MIS-C

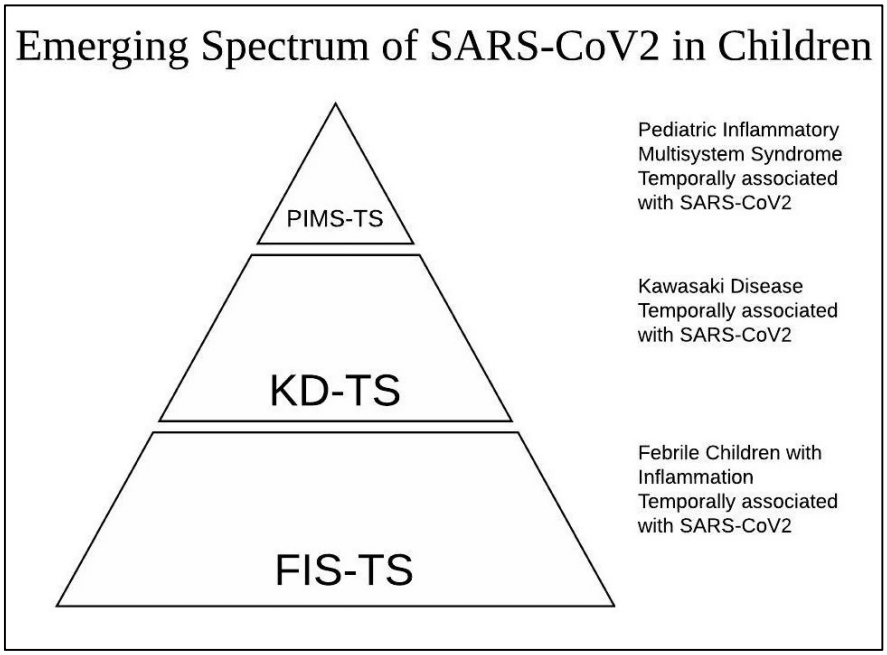
Multisystem Inflammatory Syndrome in Children

Overview

Areas hard hit by COVID-19 around the world have described a new pediatric illness that appears to follow a SARS-CoV-2 infection or exposure. Multisystem Inflammatory Syndrome in Children (MIS-C) is a clinical entity of uncertain etiology that involves significant hyper-inflammation, potentially leading to organ dysfunction and shock. Presentation features may overlap Kawasaki Disease or Toxic Shock Syndrome.

It is postulated that MIS-C is a post-infectious hyper-inflammatory process, rather than a manifestation of an acute infection. In case series in NYC and the UK, patients had antibodies for the virus despite negative nasopharyngeal SARS-CoV-2 PCR swabs.

As we gain experience with this new illness, it appears that MIS-C is on a spectrum of febrile, inflammatory illnesses associated with COVID-19. We do not know yet if they represent a single, continuous process or separate clinical entities with overlapping features, and it is unclear if that distinction is important in determining health outcomes in children with MIS-C.



Adapted from Michael Levin, "Paediatric Inflammatory Multisystem Syndrome - Temporally associated with SARS-CoV-2 –PIMS-TS," COCA Webinar, 19 May 2020

While we know that these patients are at high risk for developing cardiovascular collapse, resulting in the need for high levels of critical care support, what is less clear at this time is how these patients can be differentiated from those with more common pediatric febrile illnesses such as viral gastroenteritis or a urinary tract infection.

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This document and the associated algorithms are intended to help physicians understand the clinical presentation of MIS-C, providing a systematic framework for the evaluation and early diagnosis of patients with suspected MIS-C, when they are hopefully at lower risk of cardiovascular collapse. The algorithms are designed to be used **in addition** to your typical approach to the febrile pediatric patient.

Important Consideration

MIS-C is a very new syndrome, and little information exists in the literature regarding signs, symptoms, laboratory data, or best practices, such as basic care guidelines and treatment options. The medical community is still in the early stages of investigating this condition, and our understanding of MIS-C will surely evolve and change over time.

The recommendations are based on the expert opinions of pediatric specialists at C.S. Mott Children's Hospital. Our goal is to identify patients who are at risk for further clinical deterioration at a point prior to cardiovascular collapse, without including every child with a common febrile illness.

Keeping in mind our goal of differentiating patients with MIS-C from patients with more typical febrile childhood illnesses, we have recommended clinical criteria for initiating a laboratory workup, and then laboratory thresholds that warrant further observation and/or investigation. The clinician's judgment is an important factor as well and should be taken into consideration.

