

Multisystem Inflammatory Syndrome in Children (MIS-C): Care Guide for Children and Adolescents in Alberta

Table of Contents

Multisystem Inflammatory Syndrome in Children (MIS-C) Key Messages.....	2
Introduction.....	2
COVID-19 Pneumonia in Children.....	2
COVID-19 and MIS-C	2
MIS-C Case Definition	2
The preliminary case definition is as follows:.....	2
Other Features.....	3
Differential Diagnosis.....	3
MIS-C Algorithm	4
Labs	5
Potential MIS-C Lab Investigations (including list from RCPCH Guidance Document for PIMS):	5
Treatment.....	6
Other treatment options to consider (normal practice is to rule out TB prior to biologic commencement):	6
Other therapeutic considerations:.....	6
Discharge and Follow-Up	7
Referral.....	7
Research.....	7
Appendix	8
Definitions from CDC	8
Kawasaki Disease Definition	8
Toxic Shock Syndrome Definition.....	9
Poster for ED and Urgent Care Centres	11
References	12

Multisystem Inflammatory Syndrome in Children (MIS-C) Key Messages

1. Children and adolescents with fever of 3 or more days, with or without a past history of acute COVID infection **OR** known COVID contact, may have MIS-C
2. Febrile children with abdominal pain or significant vomiting/diarrhea may have MIS-C
3. Febrile children with shock may have MIS-C
4. MIS-C mimics Kawasaki Disease and Toxic Shock Syndrome (TSS) (see [Appendix](#))
5. Do not delay anti-microbial therapy because you suspect MIS-C—as it is a diagnosis of exclusion
6. If suspected (even if clinically well), consult with Stollery or ACH ED and/or PICU via RAAPID

Introduction

COVID-19 Pneumonia in Children

Acute infection with SARS-CoV-2 (COVID-19) in children progresses to respiratory failure less frequently than in adults, but significant acute respiratory illness has been recently described in a cohort of 48 children admitted to North American PICUs.¹ 83% were reported to have had an underlying condition, such as immunosuppression, cardiovascular or lung disease. The mortality was 4%. One child required ECLS.

COVID-19 and MIS-C

More recently, clusters of children and adolescents have been admitted to hospitals (including many in PICUs) in Europe and North America with features similar to Kawasaki Disease (KD) and Toxic-Shock Syndrome (TSS) [see [Appendix](#) for case definitions of KD and TSS] far above historic expected case numbers. These patients presented with an acute febrile illness accompanied by a hyper-inflammatory syndrome and often suffered multi-organ failure, particularly acute heart failure, some weeks after an acute COVID-19 infection or exposure to COVID-19.^{2,3} Early recognition and appropriate transfer and management of these patients is critical. Children may present with clinical features of shock and may be sensitive to large volume fluid resuscitation. These patients should be managed at a tertiary pediatric centre. Extracorporeal life support (ECLS) has been required for cardiac support. Deaths have been reported (personal communication Dr. S Riphagen, London UK). There is an urgent need for co-operative collection of data concerning these cases.

The World Health Organization has established a Preliminary Case Definition and Clinical Data Platform:

<https://www.who.int/publications-detail/multisystem-inflammatory-syndrome-in-children-and-adolescents-with-covid-19>

MIS-C Case Definition

The preliminary case definition is as follows:

Children and adolescents 0–19 years of age with fever \geq 3 days

AND two of the following:

1. Rash or bilateral non-purulent conjunctivitis or muco-cutaneous inflammation signs (oral, hands or feet)
2. Hypotension or shock
3. Features of myocardial dysfunction, pericarditis, valvulitis, or coronary abnormalities (including ECHO findings or elevated Troponin / NT-proBNP)
4. Evidence of coagulopathy (by PT, PTT, elevated d-Dimers)

5. Acute gastrointestinal problems (vomiting, abdominal pain)

AND

Elevated markers of inflammation such as LDH,
C-reactive protein, ferritin or procalcitonin (not measured in Alberta).

AND

No other obvious microbial cause of inflammation, including bacterial sepsis, staphylococcal or streptococcal shock syndromes.

AND

Evidence of recent COVID-19 (RT-PCR, antigen test or serology positive), or likely contact with patients with COVID-19.

