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Multisystem Inflammatory Syndrome Toolkit for Neurologists in Maine August 2022

Multisystem inflammatory syndrome (MIS) can affect children (MIS-C) and adults (MIS-A). MIS is a rare but serious condition associated with COVID-19 in which different body parts become inflamed, including the heart, lungs, kidneys, brain, skin, eyes, or gastrointestinal organs. The cause of MIS remains unknown. MIS-C case definition includes people who are younger than 21 years old and MIS-A case definition includes people who are 21 years or older.

This Toolkit provides some information on what is known about the epidemiology of MIS and additional resources.

Children and adults with MIS may experience fever, stomach pain, bloodshot eyes, diarrhea, dizziness, skin rash, and vomiting.

MIS-C and MIS-A are similar in many ways, however, MIS-C is more common than MIS-A. Severe outcomes might be more likely for MIS-A because of differences in the immune systems of adults compared with children, as well as higher likelihood of underlying medical conditions in adults.

Clinicians should report all patients suspected to have MIS-C or MIS-A to Maine Center for Disease Control and Prevention (Maine CDC) as soon as possible, by phone at 1-800-821-5821 or by fax at 207-287-6865. Clinicians who suspect MIS should hospitalize patients if needed, collect lab specimens, diagnose, begin medical management, and report the case.

The following materials are included in this toolkit:

- 1. MIS-C Associated with Coronavirus Disease Document:** This document includes the case definition of MIS-C, plus information about testing, treatment, symptoms, and reporting.
- 2. MIS-A Associated with Coronavirus Disease Document:** This document includes the case definition of MIS-A, plus information about testing, treatment, symptoms, and reporting.
- 3. MIS-C Reporting Document:** This one-page document can be used as a quick reference for information about clinical presentation as well as the case definition of MIS-C.
- 4. How to Recognize MIS-C Fact Sheet:** This document provides information for parents about MIS-C symptoms and emergency warning signs that parents should look out for.

Virtual Resources:

- **American College of Rheumatology Clinical Guidance for Pediatric Patients with MIS-C:** <https://www.rheumatology.org/Portals/0/Files/ACR-COVID-19-Clinical-Guidance-Summary-MIS-C-Hyperinflammation.pdf>.
- **Case Series of Multisystem Inflammatory Syndrome in Adults Associated with SARS-CoV-2 Infection — United Kingdom and United States, March–August 2020:** <https://www.cdc.gov/mmwr/volumes/69/wr/mm6940e1.htm>.
- **Clinical Characteristics of Multisystem Inflammatory Syndrome in Adults: A Systematic Review,** <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8459192/>.

This toolkit is also available online at www.maine.gov/dhhs/MIS-C.

To report a suspect case of MIS please call Maine CDC at 1-800-821-5821. You can also email disease.reporting@maine.gov with questions or to request a call back. This email is not secure and personal information should not be sent.

Thank you.



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

What is MIS-C?

Multisystem inflammatory syndrome in children (MIS-C) is a condition that causes inflammation of certain body parts, including the heart, lungs, skin, gastrointestinal organs, kidneys, brain, and eyes. MIS-C is very rare. It can be serious and children often need to be treated in the hospital.

Symptoms of MIS-C

- Fever
- Abdominal pain
- Neck pain
- Bloodshot eyes
- Feeling very tired
- Diarrhea
- Skin rash
- Vomiting

Causes and Prevention of MIS-C

The exact cause of MIS-C is not known yet, but it appears to be an excessive immune response related to COVID-19. It is unknown why some children have gotten sick with MIS-C and others have not. For more information on clinical presentation, see https://www.cdc.gov/mis/mis-c/hcp/index.html?CDC_AA_refVal=https%3A%2F%2Fwww.cdc.gov%2Fmis%2Fhcp%2Findex.html

Testing for MIS-C

Testing for SARS-COV-2 by RT-PCR or antigen test is recommended. SARS-COV-2 serologic testing is also suggested, even in the presence of positive results from RT-PCR or antigen testing. Any serologic testing should be performed prior to administering intravenous immunoglobulin (IVIG) or any other exogenous antibody treatments.

Since MIS-C frequently includes cardiac involvement, providers may consider performing cardiac testing including:

- Echocardiogram
- Electrocardiogram
- Cardiac enzyme or troponin testing (per the center's testing standards); and
- B-type natriuretic peptide (BNP) or NT-proBNP

Additional testing to evaluate multisystem involvement should be directed by patient signs or symptoms. Additionally, testing to evaluate for other potential diagnoses should be directed by patient signs or symptoms.

Case Definition of MIS-C

As described in the CDC Health Advisory, “Multisystem Inflammatory Syndrome in Children (MIS-C) Associated with Coronavirus Disease 2019 (COVID-19):

<https://emergency.cdc.gov/han/2020/han00432.asp>” the case definition for MIS-C is:

- An individual aged <21 years presenting with fever*, laboratory evidence of inflammation**, 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 exposure to a suspected or confirmed COVID-19 case within the 4 weeks prior to the onset of symptoms.

