

Update on Pediatric Multisystem Inflammatory Syndrome (MIS-C)

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Disclosure



- The authors declare that they have no relevant or material financial interests that relate to the content of this presentation.

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Objectives



- Define/describe Multisystem Inflammatory Syndrome in Children (MIS-C)
- Recognize the clinical findings, especially cardiac and GI manifestations
- Evaluate laboratory findings in the ED
- Provide anticipatory guidance for patients admitted for clinical monitoring or treatment for MIS-C

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Case Presentation



- CC: Fever
- HPI: 10-year-old boy who presents with fever and myalgia x6 days. Diagnosed with strep throat 1-day prior to arrival at urgent care and started on amoxicillin. He also has headache, fatigue, generalized abdominal pain, emesis, and joint pain in bilateral knees. Denies nasal congestion, cough, shortness of breath, chest pain.
- PMx: Previously healthy.
- Imm: Not up to date. Did not receive COVID-19 vaccine.
- SHx: Lives with mother. In 5th grade. No known COVID-19 exposures.
- FHx: Mom reports she is healthy.

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Physical Exam



- Temp 39.0 °C, HR 117 bpm, RR 36 bpm, BP 73/59, SpO2 96% on room air
- Exam (highlights):
 - General: Ill-appearing male, appears tired, uncomfortable
 - HEENT: Conjunctival injection. Dry, cracked, peeling lips. No adenopathy.
 - CV: Tachycardia, nl S1 & S2 without murmurs, cap refill 3 sec.
 - Pulm: Clear to auscultation bilaterally
 - Abd: Diffuse pain, no guarding, non-distended
 - Integumentary: No rash

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Laboratory Results

CMP	CBC	Microbiology	Cardiac
Na 133	WBC 17.6 k/uL (7894N, 796L)	RSV/FluA/FluB Negative	
K 2.4	Hgb 11.6 g/dL	Monospot Negative	
Cl 103	Hct 31.7 g/dL	Rapid COVID-19 Negative	
CO ₂ 15	Plt 86 K/uL	SARS-COV-2 Antibodies Positive	
BUN 74	Inflammatory	Blood Culture Pending	
Cr 1.3	CRP 6.4 (<0.6mg/dL)		
Glucose 91	ESR 6 mm/hr		
Ca 7.9	Procalcitonin 5.60 (<0.25 ng/dL)		Troponin 205 (0-19 pg/mL)
Albumin 3.0	Ferritin 599 (11-307 ng/mL)		EKG NSR 112 bpm

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ED/Hospital Course

- ED
 - Patient given Zofran, 40cc/kg NS, IV KCl, Cefepime, Vancomycin
 - Vital signs improved.
- Patient admitted to PICU for AKI, possible MIS-C.
- PICU
 - US and MR Abdomen did not reveal appendicitis.
 - MAPS remained above 60 mmHg without vasopressors.
 - ECHO revealed normal RV/LV size, no LVH, normal RV/LV function. No dilation of coronary arteries. Trivial pericardial effusion.
 - Treated with 2g/kg IVIG. Patient defervescenced on HD1. Troponin decreased to 65 pg/mL.
 - Low-dose aspirin started. Antibiotics stopped after 48 hours.
- Floor
 - Transferred to floor on HD3. Discharged on HD5 with daily aspirin.



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What is MIS-C?

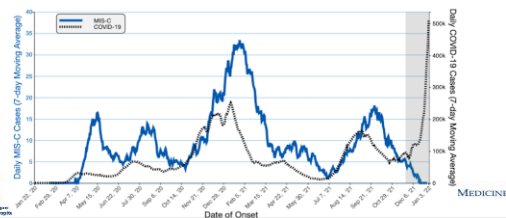
- First reported in the UK in association with COVID-19 in April 2020 about one month after the big surge in COVID disease^{1,2}
- Novel, severe hyperinflammatory illness in small subset of children and adolescents usually up to 4-6 weeks after SARS-CoV-2 infection³
 - Thought to be related to immune dysregulation that appears after an acute infection
 - Initially thought to be Kawasaki Disease and/or Toxic Shock Syndrome, quickly determined to have overlap
- In May 2020, the European and US CDC published a Health Advisory with case criteria and requested reporting of suspected cases of MIS-C¹
- Mortality rate less than 1%