Other Features

1. Neurological symptomatology is also possible, but so far is not well described
2. Non-infectious ARDS has been described⁴
3. Pleural, pericardial and peritoneal effusions
4. Coagulopathy with low fibrinogen and high D-dimers—there are reports of stroke in adult⁵ ;
Note: fibrinogen can also be elevated as part of inflammation
5. Transaminitis
6. Thrombocytopenia or thrombocytosis
7. Lymphopenia and/or leukocytosis
8. Elevated CK
9. Elevated LDH
10. Low albumin with generalized edema
11. Elevated troponin I
12. Elevated IL-1B and IL-6
13. Low Vit D levels

(Personal communication Dr. S Riphagen, London UK)

Differential Diagnosis

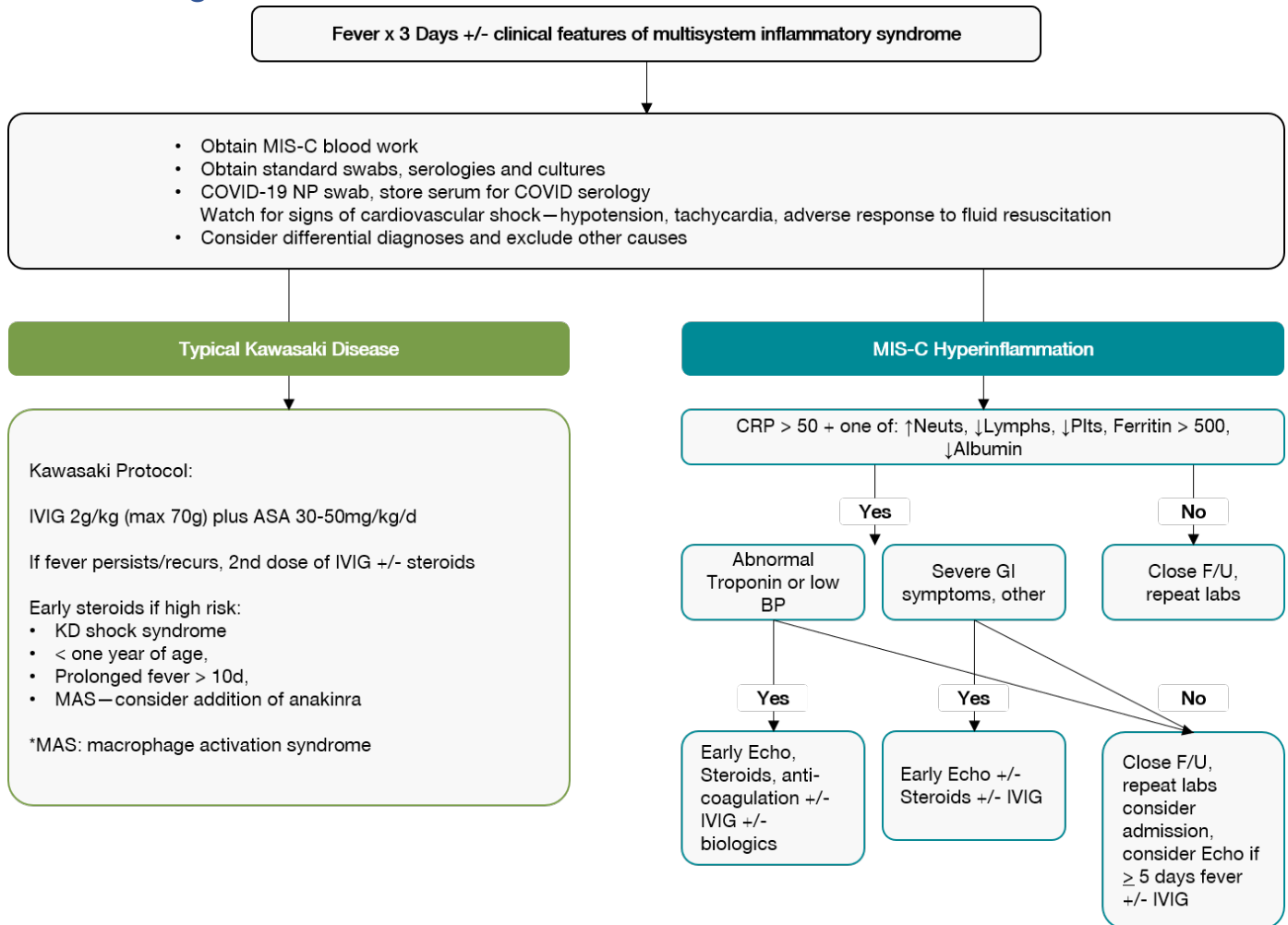
Different acronyms are being used for this condition, but the most commonly used now is multisystem inflammatory syndrome in children (MIS-C). Another commonly used term is Pediatric Inflammatory Multisystem Syndrome (PIMS).

