS-C [17, 18]. This was especially important as the United States experienced a rise in circulation of highly

transmissible SARS-CoV-2 variants including the B.1.617.2 (Delta) variant, which comprised <15% of circulating variants as of June 5, 2021, and rose to >95% by July 31, 2021 [19, 20].

In this analysis we summarize over 4,000 MIS-C cases reported to CDC's national surveillance since the start of the COVID-19 pandemic; cases reported through January 2021 have been summarized previously [13]. This period represents surveillance prior to and including the first months of authorization and recommendation for vaccination for persons aged ≥12 years. We present patient characteristics, detailed clinical and radiologic features, illness management, and clinical outcomes by each of the three waves of MIS-C over the study period.

Methods

Local, state, and territorial health departments reported cases using a standardized case report form based on medical chart abstractions performed by clinicians, hospital staff, or health department staff (**Supplement 1**). Patients' illnesses were evaluated to confirm they met the CDC MIS-C case definition: 1) clinically severe illness requiring hospitalization in persons aged <21 years, 2) fever ≥38°C for ≥24 hours or report of subjective fever for ≥24 hours, 3) laboratory evidence of inflammation, 4) multisystem (≥2) organ involvement, 5) laboratory evidence of acute or previous SARS-CoV-2 infection by reverse transcription polymerase chain reaction (RT-PCR), serology, or antigen test, or known COVID-19 exposure within 4 weeks of symptom onset, and 6) no alternative plausible diagnosis [21]. Information collected included patient demographics, clinical manifestations, complications, illness management, imaging studies, laboratory test results, outcomes, and vaccination status (added to case report form May 21, 2021).

To account for delays in reporting and maximize data completeness, we included patients with an MIS-C onset date on or before July 31, 2021 who were reported on or before August 18, 2021. Patients with known SARS-CoV-2 exposure without subsequent laboratory confirmation of infection were excluded from this analysis because of concerns about potential misclassification. We performed

clinical review of free-text responses and supplemented patient comorbidities by classifying into available categorical variables or, for obesity, calculated body mass index using national reference standards for those with available height, weight, sex, and age information [22]. Race and ethnicity data were obtained from medical records as documented at time of hospitalization and categorized in accordance with previously established methods as missing race and ethnicity data accounted for 5.8% of patients in our cohort [23].

To assess case characteristics and outcomes over time, we reviewed the epidemic curve of MIS-C illness onset dates. If onset date was unavailable, fever onset or hospitalization admission date was used as a proxy. We identified three peaks of reported MIS-C cases and two nadirs (**Figure 1**). We defined the three time periods or "waves" of MIS-C activity in the pandemic with respect to timing of MIS-C symptom onset dates among cases to (1) February 19 through June 28, 2020, (2) June 29 through October 17, 2020, and (3) October 18, 2020 through July 31, 2021. Geographic regions were categorized in accordance with the four US census regions [24]. Intensive care unit (ICU) admission was defined as having a documented date of ICU admission or known length of ICU stay or having received ICU-level care, including mechanical ventilation, vasopressor support, or extracorporeal membranous oxygenation (ECMO). We defined values for lymphopenia and thrombocytopenia using age standards [25]. We adapted previously established frameworks to describe severe organ-system involvement (**Supplement 2**)[1, 26]. We performed clinical review and supplemented radiographic findings using free-text responses when available. Analyses of laboratory markers of inflammation were performed only on those with available data collected in section 6 of the case report form (**Supplement 1**).

Using SAS version 9.4 (SAS Institute, Cary, NC) we calculated the frequency of clinical features, relevant laboratory findings, and treatments among patients stratified by wave of MIS-C onset. Continuous variables were expressed as medians and interquartile ranges (IQRs); trends in median

values over time were assessed through the Jonckheere-Terpstra test. Categorical variables were expressed as counts and percentages; trends over time were assessed through the Cochran-Armitage test. Two-sided P values were considered significant at $\alpha<0.05$.

This activity was reviewed by CDC, was determined to meet the requirements of public health surveillance and was conducted in consistence with applicable federal law and CDC policy (45 C.F.R. part 46.102(l)(2), 21 C.F.R. part 56; 42 U.S.C. §241(d); 5 U.S.C. §552a; 44 U.S.C. §3501 et seq) [27, 28].

Results

Clinical characteristics

Out of 4,901 total patients reported with suspected MIS-C, we excluded 249 patients who did not meet the case definition, 87 with missing illness onset date or onset after the study period, and 95 who otherwise met clinical criteria of the CDC case definition but who lacked laboratory evidence of SARS-CoV-2 infection (**Supplements 3 and 4**). The 4,470 included cases were reported from 49 state health departments, the District of Columbia, New York City, and Puerto Rico. Median patient age for the overall cohort of MIS-C patients was 9 years ([IQR], 5–13 years); 59.9% were male (**Table 1**). Of patients with complete race and ethnicity information, 31.1% were non-Hispanic Black, 30.6% Hispanic/Latino, and 28.9% non-Hispanic White. Underlying medical conditions were reported for 37.6% of MIS-C patients; obesity (25.1%) and chronic lung disease including asthma (9.6%) were most frequent among all MIS-C patients.