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Incidence of MIS-C

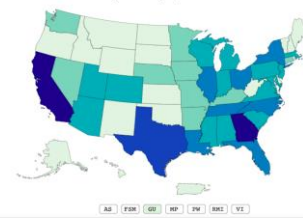
Daily MIS-C Cases and COVID-19 Cases Reported to CDC (7-Day Moving Average)



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National Distribution of MIS-C Case Ranges by Territory, State

Reported MIS-C Case Ranges by Jurisdiction, on or before January 3, 2022*



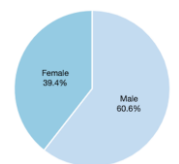
- Reported MIS-C Cases
- No case reported
 - 1-49 cases
 - 50-99 cases
 - 100-199 cases
 - 200-299 cases
 - 300-399 cases
 - 400+ cases



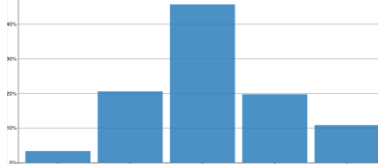
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MIS-C Patients by Age and Sex

MIS-C Patients By Sex



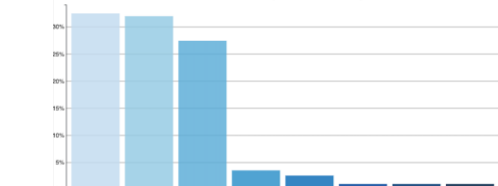
MIS-C Patients By Age Group



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Cases by Race & Ethnicity

MIS-C Patients by Race & Ethnicity



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US Reported Cases and Deaths

Last updated with cases reported to CDC on or before January 3, 2022*

TOTAL MIS-C PATIENTS MEETING
CASE DEFINITION*

6,431

TOTAL MIS-C DEATHS MEETING
CASE DEFINITION

55

*Additional patients are under investigation. After review of additional clinical data, patients may be excluded if there are alternative diagnoses that explained their illness.



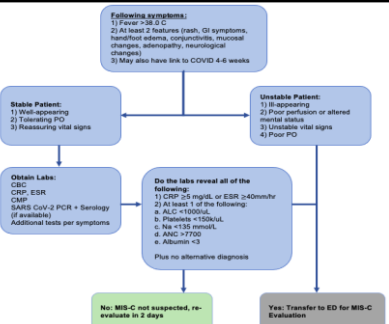
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Comparison between CDC/WHO Definition

Feature	CDC	WHO
Age	<21 years	0-19 years
Fever	>38C for 24 or more hrs	3 or more days
Organ system involvement	2 or more + hospitalization	2 or more
Laboratory findings	Elevated CSR, ESR, fibrinogen, procalcitonin, D-dimer, ferritin, LDH, L-6 or neutrophils Decreased lymphocytes, albumin	Elevated CRP, ESR, procalcitonin
COVID-19 infection	+PCR, serology, or antigen OR Exposure within 4 weeks prior to symptom onset	+PCR, serology, or antigen OR Likely contact with COVID-19

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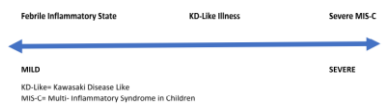
Outpatient Evaluation for Suspected MIS-C



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Spectrum & Subtypes of MIS-C

- A spectrum of severity for diagnosis of MIS-C has been created to categorize the variation in presentation
- "Febrile MIS-C": Persistent fevers, mild symptoms (i.e. headache, fatigue) elevated inflammatory markers without severe multisystem involvement
- "KD-Like" MIS-C: meets criteria for complete or incomplete KD but does not have signs of severe multisystem involvement or shock
- "Severe MIS-C": severe multisystem involvement including cardiac involvement



Misic KM 2021. SARS-CoV2 and Multisystem Inflammatory Syndrome in Children (MIS-C). Current Problems in Pediatric and Adolescent Health Care 51:101050.