There is an overlap with various other inflammatory syndromes such as cytokine storm syndrome (CSS) seen in adult and pediatric COVID-19 ARDS, macrophage activating syndrome (MAS), hemophagocytic lymphohistiocytosis (HLH), systemic inflammatory response syndrome (SIRS), culture-negative sepsis, multi-organ dysfunction syndrome seen in septic shock, cytokine release syndrome (CRS) in oncology CAR-T therapy, and as already mentioned KD and TTS. MIS-C is an overlapping entity with KD with associated cardiogenic shock/myocarditis (KDSS). Coronary aneurysms have been described in MIS-C.⁶

Other known features of MIS-C are older childhood age, childhood obesity and Asian or Afro-Caribbean descent.

In MIS-C, gastrointestinal symptoms including severe abdominal pain are very common.⁷ Cases have been mistakenly managed as surgical emergencies. As such, abdominal ultrasound (US) and/or CT scan are recommended to rule out appendicitis, intussusception and other acute abdominal pathologies. CT and US changes can mimic Crohn's disease and other forms of enterocolitis e.g. typhlitis (personal communication Dr. S Riphagen, London UK and recent ACH experience).

MIS-C Algorithm



Note: MIS-C algorithm (modified with permission from Dr. R. Berrard, Pediatric Rheumatology, London ON)

Labs

Potential MIS-C Lab Investigations (including list from RCPCH Guidance Document for PIMS):

CBC and Differential (with smear- burr cells noted in some children)
CRP
LFT
Glucose
Blood gas with lactate
Coagulation + fibrinogen D-Dimer
Albumin
LDH
Triglycerides
Ferritin
Troponin
Pro-BNP
CK
Vitamin D
Amylase
Urinalysis
Save EDTA and serum for PCR and serological studies (ideally pre IVIG)
Blood culture
Urine and stool culture
Throat swab culture
NPA or throat swab for respiratory panel plus SARS-CoV-2 PCR
Stool and blood for SARS-CoV-2
PCR
Pneumococcal, Meningococcal, Group A strep, Staph aureus Blood PCR
ASOT
SARS-CoV-2 serology
CMV, Adenovirus
Enterovirus PCR on blood
Stool for virology
Request sending microbiological sample for enterotoxin/staph toxins

Treatment

Treatment is currently based on anecdotal experience and small case series. Treatment should involve consultation (as indicated) with PICU, Infectious Disease, Rheumatology, Cardiology, and Hematology.

- Volume resuscitation—should be minimized due to cardiogenic nature of shock and significant capillary leak. We recommend 5 ml/kg aliquots of crystalloid and commencement of vasopressors (initially norepinephrine) once 20 mls/kg volume resuscitation is reached or earlier if hypotension is not responsive to fluid, cardiac function is known to be depressed (e.g. POCUS assessment) and/or the CXR shows evidence of pulmonary edema/effusions
- Initial cultures and antibiotics coverage for bacterial sepsis/TSS with ceftriaxone and clindamycin +/- vancomycin
- Norepinephrine initially for warm shock should be started early rather than excessive use of IV fluids. Consider addition of epinephrine depending on clinical circumstances and cardiac ECHO results
- IVIG 2 grams/kg IV—give slowly if volume load is of concern
- Aspirin—30-50 mg/kg/day PO divided qid, as per moderate dose KD when febrile, then 3-5 mg/kg/day MAX 81mg
- Systemic steroids methyl-prednisone—many centers suggest using initial 2mg/kg/d dosing of methylprednisolone over pulses. Reported doses have ranged from 30 mg/kg/day x 3 days then 2 mg/kg/day, 10 mg/kg/day x 5 days then 2 mg/kg/day OR 2 mg/kg initially without pulse dosing
- LMWH/heparin if evidence of immune-mediated prothrombotic state or large coronary aneurysm