All patients with MIS-C had reported fever as indicated by the case definition. The median reported duration of fever was 5 days (IQR: 4-7 days). The most common additional signs and symptoms included abdominal pain (68.5%), vomiting (66.6%), rash (55.2%), conjunctival injection (55.4%), diarrhea (53.8%), and hypotension (51.7%) (**Table 2**). Seventy-four percent of MIS-C patients reported mucocutaneous involvement (e.g., skin rash, mucocutaneous lesions, and/or conjunctivitis).

Many MIS-C patients had severe cardiovascular involvement (79.6%) including cardiac dysfunction (30.9%), particularly left ventricular dysfunction (27.4%), coronary artery aneurysm or dilatation (16.7%), myocarditis (14.6%), and congestive heart failure (5.4%) (**Table 2**). Other severe cardiovascular manifestations included shock or receipt of vasopressor medication (45.1%), elevated cardiac laboratory tests (i.e., troponin [52.7%] or brain natriuretic peptide ≥ 1000 pg/mL [36.2%]) and receipt of ECMO support (1.5%). Sixty percent of MIS-C patients experienced severe hematologic involvement, including thrombocytopenia (42.3%) and lymphopenia (35.3%). Severe respiratory involvement (43.9%), including pneumonia (23.4%), pleural effusion (21.3%), and acute respiratory distress syndrome (5.8%), was reported less frequently. Receipt of supplemental oxygen, including high-flow nasal cannula (16.8%), non-invasive mechanical ventilation (8.2%), and invasive mechanical ventilation (9.4%) were also less common. One quarter of MIS-C patients had signs of severe gastrointestinal involvement (25.3%), with abnormal findings on abdominal imaging including free fluid (24.3%), colitis/enteritis (10.2%), mesenteric adenitis (28.9%), hepatomegaly/splenomegaly (10.6%), and inflammation of the gallbladder (7.3%), and appendix (4.1%). Severe renal complications (20.3%), including acute kidney injury (19.0%), renal failure (3.3%) and receipt of dialysis (0.9%), and severe neurologic complications (8.5%), including meningitis (5.3%), encephalopathy (4.0%), and stroke (0.6%), were rare (**Table 2**).

Most MIS-C patients underwent radiography including echocardiography (94%) and chest X-ray or computed tomography (71%), and 42% underwent abdominal imaging. Over half of those for whom these radiographic studies were performed had abnormal findings, including 59% of those who underwent echocardiography, 55% of those who underwent chest imaging, and 61% of those who underwent abdominal imaging. Among laboratory markers of inflammation, C-reactive protein (CRP) (99.3%) and ferritin (87.2%) were frequently elevated among patients tested. Nearly all of the 3,997 MIS-C patients who had serologic testing for SARS-CoV-2 antibodies performed tested positive (97.7%);

52.6% of the 4,233 MIS-C patients who had SARS-CoV-2 RT-PCR performed tested positive (**Table 2**). Vaccination status was reported for 4% of MIS-C patients, only 0.4% of whom were vaccinated.

Characteristics and outcomes over time

There were three defined waves of MIS-C illness, with most cases (68.3%) occurring during the third wave, compared with the first (17.2%) and second (14.5%) (**Table 1; Figure 1**). By region, the Northeast had the highest proportion of cases in the first wave (52.2%) followed by a significant decrease over the remaining waves (P<0.001) (**Table 1**). By the third wave, cases were spread similarly across the Midwest (26%), South (32%), and West (27%), whereas the Northeast reported only 14% of cases.

The proportion of patients aged 12–15 years significantly increased over time (P<0.001) (**Table 1**). The proportion of males and of patients who were non-Hispanic White increased significantly with successive waves (P <0.001 for each), and were 62% and 35%, respectively, by the third wave. The proportion of MIS-C patients with each reported underlying medical condition did not differ significantly over time.

Figure 2 illustrates organ system involvement (defined in **Supplement 2**) over the three MIS-C waves. The proportion of patients reported to have severe hematologic and gastrointestinal involvement increased over the three waves (P<0.001 each). There were no other consistent trends for the remaining organ systems. Symptoms reported more frequently over time included abdominal pain, headache, myalgia, and neck pain (P<0.001) (**Table 2, Supplement 5**). Some cardiovascular complications, including cardiac dysfunction, myocarditis, and shock/use of vasopressor medications were significantly less frequent with successive waves. The proportion of patients receiving ECMO support decreased over time (P<0.001) (**Table 2**).

The proportion of those with severe respiratory complications peaked during the second wave, with pneumonia, pleural effusion, and acute respiratory distress syndrome the highest in the second wave (31%, 26%, and 8%, respectively). However, the proportion of patients receiving invasive mechanical ventilation trended downward over the study period (P<0.001) (**Table 2**).

The proportion of MIS-C patients with a reported elevated troponin, d-dimer and presence of lymphopenia and thrombocytopenia increased over time (P<0.001). The proportion of patients who had elevated CRP and elevated fibrinogen among those tested remained similarly high across the MIS-C pandemic waves. The number of MIS-C patients testing positive for SARS-CoV-2 on RT-PCR was highest during the second wave while positive serologic testing for SARS-CoV-2 antibody remained high across all three waves. (**Table 2**).