*Fever >38.0°C for ≥24 hours, or report of subjective fever lasting ≥24 hours

**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 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.

Coding

New ICD-10-CM Diagnosis Code for MIS: [M35.81](#)

- Applicable to:
 - Multisystem inflammatory syndrome in adults (MIS-A)
 - Multisystem inflammatory syndrome in children (MIS-C)
 - Pediatric inflammatory multisystem syndrome (PIMS)
- Use additional code, if applicable, for:
 - Sequelae of COVID-19 ([B94.8](#))
 - Personal history of COVID-19 ([Z86.16](#))
 - Exposure to COVID-19 or SARS-CoV-2 infection ([Z20.822](#))

- Code first, if applicable, COVID-19 ([U07.1](#))
- Code also any associated complications

Treatment

At this time, there have been no studies comparing clinical efficacy of various treatment options. Treatments have consisted primarily of supportive care and directed care against the underlying inflammatory process.

How to Report MIS-C

Clinicians who suspect MIS-C should collect lab specimens, diagnose, begin medical management, and report the case to Maine CDC by phone at 1-800-821-5821 or by fax to 207-287-6865.

Reporting of cases will help states and U.S. CDC monitor the occurrence of MIS-C and better understand factors possibly associated with this illness.

References and Resources

- Reporting MIS-C in Children Fact Sheet: <https://www.cdc.gov/mis-c/pdfs/hcp/MIS-Children-Handout-FINAL.pdf>.
- Information for Healthcare Providers: <https://www.cdc.gov/mis/mis-c/hcp/index.html?>.
- MIS-C Health Alert: <https://www.maine.gov/dhhs/mecdc/health-advisory.shtml?id=2523981>.
- AAP Interim Guidance: <https://www.aap.org/en/pages/2019-novel-coronavirus-covid-19-infections/clinical-guidance/multisystem-inflammatory-syndrome-in-children-mis-c-interim-guidance/>.
- Case Report Form Instructions: <https://www.aap.org/en/pages/2019-novel-coronavirus-covid-19-infections/clinical-guidance/multisystem-inflammatory-syndrome-in-children-mis-c-interim-guidance/>.
- Case Report Form: <https://www.cdc.gov/mis-c/pdfs/hcp/mis-c-form-fillable.pdf>.
- Webinar, Clinical Management: <https://emergency.cdc.gov/coca/calls/2020/>.



Multisystem Inflammatory Syndrome in Adults (MIS-A) Associated with Coronavirus Disease 2019 (COVID-19)

What is MIS-A?

MIS is a rare but serious condition associated with COVID-19 in which different body parts become inflamed, including the heart, lungs, kidneys, brain, skin, eyes, or gastrointestinal organs. Since June 2020, there have been several reports of a multisystem inflammatory syndrome in adults (MIS-A), similar to multisystem inflammatory syndrome in children (MIS-C). Adults who have been infected with the virus that causes COVID-19 can develop symptoms of MIS-A days to weeks after getting sick.

Symptoms of MIS-A

- Fever
- Bloodshot eyes
- Diarrhea
- Dizziness or lightheadedness
- Skin rash
- Vomiting

Causes and Prevention of MIS-A

The exact cause of MIS-A is unknown, and it is unknown why some adults have developed MIS-A and some have not after COVID-19 infection. Based on what we know now, the best way to prevent MIS-A is to take actions to protect yourself from getting COVID-19.

Testing for MIS-A

Testing for SARS-COV-2 by RT-PCR or antigen test is recommended. SARS-COV-2 serologic testing is also suggested, even in the presence of positive results from RT-PCR or antigen testing. Any serologic testing should be performed prior to administering intravenous immunoglobulin (IVIG) or any other exogenous antibody treatments.

Since MIS-A frequently includes cardiac involvement, providers may consider performing cardiac testing including:

- Echocardiogram
- Electrocardiogram
- Cardiac enzyme or troponin testing (per the center's testing standards); and
- B-type natriuretic peptide (BNP) or NT-proBNP

Additional testing to evaluate multisystem involvement should be directed by patient signs or symptoms. Additionally, testing to evaluate for other potential diagnoses should be directed by patient signs or symptoms.

Case Definition of MIS-A

A patient aged ≥ 21 years hospitalized for ≥ 24 hours, or with an illness resulting in death, who meets the following clinical and laboratory criteria. The patient should not have a more likely alternative diagnosis for the illness (e.g., bacterial sepsis, exacerbation of a chronic medical condition).

I. Clinical Criteria

Subjective fever or documented fever (≥ 38.0 C) for ≥ 24 hours prior to hospitalization or within the first THREE days of hospitalization* and at least THREE of the following clinical criteria occurring prior to hospitalization or within the first THREE days of hospitalization*. At least ONE must be a primary clinical criterion.