Other treatment options to consider (normal practice is to rule out TB prior to biologic commencement):

- Anakinra^{8,9,10}—for refractory hyperinflammation
- Tocalizumab¹¹—for refractory hyperinflammation
- Infliximab—refractory hyperinflammation associated with coronary aneurysms or bowel disease¹²
- Plasmapheresis¹³—not widely used

Other therapeutic considerations:

- Vit D replacement^{14,15}
- PTE/DVT prophylaxis—is associated with decreased mortality in adults with COVID ARDS, but indications in children remain uncertain^{16,17,18}

Note: Similar therapies have been used in CSS associated with COVID-19 ARDS.¹⁹

Discharge and Follow-Up

Follow-up suggested (based on national guidance):

1. Cardiology follow-up with ECHO at 2 and 6 weeks after diagnosis
2. If needing steroids—steroid taper (for Prednisone 2mg/kg x 5 days, then 1mg/kg for 5 days, then 0.5 mg/kg x 5 days), rheum follow within 4 weeks
3. Peds follow-up with repeat blood work within 2 weeks
4. Return if febrile or unwell

Referral

MIS-C is now a notifiable disease in Alberta. Click [here](#) to view Report Form.

If you are presented with a pediatric patient in Alberta with a possible case of Multi-System Hyperinflammatory Syndrome (MIS-C), please contact RAAPID North or RAAPID South and ask to speak to the ED physician on call (stable case) or Pediatric Intensivist on-call (unstable case). Refer to the MIS-C case identification brief poster ([link here](#)).

Research

Various research studies are underway in Alberta for COVID related illnesses:

Studies in Alberta- for more information contact Dr. Jim Kellner (U of C) or Dr. Joan Robinson (U of A) or Dr. Susa Benseler

University of Calgary: <https://research.ucalgary.ca/covid-19/collaboration>

Canada: [CanCOVID](#)

Appendix

Definitions from:



Kawasaki Disease Definition

For epidemiologic surveillance, CDC defines a case of KD as illness in a patient with fever of 5 or more days duration (or fever until the date of administration of intravenous immunoglobulin if it is given before the fifth day of fever), and the presence of at least 4 of the following 5 clinical signs:

- Rash
- Cervical lymphadenopathy (at least 1.5 cm in diameter)
- Bilateral conjunctival injection
- Oral mucosal changes
- Peripheral extremity changes

Patients whose illness does not meet the above KD case definition but who have fever and coronary artery abnormalities are classified as having atypical or incomplete KD.

Page last reviewed: October 24, 2018

Content source: Centers for Disease Control and Prevention , National Center for Emerging and Zoonotic Infectious Diseases (NCEZID) , Division of High-Consequence Pathogens and Pathology (DHCPP)

Toxic Shock Syndrome Definition

Streptococcal Toxic Shock Syndrome (STSS) (*Streptococcus pyogenes*)

2010 Case Definition



NOTE: A surveillance case definition is a set of uniform criteria used to define a disease for public health surveillance. Surveillance case definitions enable public health officials to classify and count cases consistently across reporting jurisdictions. Surveillance case definitions are not intended to be used by healthcare providers for making a clinical diagnosis or determining how to meet an individual patient's health needs.

CSTE Position Statement(s)

09-ID-60

Clinical Description

Streptococcal toxic shock syndrome (STSS) is a severe illness associated with invasive or noninvasive group A streptococcal (*Streptococcus pyogenes*) infection. STSS may occur with infection at any site but most often occurs in association with infection of a cutaneous lesion. Signs of toxicity and a rapidly progressive clinical course are characteristic, and the case fatality rate may exceed 50%.