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KD vs. MIS-C

	Kawasaki Disease	MIS-C
Age	Primarily <5 yrs old	~8 years old (range 2-38)
Race	Asian	Hispanic/Latino, Non-Hispanic black
Symptoms	5+ days fever + 4/5 symptoms: Conjunctivitis, rash, adenopathy, strawberry tongue, hand/foot swelling	Fever >24 hours, GI symptoms, rash, conjunctivitis
GI Symptoms	Uncommon	Very Common
Labs	Leukocytosis Thrombocytosis Elevated CRP, ESR Elevated U7s	Lymphocytopenia Thrombocytopenia Elevated CRP, ESR Elevated cardiac enzymes Elevated ferritin Elevated D-dimer
Echocardiogram	Coronary artery dilatation/aneurysm	Ventricular dysfunction, coronary artery abnormalities
Treatment	IVig, aspirin	Supportive: anticoagulation, steroids, immunomodulators IVig

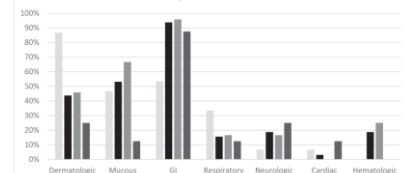
Despite these differences, there is considerable phenotypic overlap between MIS-C and KD. The present guidelines for immunomodulatory treatment are similar.

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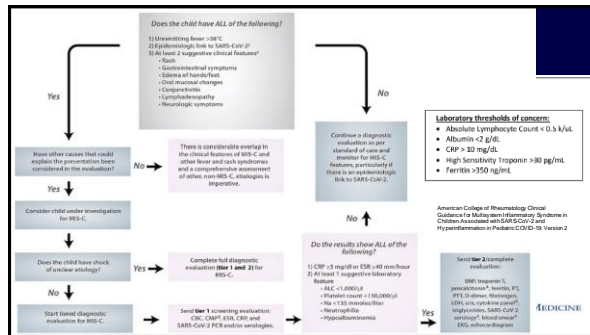
ED Presentation

- Out of 314 total patients screened for MIS-C in ED, 47 (15%) patients were evaluated and treated as MIS-C.
- 32 (68%) had laboratory-confirmed MIS-C (referred to as MIS-C or MIS-C confirmed) and 15 (32%) were admitted with an inflammatory condition and lacked confirmation of SARS-CoV-2 infection (MIS-C Suspected)⁶

Presenting Symptoms of Children Admitted with Suspicion for MIS-C



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ED Evaluation

- Initial Labs
 - CBC, CMP, ESR, CRP, Ferritin, high sensitivity troponin
- SARS-CoV-2 PCR test nasal or NP swab, SARS-CoV-2 serologies before IVig
- Additional Labs/Testing
 - D-dimer, fibrinogen, PT/PTT, ABG/VBG with lactate, CK, NT-proBNP, blood/urine/throat cultures, UA, immunoglobulins
 - EKG, ECHO, CXR
- Organ-specific based on patient symptoms
 - GI-SARS-CoV-2 stool PCR (if available), GI pathogen PCR panel, calprotectin, C. diff toxin PCR
- Consultation
 - Pediatric infectious disease
 - Pediatric cardiology
 - Pediatric rheumatology
 - Pediatric hematology
 - Disease is reported to the CDC

American College of Rheumatology Clinical Guidelines for Multisystem Inflammatory Syndrome in Children Associated with SARS-CoV-2 and Hypermethylation of Pediatric COVID-19 Version 2

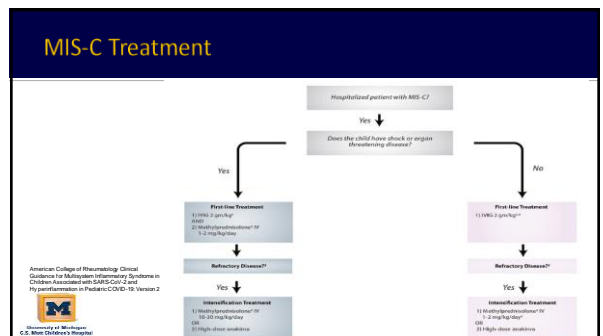
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ED Supportive Care

