9/24/2021

Multisystem Inflammatory Syndrome in Children (MIS-C) Associated with Coronavirus Disease 2019 (COVID-19)

Interim Guidance

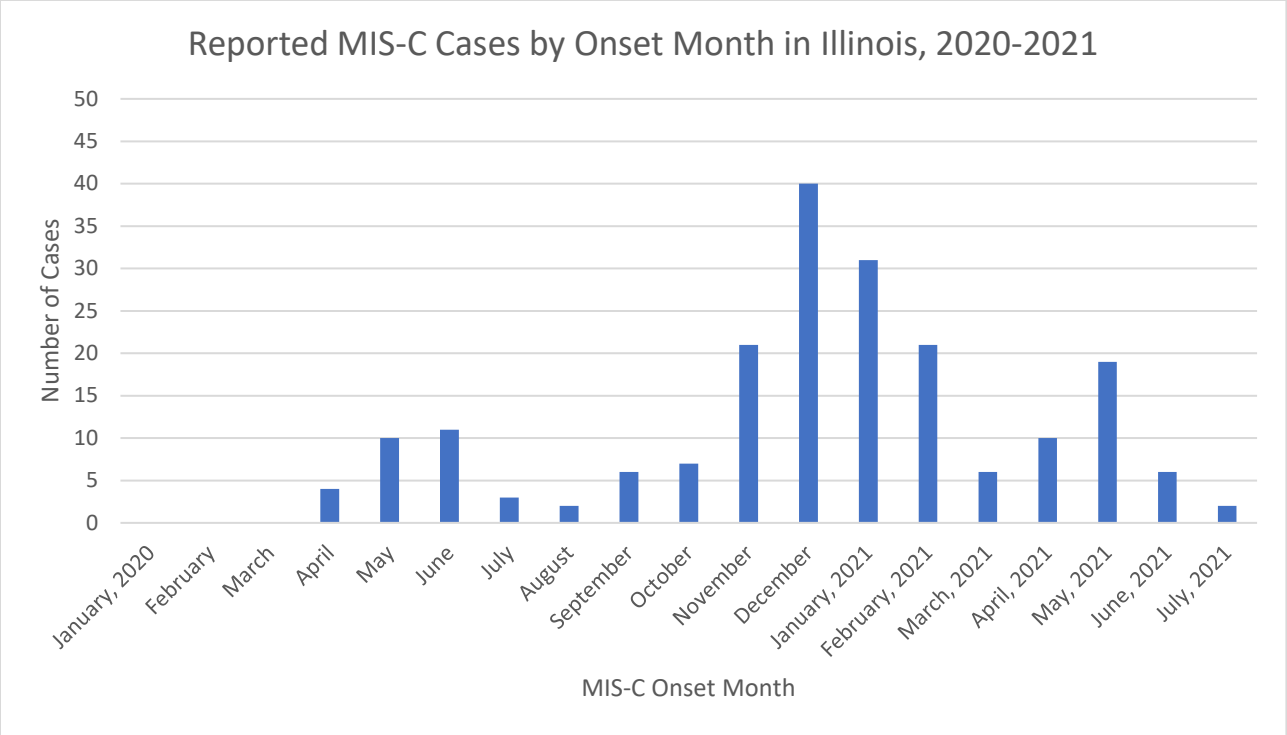
(*Subject to change: see dates and revisions on page 3*)

PURPOSE

This document serves as a reminder and aims to ensure that clinicians are aware of current guidance regarding *Multisystem Inflammatory Syndrome in Children* (*MIS-C) Associated with Coronavirus Disease 2019 (COVID-19),* including the case definition and guidance on reporting to local health departments.

CURRENT ILLINOIS MIS-C DATA

Illinois has received 199 reports of MIS-C from clinicians for cases through July 2021.These cases have been submitted to the Centers for Disease Control and Prevention (CDC) for further reporting and review. Below is a graph depicting the reported cases by the onset month of their reported MIS-C illness. IDPH anticipates additional reports will be received as reporting for these cases can lag as the critical task of treating these patients becomes the clinicians' priority.



BACKGROUND

- In spring 2020, clinicians in the United Kingdom[1], New York City, and New York State reported cases of children with multisystem inflammatory syndrome (many of whom tested positive for SARS-CoV-2 infection by RT-PCR or serologic assay).
- On May 14, 2020, CDC issued a Health Advisory regarding a multisystem inflammatory syndrome in children (MIS-C) associated with coronavirus disease 2019 (COVID-19), along with a case definition for this syndrome[2] (see below).
- Most cases of MIS-C have features of shock, with cardiac involvement; gastrointestinal symptoms; and significantly elevated markers of inflammation, with positive laboratory test results for SARS-CoV-2[3]. A recent prospective study found that ethnicity seemed to be a factor in both critical care admission and MIS-C and identified additional clinical characteristics of MIS-C versus acute COVID patients[4]. The literature continues to evolve regarding the pathogenesis and the clinical course of MIS-C[5].