Clinical Criteria

An illness with the following clinical manifestations*:

- Hypotension defined by a systolic blood pressure less than or equal to 90 mm Hg for adults or less than the fifth percentile by age for children aged less than 16 years.
- Multi-organ involvement characterized by two or more of the following:
 - Renal impairment: Creatinine greater than or equal to 2 mg/dL (greater than or equal to 177 µmol/L) for adults or greater than or equal to twice the upper limit of normal for age. In patients with preexisting renal disease, a greater than twofold elevation over the baseline level.
 - Coagulopathy: Platelets less than or equal to 100,000/mm³ (less than or equal to 100 x 10⁶/L) or disseminated intravascular coagulation, defined by prolonged clotting times, low fibrinogen level, and the presence of fibrin degradation products.
 - Liver involvement: Alanine aminotransferase, aspartate aminotransferase, or total bilirubin levels greater than or equal to twice the upper limit of normal for the patient's age. In patients with preexisting liver disease, a greater than twofold increase over the baseline level.
 - Acute respiratory distress syndrome: defined by acute onset of diffuse pulmonary infiltrates and hypoxemia in the absence of cardiac failure or by evidence of diffuse capillary leak manifested by acute onset of generalized edema, or pleural or peritoneal effusions with hypoalbuminemia.
 - A generalized erythematous macular rash that may desquamate.
 - Soft-tissue necrosis, including necrotizing fasciitis or myositis, or gangrene.

* Clinical manifestations do not need to be detected within the first 48 hours of hospitalization or illness, as specified in the 1996 case definition. The specification of the 48 hour time constraint was for purposes of assessing whether the case was considered nosocomial, not whether it was a case or not.

Laboratory Criteria for Diagnosis

Isolation of group A *Streptococcus*.

Case Classification

Probable

A case that meets the clinical case definition in the absence of another identified etiology for the illness and with isolation of group A *Streptococcus* from a non-sterile site.

Confirmed

A case that meets the clinical case definition and with isolation of group A *Streptococcus* from a normally sterile site (e.g., blood or cerebrospinal fluid or, less commonly, joint, pleural, or pericardial fluid).

Toxic Shock Syndrome (Other Than Streptococcal) (TSS) 2011 Case Definition



NOTE: A surveillance case definition is a set of uniform criteria used to define a disease for public health surveillance. Surveillance case definitions enable public health officials to classify and count cases consistently across reporting jurisdictions. Surveillance case definitions are not intended to be used by healthcare providers for making a clinical diagnosis or determining how to meet an individual patient's health needs.

CSTE Position Statement(s)

10-ID-14

Clinical Criteria

An illness with the following clinical manifestations:

- Fever: temperature greater than or equal to 102.0°F (greater than or equal to 38.9°C)
- Rash: diffuse macular erythroderma
- Desquamation: 1-2 weeks after onset of rash
- Hypotension: systolic blood pressure less than or equal to 90 mm Hg for adults or less than fifth percentile by age for children aged less than 16 years
- Multisystem involvement (three or more of the following organ systems):
 - Gastrointestinal: vomiting or diarrhea at onset of illness
 - Muscular: severe myalgia or creatine phosphokinase level at least twice the upper limit of normal
 - Mucous membrane: vaginal, oropharyngeal, or conjunctival hyperemia
 - Renal: blood urea nitrogen or creatinine at least twice the upper limit of normal for laboratory or urinary sediment with pyuria (greater than or equal to 5 leukocytes per high-power field) in the absence of urinary tract infection
 - Hepatic: total bilirubin, alanine aminotransferase enzyme, or aspartate aminotransferase enzyme levels at least twice the upper limit of normal for laboratory
 - Hematologic: platelets less than 100,000/mm³
 - Central nervous system: disorientation or alterations in consciousness without focal neurologic signs when fever and hypotension are absent

Laboratory Criteria for Diagnosis

Negative results on the following tests, if obtained:

- Blood or cerebrospinal fluid cultures blood culture may be positive for *Staphylococcus aureus*)
- Negative serologies for Rocky Mountain spotted fever, leptospirosis, or measles

Case Classification

Probable

A case which meets the laboratory criteria and in which four of the five clinical criteria described above are present

Confirmed

A case which meets the laboratory criteria and in which all five of the clinical criteria described above are present, including desquamation, unless the patient dies before desquamation occurs