Overall, MIS-C patients were hospitalized for a median of 5 days (IQR: 4–8 days). Median ICU stay was 4 days (IQR: 2–6 days). Duration of hospitalization and ICU stay decreased over time (each P<0.001). Intravenous immunoglobulin (IVIG) (84.4%), steroids (76.7%), and immune modulators (20.9%) were commonly administered to patients during hospitalization**.** The proportion of cases that received IVIG and steroids increased significantly (each P<0.001) (**Figure 3**). Sixty-three percent of MIS-C patients were admitted to the ICU or received ICU-level care. Overall, 37 (0.8%) patients died, and the case fatality ratio among MIS-C patients decreased over the three waves (P<0.001).

Discussion

This study describes the largest cohort of MIS-C patients to date, including patients from nearly all reporting jurisdictions within the United States since MIS-C national surveillance began. MIS-C is an important complication of COVID-19 in children, with half of reported cases occurring among children aged 5–13 years. Over half of MIS-C patients were of Hispanic ethnicity or Black race, particularly in the first two MIS-C waves, similar to findings from previous studies [11, 29-31]. The proportion of non-

Hispanic White patients significantly increased over the course of the pandemic; similar racial and ethnic trends have been described in studies of hospitalized COVID-19 patients, which suggest that increased COVID-19 incidence among White persons and regional and temporal patterns may be contributors [32, 33]. Further investigation into the impact of spatiotemporal trends on the racial and ethnic distribution of MIS-C patients over time is warranted given these findings.

The MIS-C patient population had a similar proportion of children with preexisting underlying medical conditions across the three MIS-C waves. There were increasing trends reported in severe hematologic and severe gastrointestinal involvement; other organ system involvement did not differ substantially. These increasing trends may be the result of changes in reporting completeness (e.g., lymphopenia, thrombocytopenia) or changing testing practices for case identification (e.g., increase in receipt of abdominal imaging) [34]. For example, the proportion of patients who underwent abdominal imaging increased from 33.0% to 41.9% to 43.6% over the 3 waves (P<0.001). Reporting of other clinical findings may reflect improved awareness of MIS-C clinical features (e.g., neck pain) [35]. Thus, increasing trends may or may not reflect an actual increase in the proportion of children experiencing each sign or symptom.

The proportion of cases with cardiac dysfunction and myocarditis, conditions associated with severe outcomes of MIS-C [3], declined after the first wave. The duration of hospitalization and death also significantly decreased over time; these decreases in case fatality were previously described [26]. These observed decreases could be associated with several factors including reporting of milder MIS-C cases or earlier case identification as awareness of the condition increased, improvements in clinical management of MIS-C, changes in the SARS-CoV-2 virus, or some other combination of factors. For example, a previous analysis showed that treatment of MIS-C with IVIG plus glucocorticoids was associated with a lower risk of new or persistent cardiovascular dysfunction than treatment with IVIG alone [36]. We did find increases in the use of medications including IVIG and steroids over the

surveillance period. However, MIS-C national surveillance does not collect information related to the timing of treatments relative to clinical findings; therefore, it is not possible to estimate therapeutic effectiveness from these observational data.

Previous studies have described a respiratory subgroup of MIS-C cases phenotypically similar to patients with acute COVID-19 [4, 37]. This study found that the proportion of MIS-C patients with severe respiratory involvement and with a positive SARS-CoV-2 RT-PCR test followed similar patterns and were highest during the second wave of MIS-C illness. These findings may support the presence of a distinct MIS-C respiratory phenotype or the unintentional misclassification of patients with acute COVID-19 because of an overly sensitive case definition. It is not clear why this phenotype would increase in the second wave and then decrease in the third, although this may be influenced by changing SARS-CoV-2 testing and MIS-C reporting practices.

This study has several limitations. Not all MIS-C cases are reported to national surveillance, resulting in under-ascertainment. Data from April through June 2020 suggest that national surveillance detected approximately two-thirds of MIS-C cases in 7 jurisdictions when data were compared with an active hospital-based surveillance network [11]. Case identification, including diagnosis, testing, and management of patients can vary by jurisdiction. MIS-C case report forms require medical chart abstractions which are resource- and time-intensive and can contribute to delays or gaps in reporting, particularly during times of public health emergency and competing demands, and availability of medical records can vary by jurisdiction. The case report form does not include specific definitions of comorbidities, clinical signs/symptoms, or complications, which may result in subjective interpretation of questions and contribute to misclassification. Additionally, the staff abstracting medical records (e.g., health department staff, clinicians) could vary in training and experience by jurisdiction and result in lack of standardized reporting practices. MIS-C is not a nationally notifiable illness; reporting of cases is voluntary, and participation varies by jurisdiction and over time. Inconsistency in completion of case

reporting forms might have affected data completeness. Vaccination status was not routinely collected until May 21, 2021 and was not analyzed because of insufficient data. Access to SARS-CoV-2 testing at time of onset might have varied by region, by hospital, and over time. Finally, the CDC MIS-C case definition is broad, which might have led to the unintentional inclusion of patients with a history of COVID-19 experiencing other acute inflammatory illnesses such as severe acute COVID-19, Kawasaki Disease, and toxic shock syndrome.