CDC Case Definition for Multisystem Inflammatory Syndrome in Children (MIS-C)[2]

- An individual aged <21 years presenting with fever[i], laboratory evidence of inflammation[ii], and evidence of clinically severe illness requiring hospitalization, with multisystem (≥2) organ involvement (cardiac, renal, respiratory, hematologic, gastrointestinal, dermatologic, or neurological); **AND**
- no alternative plausible diagnoses; **AND**
- positive for current or recent SARS-CoV-2 infection by RT-PCR, serology, or antigen test; or COVID-19 exposure within the four weeks prior to the onset of symptoms.

[i]Fever ≥38.0°C for ≥24 hours, or report of subjective fever lasting ≥24 hours,
[ii]including, but not limited to, one or more of the following: an elevated C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), fibrinogen, procalcitonin, d-dimer, ferritin, lactic acid dehydrogenase (LDH), or interleukin 6 (IL-6), elevated neutrophils, reduced lymphocytes, and low albumin.

Additional comments

- Some individuals may meet 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.

ESSENTIAL ACTIONS

- Health care providers should maintain a high index of suspicion for MIS-C.
- Refer to the attached two-page *Multisystem Inflammatory Syndrome in Children (MIS-C) Clinical Pathway - Emergency Department (ED), Inpatient Unit, Pediatric Intensive Care Unit (PICU)* document, developed by the Illinois MIS-C Workgroup.
- Suspected cases of MIS-C **should be referred immediately** to a tertiary care center with a PICU.
- Tertiary care centers are asked to consider a collaborative approach in the management of these patients by convening a multispecialty committee (comprised of pediatric critical care, cardiology, hematology, infectious disease, and rheumatology/immunology) that provides coordinated clinical care guidance for each patient while (1) confirming patients meet the case definition, and (2) ensuring that appropriate diagnostic and treatment resources are readily available for this patient population.
- Hospital infection preventionists should be notified immediately upon recognition of patients meeting case definition to initiate public health reporting.

TESTING

- In suspected cases of MIS-C, strongly recommend the following additional laboratory testing due to the potential for myocardial involvement: BNP and Troponin.
- If the BNP and/or Troponin levels are elevated, initiate transfer to a tertiary care center with a PICU.
- Hospitals must assess for current or recent SARS-COV-2 infection by performing a combination of RT-PCR, antigen test, and/or serology (as available) in patients who are under 21 years of age and present with symptoms compatible with MIS-C associated with COVID-19.

REPORTING

- Health care providers and laboratories are required by the Control of Communicable Disease Code to report suspected or known MIS-C associated with COVID-19 cases to the local health department.
- When an MIS-C case associated with COVID-19 is suspected to be or is known to be the cause of death in an individual (laboratory-confirmed case), this should be reported to the local health department.
- Hospitals must submit pre-defined data elements on MIS-C patients through the Illinois National Electronic Disease Surveillance System (I-NEDSS). NOTE: Electronic laboratory reporting alone will not suffice for this syndrome. **IMPORTANT REMINDER: When reporting these cases in I-NEDSS, select "Multisystem Inflammatory Syndrome" as the condition.**
- Hospitals should ensure complete reporting of co-morbidities and details of previous outpatient, inpatient, or emergency department visits through I-NEDSS, as applicable.
- **In addition to reporting through I-NEDSS, providers should complete the MIS-C Case Report Form (CRF) when they suspect a case and submit it to their local health department.**
    - **Printable and fillable form:** https://www.cdc.gov/mis/pdfs/hcp/mis-c-form-fillable.pdf **Instructions:** https://www.cdc.gov/mis/pdfs/hcp/mis-c-form-instructions.pdf
- **Follow the steps below to ensure appropriate completion of the reporting process:**
    - **Identify suspected MIS-C case.**
    - **Promptly report the case to the local health department thru I-NEDSS.**
        - **Choose "Multisystem Inflammatory Syndrome" as the condition.**
    - **Submit a completed MIS-C Case Report Form (CRF) to the local health department.**
    - **NOTE: Local health departments submit the CRF forms to IDPH to determine if MIS-C classification is met, prior to submission to the CDC.**

Revisions and Updates

5/21/2020	Interim Guidance developed
7/1/2020	Essential Actions section, 2nd bullet - Added pediatric intensive care unit (PICU); Testing section - Added 2 new bullets related to BNP and Troponin lab testing.
3/1/2021	Page 1: New section added with current Illinois data; Page 2: Background section - added findings from more recent literature; Essential Actions section - added bullet regarding MIS-C Clinical Pathway; Page 3 – Reporting section - corrected typo, clarified/expanded the reporting section/process, and added link to CRF instructions; Page 4 – deleted a reference and added three recent articles; Pages 5 and 6 - added MIS-C Clinical Pathway as an attachment.
09/24/2021	Page 1: Updated current data. Page 3: Updated weblinks for MIS-C Case Report form and instructions.