A. Primary clinical criteria

1. Severe cardiac illness includes myocarditis, pericarditis, coronary artery dilatation/aneurysm, or new-onset right or left ventricular dysfunction (LVEF $<50\%$), 2nd/3rd degree A-V block, or ventricular tachycardia. (Note: cardiac arrest alone does not meet this criterion)
2. Rash AND non-purulent conjunctivitis

B. Secondary clinical criteria

1. New-onset neurologic signs and symptoms includes encephalopathy in a patient without prior cognitive impairment, seizures, meningeal signs, or peripheral neuropathy (including Guillain-Barré syndrome)
2. Shock or hypotension not attributable to medical therapy (e.g., sedation, renal replacement therapy)
3. Abdominal pain, vomiting, or diarrhea
4. Thrombocytopenia (platelet count $<150,000$ / microliter)

II. Laboratory evidence

The presence of laboratory evidence of inflammation AND SARS-CoV-2 infection.

- A. Elevated levels of at least TWO of the following: C-reactive protein, ferritin, IL-6, erythrocyte sedimentation rate, procalcitonin
- B. A positive SARS-CoV-2 test for current or recent infection by RT-PCR, serology, or antigen detection

NOTE: *These criteria must be met by the end of hospital day 3, where the date of hospital admission is hospital day 0.

Coding

New ICD-10-CM Diagnosis Code for MIS: [M35.81](#)

- Applicable to:
 - Multisystem inflammatory syndrome in adults (MIS-A)

- Multisystem inflammatory syndrome in children (MIS-C)
- Pediatric inflammatory multisystem syndrome (PIMS)
- Use additional code, if applicable, for:
 - Sequelae of COVID-19 ([B94.8](#))
 - Personal history of COVID-19 ([Z86.16](#))
 - Exposure to COVID-19 or SARS-CoV-2 infection ([Z20.822](#))
- Code first, if applicable, COVID-19 ([U07.1](#))
- Code also any associated complications

Treatment

At this time, there have been no studies comparing clinical efficacy of various treatment options. Treatments have consisted primarily of supportive care and directed care against the underlying inflammatory process.

How to Report MIS-A

Clinicians who suspect MIS-A should collect lab specimens, diagnose, begin medical management, and report the case to Maine CDC by phone at 1-800-821-5821 or by fax to 207-287-6865. Reporting of cases will help Maine and US CDC monitor the occurrence of MIS-A and better understand the factors possibly associated with this illness.

References and Resources

- US Centers for Disease Control and Prevention, Multisystem Inflammatory Syndrome in Adults (MIS-A): <https://www.cdc.gov/mis/mis-a.html>.
- MMWR: Case Series of Multisystem Inflammatory Syndrome in Adults Associated with SARS-CoV-2 Infection — United Kingdom and United States, March–August 2020: <https://www.cdc.gov/mmwr/volumes/69/wr/mm6940e1.htm>.
- Clinical Characteristics of Multisystem Inflammatory Syndrome in Adults: A Systematic Review, <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8459192/>.

Reporting Multisystem Inflammatory Syndrome in Children (MIS-C)

Accessible version: <https://www.cdc.gov/mis-c/hcp/index.html>

Clinical Presentation

Patients with MIS-C have presented with a persistent fever, fatigue, and a variety of signs and symptoms, including multiorgan (e.g., cardiac, gastrointestinal, renal, hematologic, dermatologic, neurologic) involvement and elevated inflammatory markers. Not all children will have the same signs and symptoms, and some children may have symptoms not listed here.

MIS-C may present weeks after a child is infected with SARS-CoV-2. The child may have been infected from an asymptomatic contact and, in some cases, the child and their caregivers may not even know they had been infected.

Case Definition

- An individual aged <21 years presenting with fever*, laboratory evidence of inflammation**, 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 exposure to a suspected or confirmed COVID-19 case within the 4 weeks prior to the onset of symptoms

*Fever >38.0°C for ≥24 hours, or report of subjective fever lasting ≥24 hours

Report possible cases of MIS-C to your local, state, or territorial health department.

Visit [cdc.gov/mis-c/hcp](https://www.cdc.gov/mis-c/hcp) for more information and a case report form.

Questions? Contact CDC's 24-hour Emergency Operations Center at 770-488-7100.

**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 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.

Visit [Information for Healthcare Providers about Multisystem Inflammatory Syndrome in Children \(MIS-C\)](https://www.cdc.gov/mis-c/hcp) for more information about MIS-C.



[cdc.gov/coronavirus](https://www.cdc.gov/coronavirus)

How to Recognize

Multisystem Inflammatory Syndrome in Children (MIS-C)

A Delayed Immune Response Related to COVID-19

Children, adolescents, or young adults who develop certain symptoms after having COVID-19 might have MIS-C. They should see a doctor if they had COVID-19, or have been in close contact with someone who had COVID-19, within the past 6 weeks and now have the following:

**Ongoing
Fever**



**PLUS more than one
of the following:**



Stomach Pain



Diarrhea



Vomiting



Skin Rash



**Blood Shot
Eyes**



**Dizziness or
Lightheadedness**

**Go to the nearest hospital Emergency Room if your child is showing
any severe MIS-C warning signs such as:**

Trouble breathing | Pain or pressure in the chest that does not go away
Confusion or unusual behavior | Severe abdominal pain | Inability to wake or stay awake
Pale, gray, or blue-colored skin, lips, or nail beds; depending on skin tone



Centers for Disease
Control and Prevention
National Center for Immunization
and Respiratory Diseases

For More Information

www.cdc.gov/mis/mis-c.html