In conclusion, MIS-C is a rare but severe complication of COVID-19 in children and adolescents, with a clinical presentation that has remained similar over the first year and a half of national MIS-C surveillance and outcomes such as length of hospitalization and death that have shown improvement over time. The ongoing transmission of SARS-CoV-2 and the emergence of potentially more severe and highly transmissible variants, such as the Delta variant, are likely to contribute to increased incidence of MIS-C following increased SARS-CoV-2 transmission in the United States. This U.S. surveillance summary describes clinical characteristics of MIS-C patients prior to widespread Delta variant circulation, and before vaccination was authorized and widespread among children and adolescents. These national surveillance data provide a baseline for future comparisons of the characteristics of MIS-C patients infected with B.1.617.2 (Delta) or other SARS-CoV-2 variants and for measuring the impact of increased COVID-19 vaccination coverage among children and adolescents.

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Table 1. Characteristics of Patients with MIS-C by Wave, United States, February 2020 to July 2021. The 3 time periods were (1) February 19, 2020 through June 28, 2020, (2) June 29, 2020 through October 17, 2020, and (3) October 18, 2020 through July 31, 2021.

Characteristic	All MIS-C cases (n= 4,470) No. (%)	MIS-C onset, No. (%)			
		Wave 1 (n= 649)	Wave 2 (n= 769)	Wave 3 (n= 3,052)	Test for trend p value[a]
Age group, years[b]					
<1	139 (3.1)	27 (4.2)	28 (3.6)	84 (2.8)	0.038
1-4	946 (21.2)	158 (24.3)	164 (21.4)	624 (20.5)	0.035
5-11	1,756 (39.3)	251 (38.7)	305 (39.7)	1,200 (39.4)	0.824
12-15	1,148 (25.7)	136 (21.0)	188 (24.5)	824 (27.0)	<0.001
16-20	477 (10.7)	77 (11.9)	83 (10.8)	317 (10.4)	0.281
Age, years, median (IQR)	9 (5–13)	8 (4–13)	9 (5–13)	9 (5–13)	<0.001
Sex, No. (%)[c]					
Male	2,674 (59.9)	355 (54.7)	434 (56.4)	1,885 (61.9)	<0.001
Female	1,790 (40.1)	294 (45.3)	335 (43.6)	1,161 (38.1)	<0.001
Race/Ethnicity, No. (%)[d]					
Hispanic	1,288 (30.6)	215 (39.0)	292 (39.9)	781 (26.7)	<0.001
Non-Hispanic Black	1,307 (31.1)	194 (35.2)	269 (36.8)	844 (28.9)	<0.001
Non-Hispanic White	1,217 (28.9)	73 (13.2)	118 (16.1)	1,026 (35.1)	<0.001
Non-Hispanic Asian	103 (2.4)	14 (2.5)	7 (1.0)	82 (2.8)	0.167
American Indian or Alaska Native	37 (0.9)	9 (1.6)	6 (0.8)	22 (0.8)	0.068
Native Hawaiian or Other Pacific Islander	33 (0.8)	8 (1.5)	9 (1.2)	16 (0.5)	0.009
Non-Hispanic Other	154 (3.7)	25 (4.5)	21 (2.9)	108 (3.7)	0.653
Non-Hispanic Multiple	68 (1.6)	13 (2.4)	9 (1.2)	46 (1.6)	0.357
Region[e]					
Northeast	811 (18.2)	339 (52.2)	48 (6.3)	424 (13.9)	<0.001
Midwest	986 (22.1)	109 (16.8)	87 (11.3)	790 (26.0)	<0.001
South	1,558	144	430	984 (32.4)	0.864

	(35.0)	(22.2)	(56.1)		
West	1,101 (24.7)	57 (8.8)	202 (26.3)	842 (27.7)	<0.001
Any comorbidity reported	1,688 (37.8)	239 (36.8)	293 (38.1)	1,156 (37.9)	0.688
Obesity[f]	1,121 (25.1)	148 (22.8)	189 (24.6)	784 (25.7)	0.117
Chronic lung disease including asthma	428 (9.6)	75 (11.6)	81 (10.5)	272 (8.9)	0.022
Other congenital malformations	144 (3.2)	20 (3.1)	27 (3.5)	97 (3.2)	0.962
Neurologic/neuromuscular disorder[g]	108 (2.4)	17 (2.6)	24 (3.1)	67 (2.2)	0.285
Congenital heart disease	94 (2.1)	11 (1.7)	22 (2.9)	61 (2.0)	0.940
Seizures	91 (2.0)	16 (2.5)	19 (2.5)	56 (1.8)	0.198
Diabetes[h]	39 (0.9)	5 (0.8)	6 (0.8)	28 (0.9)	0.656
Immunosuppressive disorder/malignancy	36 (0.8)	4 (0.6)	8 (1.0)	24 (0.8)	n/a[i]
Sickle cell disease	24 (0.5)	5 (0.8)	4 (0.5)	15 (0.5)	n/a[i]
Other conditions[j]	112 (2.5)	9 (1.4)	31 (4.0)	72 (2.4)	0.716

[a] P values from Cochran-Armitage test for trend for categorical variables and Jonckheere-Terpstra trend test for continuous variables

[b] Percentages calculated among 4,466 persons with known age.