REFERENCES

[1] Royal College of Paediatrics and Child Health Guidance: Paediatric multisystem inflammatory syndrome temporally associated with COVID-19, May 2020. https://www.rcpch.ac.uk/sites/default/files/2020-05/COVID-19-Paediatric-multisystem-%20inflammatory%20syndrome-20200501.pdf

[2] CDC Health Advisory, Multisystem Inflammatory Syndrome in Children (MIS-C) Associated with Coronavirus Disease 2019 (COVID-19), CDCHAN-0032, May 14, 2020

[3] Godfred-Cato S, Bryant B, Leung J, et al. COVID-19-Associated Multisystem Inflammatory Syndrome in Children – United States, March-July 2020. MMWR Morb Mortal Wkly Rep 2020; 69: 1074-1080. doi: http://dx.doi.org/10.15585/mmwr.mm6932e2

[4] Swann O, Holden K, Turtle L, et al. Clinical characteristics of children and young people admitted to hospital with covid-19 in United Kingdom: prospective multicenter observational cohort study. BMJ 2020; 370: m3249. doi: http://dx.doi.org/10.1136/bmj.m3249

[5] Consiglio C, Cotugno N, Sardh F, et al. The Immunology of Multisystem Inflammatory Syndrome in Children with COVID-19. Cell 183, 968-981. November 12, 2020. doi: https://doi.org/10.1016/j.cell.2020.09.016

Multisystem Inflammatory Syndrome in Children (MIS-C) Clinical Pathway
Emergency Department (ED), Inpatient Unit, Pediatric Intensive Care Unit (PICU)

Appendices (see page 2)

A. Common Features of Shock in Children
B. Principal Clinical Features of Classic Kawasaki Disease
C. Differential Diagnosis of MIS-C

ED Evaluation for Possible MIS-C

ED Team Assessment
- History and Physical Exam (PE)
- COVID-19 Eval re: exposure, diagnosis

Assess for Evidence of Inflammation
Consider Differential Diagnosis for MIS-C
Assess for Evidence of Shock
- ED Sepsis Triage
- Sepsis Huddle as clinically indicated
- See Appendix A *Common Features of Shock in Children*

CLINICAL/HISTORICAL FEATURES

GI Symptoms
Abdominal pain (mild/severe), vomiting, and/or diarrhea

Rash
Polymorphic, maculopapular, petechial, NOT vesicular

Extremity changes
Erythema and edema of the hands and feet

Oral Mucosal changes
Erythema of oropharyngeal mucosa

Conjunctivitis
Bilateral bulbar conjunctival injection without exudate

Lymphadenopathy
Cervical > 1.5 cm

Neurologic Symptoms
Headache, irritability, lethargy, altered mental status

Epidemiologic Link to COVID-19
Patient with history of COVID-19 disease or close contact with known Positive COVID-19 case in past 4 weeks, or person placed in quarantine

Evaluation for Possible MIS-C Without Shock

Fever/history of fever ≥ 38.0°C for ≥ 3days
+
≥2 Clinical/Historical Features
* Review Appendix B *Clinical Features of Classic Kawasaki Disease*

Initial Laboratory Testing

CBC, CMP, CRP, ESR
Other testing as clinically indicated to identify cause of fever, based on clinical features

Labs and Physical Exam (PE) Reassuring

Discharge with PCP follow-up within 24-48 hours

Labs or exam concerning but inconsistent with MIS-C

Admit to Inpatient Pediatric Unit if available or consult with tertiary care center

* Review Appendix B *Clinical Features of Classic Kawasaki Disease*

Consider differential diagnosis for MIS-C
See Appendix C *Differential Diagnosis of MIS-C*

If progression or worsening of lab/clinical status

Suspected MIS-C with Shock

Fever/history of fever ≥ 38.0°C for ≥ 1 day
+
Evidence of myocardial dysfunction or Hypotension/vasopressor requirement
+
≥ 2 Clinical/Historical Features

Follow ED/Hospital Sepsis Pathway and Order Sets
Additional diagnostic laboratory studies
Add: COVID PCR, COVID Antibody, Troponin, BNP, D-dimer, Ferritin, ECG
Fluid resuscitation, vasopressors
Antibiotics
Echocardiogram as clinically indicated