As MIS-C becomes better understood and more data become available, we anticipate that these guidelines will be updated periodically to reflect new information.

Presentation

Children with MIS-C exhibit signs and symptoms that significantly overlap with typical pediatric febrile illnesses. It is therefore important to consider the fever curve carefully. Patients universally present with prolonged or persistent fever and often complain of fever that is resistant to antipyretics. Most patients experience gastrointestinal symptoms, including abdominal pain, diarrhea, nausea, and vomiting. Additional features include rash, conjunctivitis, headache, and sore throat. A subset of patients present with shock and require high levels of supportive care in addition to coverage for sepsis and consideration for MIS-C.

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Concerning presenting signs and symptoms

- Persistent fever ≥ 38.5C
- Nausea, vomiting, diarrhea, abdominal pain (may mimic appendicitis)
- Rash
- Conjunctivitis
- Oral mucosal changes
- Headache, irritability
- Cough, shortness of breath
- Sore throat
- Chest pain
- Extremity swelling
- Lymphadenopathy

Initial Workup

As MIS-C is an inflammatory syndrome, the initial laboratory workup is focused on uncovering signs of inflammation. Moreover, as the disease progresses, patients often develop end-organ dysfunction, in particular cardiac involvement and coagulopathies, and the recommended testing seeks to screen for those concerns as well.
Note: Work-up of alternative diagnoses should be concurrent with initial MIS-C evaluation.

Initial laboratory testing

- CBCPD
- Comprehensive Panel
- CRP
- High Sensitivity Troponin
- Ferritin

Laboratory thresholds of concern:

- Absolute Lymphocyte Count < 0.5 k/uL
- Albumin <2 g/dL
- CRP > 10 mg/dL
- High Sensitivity Troponin >30 pg/mL
- Ferritin >350 ng/mL

Please refer to the ED/Inpatient Algorithm for further decision-making guidance.

Case Definitions

Since MIS-C is such a poorly understood condition at this time, with more questions than answers, data collection is a high priority for the medical community and public health agencies around the world. The Centers for Disease Control and the World Health Organization have established case definitions and registries for the syndrome to allow for a more systematic approach to diagnosis, better recognition of risk factors and causality, and more standardized collection of data for subsequent research. At Michigan Medicine, we are using the CDC case definition.

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CDC case definition:

A. Age < 21 years
B. Clinical presentation including **all** of the following:
    1. Fever >38.0C (100.4F) for ≥ 24 hours or subjective fever lasting ≥ 24 hours
    2. Laboratory evidence of inflammation, including but not limited to:
        - Elevated CRP
        - Elevated ESR
        - Elevated fibrinogen
        - Elevated procalcitonin
        - Elevated D-dimer
        - Elevated ferritin
        - Elevated LDH
        - Elevated IL-6 level
        - Neutrophilia
        - Lymphocytopenia
        - Hypoalbuminemia
    3. Severe illness requiring hospitalization
    4. Multisystem (2 or more) involvement
        - Cardiovascular
        - Renal
        - Respiratory
        - Hematologic
        - Gastrointestinal
        - Dermatologic
        - Neurologic
C. No alternative plausible diagnosis
D. Recent or current SARS-CoV-2 infection or exposure, with **any** of the following:
    - Positive SARS-CoV-2 RT-PCR
    - Positive serology
    - Positive antigen test
    - COVID-19 exposure within the 4 weeks prior to the onset of symptoms

Additional comments

- Some individuals may fulfill full or partial criteria for Kawasaki disease but should be reported if they meet the case definition for MIS-C
- Consider MIS-C in any pediatric death with evidence of SARS-CoV-2 infection

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Inpatient Considerations

Once a patient suspected of having MIS-C is admitted, further workup to look for specific areas of inflammation will be initiated. Given the high risk of cardiovascular collapse, patients admitted with a diagnosis of presumed MIS-C also warrant very close monitoring and a multidisciplinary approach to care.

Additional Workup at Admission

SARS-CoV-2 swab	Procalcitonin	BNP
SARS-CoV-2 serologies	PT/PTT	LDH
RPAN	Fibrinogen	Cytokine Panel
Blood culture	ESR	EKG
UA w/ reflex urine culture	CK	Peripheral smear
VBG	Triglycerides	

- If ALC <0.5, order a Primary Immunodeficiency Flow Panel
- Consider obtaining IgG levels
- To order the peripheral smear:
  Order "Peripheral Smear Morphology Review Request"
  Type in "for Cellavision Review" in the additional comments box

Daily Labs

CBCPD	Ferritin	BNP, if elevated initially
CMP	PT/PTT	Troponin, if elevated initially
CRP	Fibrinogen	
ESR	D-Dimer	

Special Pathogen Isolation

Patients with MIS-C are presumed to have current or recent SARS-CoV-2 infection and should be considered Persons Under Investigation and placed in special pathogen precautions initially. Patients do not need negative pressure rooms unless they are likely to undergo aerosol-generating procedures.