[c] Percentages calculated among 4,464 persons with known sex.

[d] Percentages calculated among 4,207 persons with known race and ethnicity data. Racial and ethnic classifications followed CDC's Office of Minority Health and Health Equity (OMHHE) guidance. Non-Hispanic ethnicity was assumed if Hispanic ethnicity was not noted. Hispanic ethnicity was top-coded over White, Black, and Asian race. Because of small patient sizes, Native Hawaiian/Pacific Islander and American Indian/Alaskan Native populations were reported as such, regardless of ethnicity.

[e] Percentages calculated among 4,456 persons; territories not included in regional count.

[f] By either clinician diagnosis of obesity or body mass index-based obesity; calculated only in children >2 years.

[g] Includes cerebral palsy, developmental disabilities, autism and other neurologic conditions

[h] Includes type 1 diabetes, type 2 diabetes, and unspecified diabetes

[i] Unable to assess significance because of small cell size

[j] Includes chronic kidney disease, Down syndrome, failure to thrive, obstructive sleep apnea, prematurity, and other reported conditions

Table 2. Clinical Features of Patients with MIS-C by Wave, United States, February 2020 to July 2021. The 3 time periods were (1) February 19, 2020 through June 28, 2020, (2) June 29, 2020 through October 17, 2020, and (3) October 18, 2020 through July 31, 2021

Characteristic	All MIS-C cases (n= 4,470) No. (%)	MIS-C onset, No. (%)			
		Wave 1 (n= 649)	Wave 2 (n= 769)	Wave 3 (n= 3,052)	Test for trend p-Value [a]
Signs and symptoms					
Fever (>38°C or subjective)	4,470 (100.0)	649 (100.0)	769 (100.0)	3,052 (100.0)	N/A
Abdominal pain	3,061 (68.5)	407 (62.7)	517 (67.2)	2,137 (70.0)	<0.001
Vomiting	2,975 (66.6)	395 (60.9)	512 (66.6)	2,068 (67.8)	0.002
Conjunctival injection	2,476 (55.4)	334 (51.5)	437 (56.8)	1,705 (55.9)	0.102
Rash	2,467 (55.2)	360 (55.5)	423 (55.0)	1,684 (55.2)	0.928
Diarrhea	2,463 (53.8)	349 (53.8)	415 (54.0)	1,699 (55.7)	0.288
Hypotension	2,313 (51.7)	329 (50.7)	411 (53.4)	1,573 (51.5)	0.982
Headache	1,993 (44.6)	222 (34.2)	331 (43.0)	1,440 (47.2)	<0.001
Myalgia	1,332 (29.8)	150 (23.1)	225 (29.3)	957 (31.4)	<0.001
Cough	1,313 (29.4)	191 (29.4)	229 (29.8)	893 (29.3)	0.863
Shortness of breath	1,252 (28.0)	172 (26.5)	239 (31.1)	841 (27.6)	0.854
Mucocutaneous lesions	1,008 (22.6)	197 (30.4)	165 (21.5)	646 (21.2)	<0.001
Neck pain	985 (22.0)	85 (13.1)	158 (20.5)	742 (24.3)	<0.001
Chest pain	631 (14.1)	88 (13.6)	108 (14.0)	435 (14.3)	0.649
Periorbital edema	533 (11.9)	47 (7.2)	94 (12.2)	392 (12.8)	<0.001
Cervical lymphadenopathy	503 (11.3)	87 (13.4)	82 (10.7)	334 (10.9)	0.131
Altered mental status	497 (11.1)	65 (10.0)	100 (13.0)	332 (10.9)	0.991
Syncope	216 (4.8)	28 (4.3)	35 (4.6)	153 (5.0)	0.399
Severe cardiovascular involvement	3,556 (79.6)	503 (77.5)	615 (80.0)	2,438 (79.9)	0.238
Elevated troponin	2,356 (52.7)	279 (43.0)	431 (56.0)	1,646	<0.00