Poster for ED and Urgent Care Centres

Multisystem Inflammatory Syndrome in Children (MIS-C) Associated with COVID

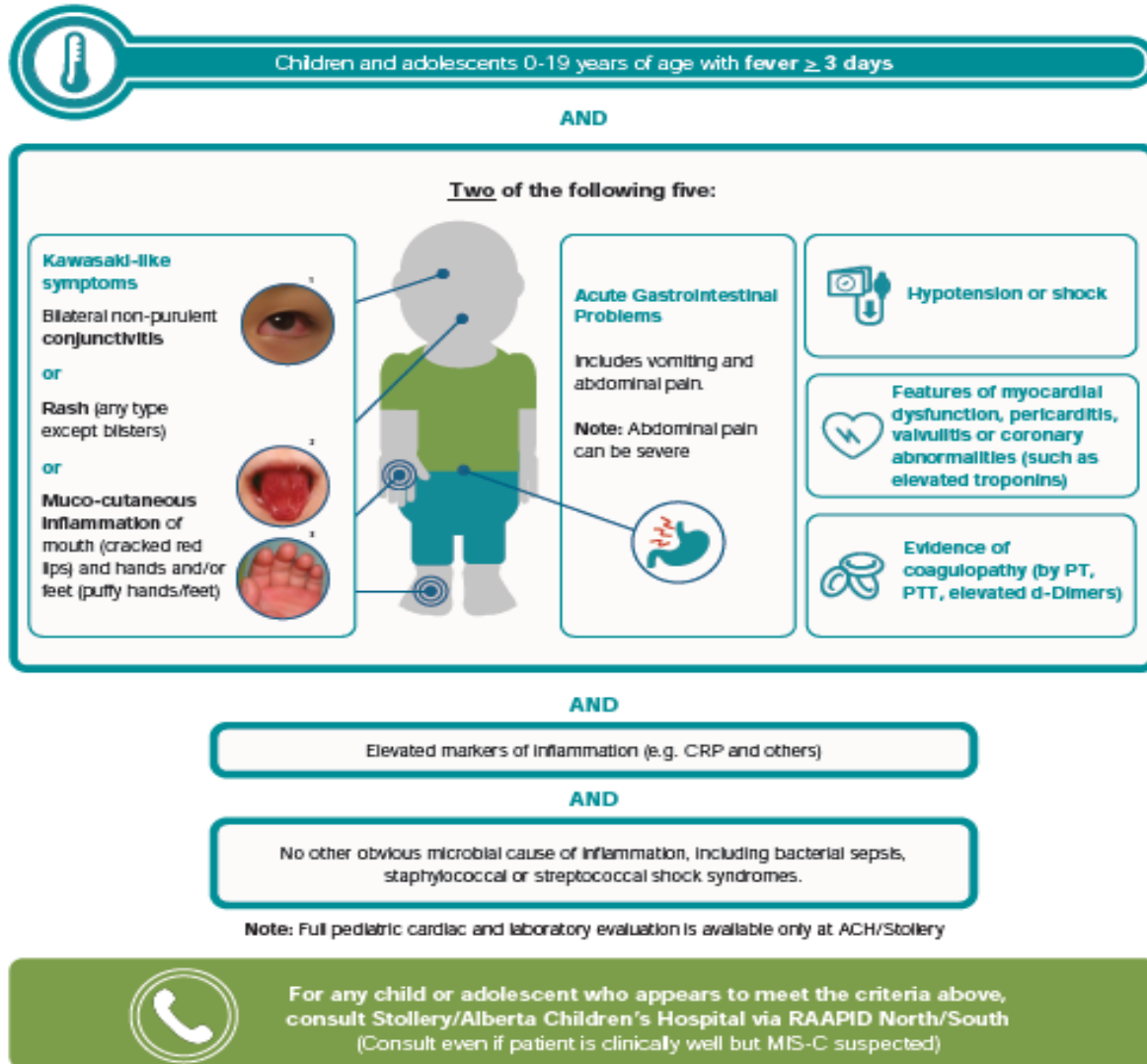
Children and adolescents can develop a severe inflammatory syndrome thought to follow exposure to COVID which has features similar to Kawasaki Disease and/or Toxic Shock Syndrome (TSS).

Vigilance for this uncommon but serious disease is critically important.

Children and adolescents can present in a wide variety of ways and ranging severity, including fever and shock.

Note: Patient may not have known COVID exposure or positive COVID testing.

Criteria of MIS-C:



While awaiting disposition decision, continue to provide supportive care and watch for adverse response to fluid resuscitation. Do not delay anti-microbial therapy because of suspected MIS-C.

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RAAPID North
(for patients north of Red Deer)
(780) 735-0811

RAAPID South
(for patients in and south of Red Deer)
(403) 944-4496

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