- To discontinue special pathogen precautions, patients will need to have two negative SARS-CoV-2 PCR swabs, at least 24 hours apart. They should remain in special pathogen isolation until the 2nd swab has returned as negative.
- Once cleared for COVID-19, patients will require isolation precautions appropriate to their clinical presentation and diagnosis.
- Please refer to the Infection Prevention and Epidemiology (IPE) website for the most up-to-date recommendations regarding special pathogen precautions: http://www.med.umich.edu/i/ice/resources/clinical_guidance.html

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Disease Reporting

MIS-C is currently a reportable disease process, but should only be reported after there is sufficient evidence to make a diagnosis of presumed MIS-C. At this time, we are using the CDC case definition.

- Notify IPE at pager 30032 or by email at UM-ICE@med.umich.edu to report the case. IPE will enter the case into the state database.
- Please document in the chart once IPE has been notified.

Vital Sign Monitoring

All patients admitted for presumed MIS-C require close and continuous monitoring to ensure hemodynamic stability.

- Place on a continuous cardiorespiratory monitor (+/- telemetry).
- Place on continuous pulse oximetry.
- Consider checking vital signs every 2 hours initially if there is increased concern for instability.

Subspecialty Consultations

The management of MIS-C requires a multidisciplinary team approach as it is a complex, multi-organ disease. Consultations should be ordered whenever there are clinical concerns, but the following services are frequently involved in the care of MIS-C patients.

- ID – Consult if there are clinical concerns
- Hematology – Consult if there is clinical concern for coagulopathy
- Rheumatology – Consult if there are clinical concerns
- Cardiology – Consult for criteria listed below

Antibiotic Coverage

As MIS-C is not a bacterial process, patients do not require coverage with antibiotics unless there is concern for concomitant bacterial infection or sepsis. Empiric antibiotic coverage should be determined according the institutional sepsis guidelines and should be tailored if a bacterial process is identified.

- http://www.med.umich.edu/asp/pdf/pediatric_guidelines/Sepsis_PEDS.pdf

Anticoagulation

Although patients with MIS-C often have evidence of hypercoagulability, not all patients develop thromboses or require anticoagulation. Hematology should be consulted if there are clinical concerns for coagulopathy to help determine the need for anticoagulation and the appropriate medication choices. Before starting anticoagulation, please check platelet count and kidney function.

Cardiac Workup

MIS-C was first recognized due to the unexpected incidence of atypical Kawasaki Disease in pediatric COVID-19 patients. It is now recognized as a separate clinical entity, but similar to KD, patients have an increased risk of cardiovascular abnormality, ranging from myocarditis to coronary aneurysms to ventricular dysfunction.

- A cardiac workup should be initiated at the time of admission, including high-sensitivity troponin, BNP, EKG.
- Patients under consideration for MIS-C require an echocardiogram only if there are clinical concerns. A transthoracic echocardiogram can be performed without sedation, unless the clinical situation warrants a more expedited evaluation.

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- Note that the coronary arteries may be difficult to visualize in non-sedated patients, but the risk/benefit analysis does not currently justify sedating all patients. We suggest beginning with a non-sedated echocardiogram, and if views are suboptimal or there is a suspicion for important findings, a discussion between the inpatient and cardiology attendings should take place to decide if sedation is warranted.
- Consult cardiology for all patients with abnormal screening cardiac labs, EKG, echocardiogram or other clinical concerns for cardiac involvement.
- Follow-up recommendations below:

Initial cardiac workup	Clinical condition	Recommendations
Normal labs AND Normal echo	• Inflammatory markers improving • Hospitalization <72hrs	• Repeat echo 2 weeks after discharge
	• Inflammatory markers improving • >72hrs	• Repeat echo prior to discharge
	• Inflammatory markers significantly abnormal or worsening • Clinical deterioration	• Repeat echo and cardiac screening labs prior to discharge • Follow-up 2 weeks after discharge with clinic visit and repeat echo
	• Meets criteria for Kawasaki Disease or atypical KD	•Cardiology consult •Management for KD as per AHA algorithm
Abnormal labs OR Abnormal echo	• Variable	• Cardiology consult • Follow-up per consult team

Additional Considerations

Consider undertaking genetic testing to help identify underlying susceptibilities in patients with MIS-C. They may share genetic predispositions with other inflammatory syndromes. The recommended genetic test is the Blueprint Genetics Comprehensive Immune and Cytopenias panel. It is a very new test, and only certain providers (Rheumatology and Hematology) have access to order it, and they will often already be consulted.