				(53.9)	1
Shock/receipt of vasopressors	2,018 (45.1)	312 (48.1)	364 (47.3)	1,342 (44.0)	0.025
BNP or NT-pro BNP ≥ 1000 pg/mL	1,617 (36.2)	224 (34.5)	259 (33.7)	1,134 (37.2)	0.084
Cardiac dysfunction[b]	1,296 (30.9)	238 (40.1)	191 (27.4)	867(29.8)	<0.001
Pericardial effusion/pericarditis	989 (22.1)	159 (24.5)	171 (22.2)	659 (21.6)	0.120
Coronary artery aneurysm/dilatation[c]	700 (16.7)	110 (18.5)	114 (16.4)	476 (16.4)	0.263
Myocarditis[d]	665 (14.6)	139 (21.4)	115 (15.0)	411 (13.5)	<0.001
Arrhythmia[e]	331 (7.4)	49 (7.6)	71 (9.2)	211 (6.9)	0.215
Congestive heart failure	240 (5.4)	45 (6.9)	29 (3.8)	166 (5.4)	0.469
ECMO	69 (1.5)	17 (2.6)	10 (1.3)	42 (1.4)	0.046
Severe hematologic involvement	2,663 (59.6)	290 (44.7)	464 (60.3)	1,909 (62.5)	<0.001
Thrombocytopenia[f]	1,890 (42.3)	214 (33.0)	352 (45.8)	1,324 (43.4)	<0.001
Lymphopenia[g]	1,580 (35.3)	150 (23.1)	233 (30.3)	1,197 (39.2)	<0.001
Neutropenia[h]	47 (1.1)	4 (0.6)	8 (1.0)	35 (1.1)	n/a[i]
Deep vein thrombosis/pulmonary embolism	38 (0.9)	6 (0.9)	5 (0.7)	27 (0.9)	0.899
Severe respiratory involvement	1,962 (43.9)	295 (45.5)	412 (53.6)	1,255 (41.1)	<0.001
Pneumonia[j]	1,044 (23.4)	172 (26.5)	236 (30.7)	636 (20.8)	<0.001
Pleural effusion[k]	954 (21.3)	121 (18.6)	202 (26.3)	631 (20.7)	0.887
Oxygen, high flow nasal cannula	753 (16.8)	107 (16.5)	162 (21.1)	484 (15.9)	0.130
Invasive mechanical ventilation (intubation)	419 (9.4)	82 (12.6)	96 (12.5)	241 (7.9)	<0.001
Non-invasive mechanical ventilation	368 (8.2)	59 (9.1)	75 (9.8)	234 (7.7)	0.091
Acute respiratory distress syndrome	261 (5.8)	45 (6.9)	64 (8.3)	152 (5.0)	0.004
Severe gastrointestinal involvement[l]	1,133 (25.3)	133 (20.5)	176 (22.9)	824 (27.0)	<0.001
Mesenteric adenitis	540 (28.9)	45 (21.0)	70 (21.7)	425 (31.9)	<0.001
Free fluid	460 (24.6)	55 (25.7)	80 (24.8)	325 (24.4)	0.677
Hepatomegaly/splenomegaly[m]	198 (10.6)	26 (12.1)	35 (10.9)	137 (10.3)	0.410
Colitis/enteritis	191 (10.2)	27 (12.6)	33 (10.2)	131 (9.8)	0.250
Cholecystitis/gallbladder abnormalities	137 (7.3)	15 (7.0)	29 (9.0)	93 (7.0)	0.605
Appendicitis/appendiceal changes	77 (4.1)	5 (2.3)	17 (5.3)	55 (4.1)	0.506
Severe renal involvement	908 (20.3)	133 (20.5)	171 (22.2)	604 (19.8)	0.386
Acute kidney injury	849 (19.0)	106 (16.3)	166 (21.6)	577 (18.9)	0.449
Renal failure	148 (3.3)	39 (6.0)	27 (3.5)	82 (2.7)	<0.00

					1
Dialysis	42 (0.9)	5 (0.8)	4 (0.5)	33 (1.1)	n/a[i]
Severe neurologic involvement	382 (8.5)	45 (6.9)	66 (8.6)	271 (8.9)	0.133
Meningitis	238 (5.3)	26 (4.0)	45 (5.9)	167 (5.5)	0.236
Encephalopathy	168 (4.0)	23 (4.8)	287 (3.8)	117 (4.0)	0.524
Stroke	29 (0.6)	8 (1.2)	2 (0.3)	19 (0.6)	n/a[i]
Any mucocutaneous involvement	3,323 (74.3)	472 (72.7)	575 (74.8)	2,276 (74.6)	0.411
Laboratory markers of inflammation					
Elevated C-reactive protein[n]	4,033 (99.3)	563 (99.5)	669 (99.3)	2,801 (99.3)	.788
Elevated d-dimer	4,125 (92.3)	572 (88.1)	717 (93.2)	2,836 (92.9)	<0.001
Elevated ferritin[o]	2,982 (87.2)	406 (88.3)	527 (90.5)	2,049 (86.2)	0.041
Elevated IL-6[p]	692 (80.8)	147 (96.1)	145 (84.8)	400 (75.2)	<0.001
Elevated fibrinogen[q]	2,761 (80.3)	368 (78.0)	456 (80.4)	1,937 (80.7)	0.202
SARS-CoV-2 results					
Serology[r] positive	3,905 (97.7)	512 (97.3)	626 (96.5)	2,767 (98.1)	0.079
RT-PCR[s] positive	2,225 (52.6)	331 (52.0)	446 (60.1)	1,448 (50.7)	0.040
Length of stay					
Total days in hospital, days, median (IQR) [t]	5 (4–8)	6 (4–10)	6 (4–8)	5 (4–8)	<.001
ICU admission, days, median (IQR) [u]	4 (2–6)	5 (3–7)	4 (2–6)	3 (2–5)	<.001