- Fluid Resuscitation
 - Caution with boluses due to cardiac compromise
- Continuous cardiorespiratory monitor
- Vital signs q2h if increased concern for instability
- Continuous pulse oximetry
- Empiric Antibiotics
 - Ceftriaxone PLUS metronidazole for possible appendicitis
 - Ceftriaxone PLUS vancomycin and clindamycin for possible toxic shock
- Inotropes
 - Vasopressors per Surviving Sepsis Campaign and the American College of Critical Care Medicine guidelines. May use epinephrine or dopamine as first-line vasopressors, norepinephrine as second-line.
 - Norepinephrine and epinephrine can be given through peripheral IV. Risk of extravasation injury 2-3% in 1st 12 hours
- Mechanical Ventilation

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Management of Shock by Clinical Severity

Therapeutic Category	Mild	Moderate	Severe
Standard Initial Dosing For 2mg/kg/day dosing max 10mg/kg	4-6 Methylprednisolone 2mg/kg/day (second line)	Methylprednisolone 10mg/kg x1, then 2mg/kg/day	Methylprednisolone 20-30mg/kg/day for 1-3 days, then 2mg/kg/day
Other Immunomodulators For anakinra dosing 2-10mg/kg	Consider pulse Methylprednisolone or Anakinra if refractory to steroids	Consider 1-3 days pulse Methylprednisolone, consider Anakinra if refractory to steroids	Consider Anakinra 10mg/kg/day qbid if refractory to steroids, consider other biologics if refractory to Anakinra
Anticoagulation: Monitor for bleeding, thrombocytopenia, coagulopathy	LMWH prophylactic or low-dose ASA	LMWH prophylactic or low-dose ASA	LMWH prophylactic low-dose ASA
Broad-spectrum antibiotics	Yes	Yes	Yes
Standard Taper	2-3 weeks	6-8 weeks	Standard taper with suboptimal remission

Classify Clinical Severity

- Mild: No vasoactive requirement, minimal/no respiratory support, and/or minimal organ injury
- Moderate: Significant supplemental oxygen requirement, and/or mild or isolated organ injury
- Severe: Non-invasive or invasive ventilatory support, and/or moderate or severe organ injury including moderate to severe ventricular dysfunction

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MIS-C Treatment

- MIS-C Treatment^{10,11}
 - 63% received IVig (7% required 2nd dose for ongoing fever)
 - 49% received corticosteroids
 - 8% received anakinra
 - 6.5% received tocilizumab
 - 1.2% received infliximab
- Critical Care Therapies^{10,11}
 - 40% received inotropes
 - 15% received mechanical ventilation (often as result of CV collapse)
 - 2.7% were on ECMO
 - Antibiotics for rule out sepsis
- Other Therapies
 - 34% received therapeutic anticoagulation
 - Antiplatelet agents for KD-like features

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Complications

- High prevalence of cardiac involvement
 - In a small observational study in Italy, there is increase rate of cardiac involvement from KD-like disease after outbreak of COVID-19; the rate was 6/10 cases post-pandemic compared to 2/19 cases pre-pandemic¹²
- Main complications: shock-like syndrome requiring vasopressor support
 - Shock is seen in 35-50% of patients^{12,13}
- Coronary dilation/aneurysm (35-50%), cardiac dysfunction (28-62%), myocarditis (17-22%), mitral valve regurgitation or pericardial effusion
- Pleural, pericardial, ascitic effusions (24-57%)
- Acute kidney injury (28-52%)
- Most patients (71-90%) present with involvement of at least four organ systems, and over half of patients require admission to ICU during hospital stay^{14,15}



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Prognosis & Follow-up

- Approximately 75% of children with MIS-C require critical care during admission⁶
- Majority of MIS-C patients, even with severe cardiovascular involvement, recover without sequelae (70-97%)¹⁴
- ECHO follow-up is needed, even in patients with no cardiac involvement in the acute phase of illness¹³
- It is reasonable to use KD guidelines to guide outpatient follow-up, as long-term monitoring has not been standardized to date¹³



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Summary

- MIS-C, a SARS-CoV-2 related condition, is characterized by presence of fever, elevated inflammatory markers, multi-organ involvement
- Fever, abdominal pain, diarrhea, vomiting are most common symptoms in MIS-C
- Clinical characteristics are shared to some extent with KD
- Investigations into a variety of treatment/supportive care domains are ongoing
- Further research is required to create diagnostic criteria consensus, optimize treatment protocols, and assess short- and long-term outcomes



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Questions?

Thank you for your attention



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