Discharge Criteria

Patients can be considered for discharge once they have been afebrile for at least 24 hours and their lab work is returning to baseline. Naturally, discharge decisions will be dependent on the patient's condition and the provider's clinical judgment.

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Inpatient Quick Reference

Multisystem Inflammatory Syndrome in Children (MIS-C) is a newly recognized inflammatory syndrome presenting in pediatric patients, associated with current or recent SARS-CoV-2 infection. The pathogenesis is unclear, and the manifestations are still being clarified. At present, we know that children present with prolonged or persistent fever and a constellation of variable symptoms. They exhibit many markers of significant inflammation and are at high risk for cardiovascular collapse. This document accompanies the MIS-C protocol and is designed to be a quick reference guide when admitting these patients.

Initial evaluation criteria

T ≥ 38.5C for at least 3 days, plus 2 or more concerning signs/symptoms

No other etiology identified

Concerning signs and symptoms

- Persistent fever ≥ 38.5C
- Nausea, vomiting, diarrhea, abdominal pain (may mimic appendicitis)
- Rash
- Conjunctivitis
- Oral mucosal changes
- Headache, irritability
- Cough, shortness of breath
- Sore throat
- Chest pain
- Extremity swelling
- Lymphadenopathy

Initial lab testing and thresholds of concern:

- Absolute Lymphocyte Count < 0.5 k/uL
- Albumin <2 g/dL
- CRP > 10 mg/dL
- High Sensitivity Troponin >30 pg/mL
- Ferritin >350 ng/mL

Note: Work-up of alternative diagnoses should be concurrent with initial MIS-C evaluation

Additional Workup at Admission

SARS-CoV-2 swab	Procalcitonin	BNP
SARS-CoV-2 serologies	PT/PTT	LDH
RPAN	Fibrinogen	Cytokine Panel
Blood culture	ESR	EKG
UA w/ reflex urine culture	CK	Peripheral smear
VBG	Triglycerides	

- If ALC <0.5, order a Primary Immunodeficiency Flow Panel
- Consider obtaining IgG levels
- To order the peripheral smear:
  Order “Peripheral Smear Morphology Review Request”
  Type in “For Cellavision Review” in the additional comments box

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Daily Labs

CBCPD	Ferritin	BNP, if elevated
CMP	PT/PTT	Troponin, if elevated
CRP	Fibrinogen	
ESR	D-Dimer	

Vital Signs Monitoring

- Continuous cardiorespiratory monitor (+/- telemetry)
- Continuous pulse oximetry
- Consider checking vital signs every 2-4 hours initially if there is any concern for instability

Special Pathogen Isolation

- Place patients in special pathogen precautions
- Negative pressure rooms are not needed unless patients are likely to undergo aerosol-generating procedures
- May discontinue precautions after 2 negative SARS-CoV-2 PCR swabs, at least 24 hours apart
- Most up-to-date recommendations regarding special pathogen precautions: http://www.med.umich.edu/i/ice/resources/clinical_guidance.html

Disease Reporting

- Must report disease if there is sufficient evidence to make diagnosis of presumed MIS-C, based on the CDC case definition
- Notify IPE at pager 30032 or by email at UM-ICE@med.umich.edu to report the case. IPE will enter the case into the state database
- Please document in the chart once IPE has been notified

Subspecialty Consultations

- ID – Consult if there are clinical concerns
- Hematology – Consult if there is clinical concern for coagulopathy
- Rheumatology – Consult if there are clinical concerns
- Cardiology – Consult if abnormal cardiac screening labs, abnormal EKG, or abnormal echo, or if there is clinical concern for cardiac involvement

Antibiotic Coverage

- Only if concerned about concomitant bacterial infection or sepsis
- Empiric antibiotic coverage for sepsis per the institutional sepsis guidelines and should be tailored if a bacterial process is identified
- http://www.med.umich.edu/asp/pdf/pediatric_guidelines/Sepsis_PEDS.pdf

Increasing Level of Care

- Please have a lower threshold for calling an RRT on these patients; the PICU is aware this will occur

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