Abbreviations: BNP = brain natriuretic peptide; ICU = intensive care unit; IL-6 = Interleukin 6; IQR = interquartile range; NT-proBNP = N-terminal pro b-type natriuretic peptide; RT-PCR = reverse transcription polymerase chain reaction

[a] P values from Cochran-Armitage test for trend for categorical variables and Jonckheere-Terpstra trend test for continuous variables

[b] Includes specified left ventricular dysfunction (n=1,151) and right ventricular dysfunction (n=304); percentages calculated among 4,198 persons with an echocardiogram performed (Wave 1 n=594; Wave 2 n=697; Wave 3 n=2,907)

[c] Percentages calculated among 4,198 persons with an echocardiogram performed (Wave 1 n=594; Wave 2 n=697; Wave 3 n=2,907)

[d] Indicated on case report form

[e] Includes ventricular arrhythmia (n=116), supraventricular arrhythmia (n=107), atrioventricular block (n=23), and other electrocardiogram changes (n=86)

[f] Thrombocytopenia was collected under signs and symptoms or calculated from laboratory results as platelets <150 /µl

[g] Lymphopenia was defined as lymphocyte count <4,500 cells/µl if age <8 months or <1,500 cells/µl if age ≥8 months

[h] Neutropenia was defined as absolute neutrophil count <500 cells/µL

[i] Unable to assess significance because of small cell size

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

[k] Percentages calculated among 3,522 persons with chest imaging performed (Wave 1 n=444; Wave 2 n=664; Wave 3 n=2,414)

[l] Percentages calculated among 1,868 persons with an abdominal imaging performed (Wave 1 n=214; Wave 2 n=322; Wave 3 n=1,332)

[m] Includes hepatosplenomegaly

[n] Defined by C-reactive protein ≥0.6 mg/dL. Percentages calculated among 4,060 persons with C-reactive protein testing results available (Wave 1 n=566; Wave 2 n=674; Wave 3 n=2,820)

[o] Defined by ferritin ≥300 ng/mL. Percentages calculated among 3,418 persons with ferritin testing results available (Wave 1 n=460; Wave 2 n=582; Wave 3 n=2,049)

[p] Defined by IL-6 >1.8 pg/mL. Percentages calculated among 856 persons with IL-6 testing results available (Wave 1 n=153; Wave 2 n=171; Wave 3 n=532)

[q] Defined by fibrinogen >400 mg/dL. Percentages calculated among 3,438 persons with fibrinogen testing results available (Wave 1 n=472; Wave 2 n=567; Wave 3 n=2,399)

[r] Percentages calculated among 3,997 patients with serology testing

[s] Percentages calculated among 4,233 patients with PCR testing

[t] Calculated based on hospitalization duration available for 3,988 patients

[u] Calculated based on ICU duration available for 1,810 patients

Figure Legends

Figure 1. MIS-C Cases by U.S. Census Geographic Region with 3 MIS-C Waves and Million COVID-19 Cases by Week, United States, February 2020 – July 2021. The 3 MIS-C waves were (1) February 19, 2020 through June 28, 2020, (2) June 29, 2020 through October 17, 2020, and (3) October 18, 2020 through July 31, 2021.

Note: Grey dotted lines denote divider for each of the 3 MIS-C waves. The scale for the Y-axis differs on the left and the right sides of the figure. The left Y-axis marks the number of MIS-C cases in units of 50 with a scale of 0 to 250; the right Y-axis marks the number of COVID-19 cases in units of 500,000 with a scale from 0 to 1,500,000. Each bar on the X-axis represents one week.

Figure 2. Proportion of MIS-C Patients by Organ System Involvement over 3 Time Periods, United States, February 2020 – July 2021. The 3 MIS-C waves were (1) February 19, 2020 through June 28, 2020, (2) June 29, 2020 through October 17, 2020, and (3) October 18, 2020 through July 31, 2021.

*Represents significance using Cochran-Armitage test for trend across the three waves (P<0.001).

Note: p-Values for severe cardiovascular (P=0.238), any mucocutaneous (P=0.411), severe renal (P=0.386), and severe neurologic (P=0.133) were not significant using Cochran-Armitage test for trend across the three waves.

Figure 3. Proportion of MIS-C Patients by Treatment and Outcomes over 3 Time Periods, United States, February 2020 – July 2021. The 3 MIS-C waves were (1) February 19, 2020 through June 28, 2020, (2) June 29, 2020 through October 17, 2020, and (3) October 18, 2020 through July 31, 2021.

Abbreviations: ICU = intensive care unit; IVIG = intravenous immune globulin
*Represents significance using Cochran-Armitage test for trend across the three waves (P<0.001).

Note: p-Values for immune modulators (P=0.513) and ICU admission (P=0.056) were not significant using Cochran-Armitage test for trend across the three waves.