- CRP > 3 mg/dL *and/or* ESR ≥ 40 mm/hour *AND*
- Lymphopenia < 1k *or* Thrombocytopenia < 150k

Consult with Tertiary Care Center w/PICU regarding probable transfer, cardiac monitoring and patient status

Consider additional ancillary laboratory studies:
- Troponin, BNP
- ECG, COVID PCR, COVID Antibody testing

Cardiology Consultation if:
- Abnormal ECG, BNP, Troponin
- Cardiac insufficiency on PE, e.g. delayed capillary refill, hepatomegaly, crackles

Consider cultures (e.g. blood/urine), antibiotics

Transfer to Tertiary Care Center w/PICU

Admit to PICU at Pediatric Tertiary Care Center

- Isolation (per infection control policies)
- Care provided by PICU/inpatient team, and consultants as indicated
- Additional laboratory studies/imaging for PICU patients with MIS-C
- PICU Sepsis Pathway
- Consider inotropes, vasopressors, milrinone
- Consider bedside echocardiogram
- Consults – Infectious Disease, Rheumatology, Cardiology, Hematology as indicated
- Obtain COVID-19 Antibody testing and consider repeating COVID-19 PCR if initially negative at 48 hours.
- Consider differential diagnosis for MIS-C
  See Appendix C *Differential Diagnosis of MIS-C*

Consider treatment AFTER multidisciplinary evaluation:
- Antibiotics
- Steroids, IVIG
- Aspirin, Anticoagulation
- Anticytokine therapy
- Monitoring Clinical, Lab, Imaging Response
- Discharge and Follow-Up Plan

*** NOTE**: If considering Kawasaki disease, see Appendix B *Clinical Features of Classic Kawasaki Disease* and consult with a Kawasaki expert.

- Developed by the Illinois MIS-C Workgroup
- Adapted from the *Emergency Department, ICU, and Inpatient Clinical Pathway for Evaluation of Possible Multisystem Inflammatory Syndrome (MIS-C)*, Children's Hospital of Philadelphia, July 2020.

Appendix A

Common Features of Shock in Children

Hypotensive (decompensated) shock is characterized by poor perfusion and an abnormally low blood pressure. It can be difficult to recognize children with ***compensated shock***, as these children will have normal blood pressures. Other important clinical findings that may suggest either decompensated or compensated shock are:

- Tachycardia out of proportion to fever, or present despite resolution of fever
- Tachypnea
- Altered mental status
- Diminished urine output
- Cool extremities with weak pulses and prolonged capillary refill (> 3 seconds) OR warm extremities with bounding pulses and flash capillary refill (< 1 second).
- Children with cardiogenic shock and/or myocardial dysfunction may have hepatomegaly or crackles; it is important to assess for these signs initially and monitor for them as patients receive fluid resuscitation.
- Acidosis (including low serum bicarbonate, base deficit on blood gas testing)
- Elevated lactate

Appendix B

Principal Clinical Features of Classic Kawasaki Disease

May not all be present at the same time.

Fever
Presence of fever for ≥ 5 days as well as four of the five following additional features:

- **Oral changes -** Erythema and cracking of lips, strawberry tongue, and/or erythema of oral and pharyngeal mucosa
- **Conjunctivitis** - Bilateral bulbar conjunctival injection without exudate
- **Rash -** Maculopapular, diffuse erythroderma, or erythema multiforme-like
- **Extremity changes** - Erythema and edema of the hands and feet in acute phase and/or periungual desquamation in subacute phase
- **Lymphadenopathy** - Cervical lymphadenopathy (≥ 1.5 cm diameter), usually unilateral

NOTE: Kawasaki disease (KD) can occur in the absence of full diagnostic criteria (incomplete KD), particularly in infants. Therefore consultation with an expert in KD is recommended if incomplete KD is being considered.

Appendix C

Differential Diagnosis of MIS-C

- Acute COVID-19
- Kawasaki Disease
- Non-SARS-CoV-2 Viral Sepsis
- Toxic Shock Syndrome
- Bacterial Sepsis
- Systemic Onset Juvenile Idiopathic Arthritis
- Macrophage Activation Syndrome (MAS)
- Hemophagocytic Lymphohistiocytosis (HLH)

REMINDER: In addition to reporting through I-NEDSS, hospitals should complete the *MIS-C Case Report Form* when they suspect a case and submit to their local health department. The form can be accessed at https://www.cdc.gov/mis-c/pdfs/hcp/mis-c-form-printable.pdf

NOTE: This clinical pathway is current at the time of publication and may need to be adapted for each patient based on practitioner judgment and evolving information on Multisystem Inflammatory Syndrome in Children (MIS-C).