Figure 1

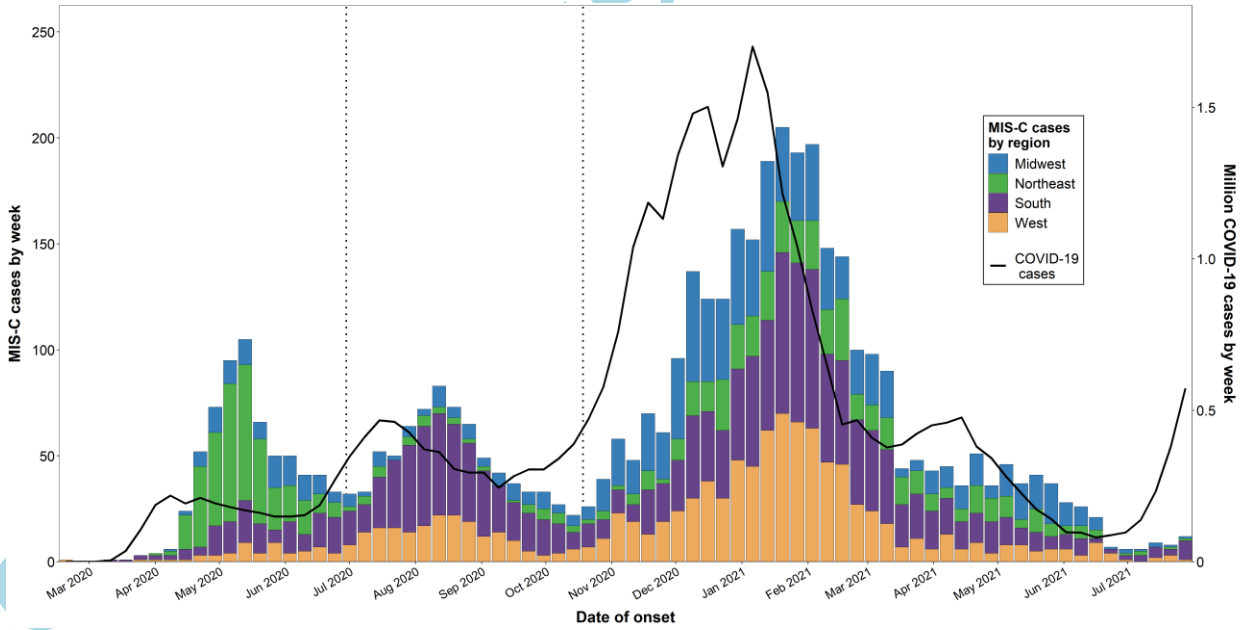

Figure 2

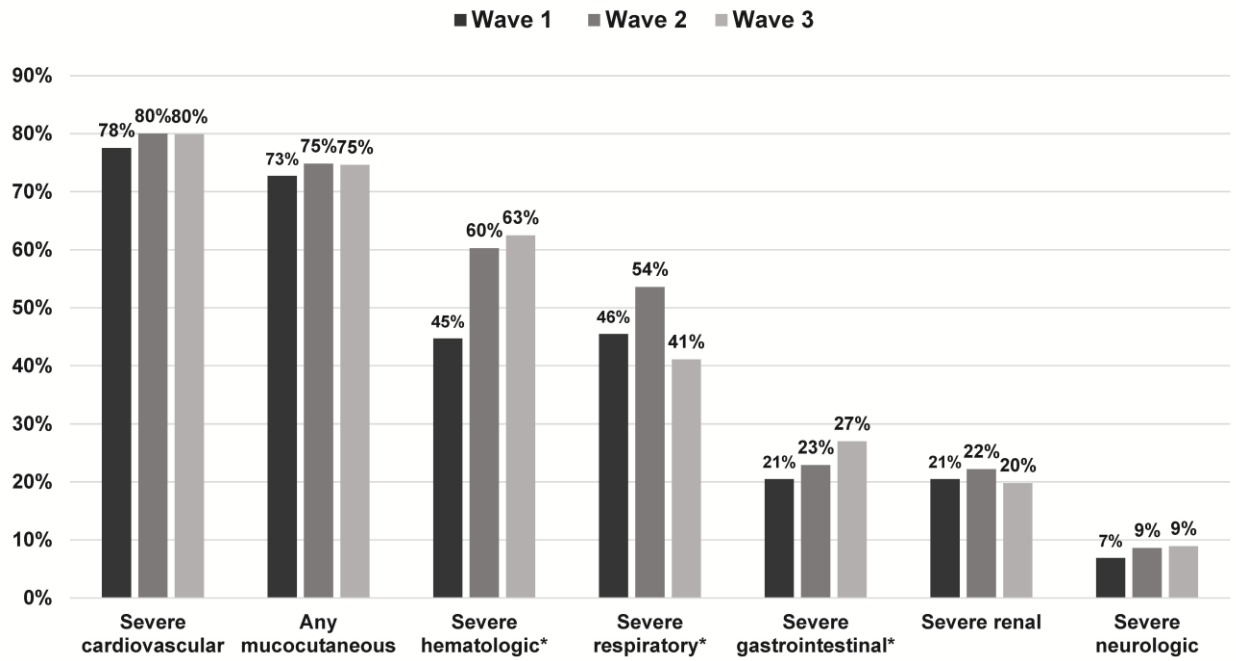

Figure 3